From: [redacted]
To:

Cc:

Date: Friday, July 06, 2018 10:31AM
Subject: ECIG use pathway to COPD

History: This message has been forwarded.

If smoking was just invented, given the scientific knowledge now available, it would be banned.

There is zero evidence that E-cigarette use has any beneficial effect on smoking reduction (longitudinal 10 year study of 200,000 adults in UK).

CDC data shows 59% of US adult smokers are dual combustible / e-cig users – double toxic whammy.

There is increasing evidence of Ecig dangers to health in recent studies showing toxic flavors when heated, cinnamon flavor paralyses throat and lung ciliae, endothelial cell damage, toxic aldehydes, acetaldehyde, benzene, glycidol, propylene oxide, formaldehyde, lead, nickel, chromium heavy metals from the coils, bladder cancer, DNA strand mutations, heart disease, CVD and now, COPD.

Electronic nicotine delivery systems are fit for one purpose which is to **addict people to nicotine for profit, previously first admitted by Brown and Williamson lead counsel in 1963 – "we are then in the business of selling nicotine, an addictive drug " .**

Nothing changed, just the delivery method.

Any sensible Government must ban their use.

Attachments:

Ecig-use-pathway-to-COPD.pdf
drugabuse.gov-Electronic Cigarettes E-cigarettes.pdf
e016046.full.pdf

First evidence linking e-cigs to COPD in the population

The biological and clinical evidence that e-cigarettes are really bad for lungs has been rapidly piling up; now the first evidence linking e-cigarette use with chronic obstructive pulmonary disease (COPD) has been presented. At the American Thoracic Society meeting in May 2018, Mario Perez and colleagues presented an analysis of the NIDA/FDA PATH study and found a strong link between e-cigarette use and COPD.

They compared having been told they were diagnosed with COPD (including COPD, chronic bronchitis, or emphysema) among current (some day or every day) with people who did not use e-cigarettes. They controlled for other tobacco product usage and secondhand smoke exposure using a technique called propensity score matching. Accounting for matched propensities, there were 1321 e-cigarette users and 1321 nonusers. E-cigarette users were about twice as likely to have COPD (odds ratio, 1.86; 95% CI, 1.22-2.83).

Like our earlier paper that showed that daily e-cigarette users are about twice as likely to have had a heart attack, Perez and colleagues' result is based on a cross-sectional analysis, a snapshot in time, that finds an association between e-cigarette use and COPD. PATH is a longitudinal study, so, over time, it will become possible to test for a longitudinal association. But that will likely take years for the necessary new cases to accumulate.

The important thing to do is to interpret this cross-sectional COPD association in the context of all the biological and clinical evidence that would lead you to expect such a link. Since we reviewed the evidence that e-cigarettes trigger inflammatory processes and depress immune function in lungs and are associated with kids having chronic bronchitis, the biological evidence has rapidly accumulated. Two recent animal and human studies (Reinikovaite et al, and Garcia-Arcos et al) have shown that exposure to e-cigarettes produces COPD-like changes to the alveoli (air sacs). You don't have to be a molecular biologist to understand this damage. Just look at the pictures in these papers. There is also evidence of genetic changes in nonsmokers who never used an e-cigarette in one session that explain these effects (Staudt et al). These genetic changes include suppression of the p53 tumor suppressor gene, that suggests that, despite delivering lower levels of carcinogens, e-cigarettes could be increasing the risk of lung cancer.

Viewed from this perspective, Perez' epidemiological findings are exactly what one would expect based on the biology.

In addition, nicotine is directly implicated as causing some of these changes and directly damages lungs. It is time for FDA and e-cigarette enthusiasts to stop ignoring the evidence that nicotine itself has adverse biological effects beyond its addictive properties.

The more we learn about e-cigs the more dangerous they look.

Here is the full citation: Perez MF, Atuegwu N, Mead E, Oncken C, Mortensen EM. E-cigarette use is associated with emphysema, chronic bronchitis and COPD. Presented at: American Thoracic Society 2018 International Conference; May 18-23, 2018; San Diego, CA. Poster 402. The abstract is available here.

E-Cigarette Use Associated With Increased Risk for COPD

Pulmonology Advisor Contributing Writer

May 23, 2018

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Researchers used data from the 2013-2014 Population Assessment of Tobacco and Health to assess the risk for COPD in e-cigarette users.

Pulmonology Advisor

This article is part of *Pulmonology Advisor*'s coverage of the American Thoracic Society's International Conference, taking place in San Diego, California. Our staff will report on medical research related to asthma and other respiratory conditions, conducted by experts in the field. Check back regularly for more news from ATS 2018.

SAN DIEGO — A study has shown an association between regular e-cigarette use and higher likelihood of having chronic obstructive pulmonary disease (COPD). This research was presented at the American Thoracic Society International Conference, held May 18-23, 2018, in San Diego, California.

Study researchers included 32,247 subjects from the Population Assessment of Tobacco and Health (PATH) study, 1575 of whom used e-cigarettes daily or regularly. COPD prevalence was defined as a diagnosis of either chronic bronchitis, emphysema, or COPD. Possible confounders such as other tobacco product usage and secondhand smoke between e-cigarette users and nonusers were accounted for using propensity score matching. Researchers also adjusted for possible confounders in employing logistic regression to study the link between usage of e-cigarettes and COPD. Balanced repeated replication techniques and replicate weights were used to manage the complex design of the PATH study's survey.

Of the e-cigarette users in the PATH study, COPD occurred in 4.45% (95% CI, 3.70-5.19). Accounting for matched propensities, there were 1321 e-cigarette users and 1321 nonusers. E-cigarette users were significantly more likely to have COPD (odds ratio, 1.86; 95% CI, 1.22-2.83).

Related Articles

The study researchers concluded that “fairly regular use of e-cigs every day or some days is associated with an increased odds of having COPD in a large representative US adult cohort. This association exists even after adjusting for potential confounding factors. Due to

the fact that the data is cross-sectional, it is unknown whether e-cigs could contribute to COPD development, or if people who have COPD are more likely to use e-cigs (possibly as a harm reduction method)."

Visit *Pulmonology Advisor*'s conference section for continuous coverage from ATS 2018

Reference

Perez MF, Atuegwu N, Mead E, Oncken C, Mortensen EM. E-cigarette use is associated with emphysema, chronic bronchitis and COPD. Presented at: American Thoracic Society 2018 International Conference; May 18-23, 2018; San Diego, CA. Poster 402.

The effect of electronic cigarette and tobacco smoke exposure on COPD bronchial epithelial cell inflammatory responses

Original Research

Authors Higham A, Bostock D, Booth G, Dungwa JV, Singh D

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Background: Electronic cigarettes (e-cigs) are used to help smoking cessation. However, these devices contain harmful chemicals, and there are safety concerns. We have investigated the effects of e-cigs on the inflammatory response and viability of COPD bronchial epithelial cells (BECs).

Methods: BECs from COPD patients and controls were exposed to e-cig vapor extract (ECVE) and the levels of interleukin (IL)-6, C-X-C motif ligand 8 (CXCL8), and lactate dehydrogenase release were measured. We also examined the effect of ECVE pretreatment on polyinosinic:polycytidylic acid (poly I:C)-stimulated cytokine release from BECs. Parallel experiments using Calu-3 cells were performed. Comparisons were made with cigarette smoke extract (CSE).

Results: ECVE and CSE caused an increase in the release of IL-6 and CXCL8 from Calu-3 cells. ECVE only caused toxicity in BECs and Calu-3 cells. Furthermore, ECVE and CSE dampened poly I:C-stimulated C-X-C motif ligand 10 release from both cell culture models, reaching statistical significance for CSE at an optical density of 0.3.
Conclusion: ECVE caused toxicity and reduced the antiviral response to poly I:C. This raises concerns over the safety of e-cig use.

Keywords: e-cigs, epithelial cells, COPD, air–liquid interface, cigarette smoke

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TC Online First, published on July 22, 2017 as 10.1136/tobaccocontrol-2017-053817

Automated dripping devices for vapers: RDTAs, bottomfeeders, squonk mods and dripboxes

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INTRODUCTION

The standard e-cigarette involves an electric heating coil that vaporises a liquid solution consisting of propylene glycol and/or vegetable glycerin, flavourants and, frequently, nicotine. Typically, the liquid is delivered to the heating coil via saturated wicking material. However, 'dripping' is another method that involves the application of liquid to the coil of a direct drip atomiser or rebuildable dripping atomiser.[1 2] Users report that dripping provides greater vapour yields, stronger throat hit and a better flavour.[3]

Dripping is not without drawbacks. Notably, the higher temperatures involved may increase toxicant yield, although an update examining more contemporary designs may be needed.[1 4] Additionally, dripping is time consuming. It requires transferring liquid from a separate container to the coil.[1] This process must be repeated every few puffs to avoid 'dry puffs', as the liquid is vaporised and the heating coil dries out. Dry puffs yield more toxicants and may be accompanied by an aversive taste.[1 5] Avoiding dry puffs by adding more liquid is challenging, as too much liquid 'floods' the coil, preventing vapour production. Furthermore, monitoring the amount of liquid consumed sometimes was challenging.

Automated dripping devices

To circumvent the inconvenience of direct dripping, e-cigarette users and manufacturers have developed several novel technologies, referred to here as automated dripping devices (ADD). Arguably, these include rebuildable dripping tank atomisers (RDTAs). RDTAs are advertised as offering the 'best of both worlds.'[6] As shown in figure 1, this device typically includes a cotton wick inside the atomiser that reaches down into the tank below, allowing liquid to flow from the bottom through the cotton into the coil. Alternatively, users can apply liquid into the 'drip tip' (mouthpiece).[7] Figure 2 illustrates the two different methods of liquid application on another RDTA.[8] In other cases, distributors claim that the device allows for the benefits of dripping, such as enhanced flavour, but with the practicability of a tank reservoir instead of dripping a few drops of liquid at a time.[9] An additional claim is that these devices often use large amounts of coil and wick, which may allow for higher temperature use without overheating due to larger amounts of liquid available.

Another category of devices, sometimes referred to as 'bottomfeeder' or 'squonk mods', more clearly provides a unique experience. Here, the liquid sits in a plastic bottle at the bottom of the device and squeezing (or 'squonking') the bottle feeds the liquid onto the coil. One purported advantage of this design is the large bottle reservoir. Initially, these devices were manufactured by e-cigarette enthusiasts. More recently, these devices have been mass produced (see figure 3).[10]

DISCUSSION

We know very little about dripping, RDTAs and squonk mods. However, what we do know suggests that dripping may produce more toxicant-laden aerosol than standard e-cigarettes.[1 5] There is some controversy regarding the levels of toxicants produced without dry puffs and the frequency of consumption of dry puffs by users.[11 12] As a result of the lack of regulations and relative novelty of the e-cigarette market, considerable ambiguity exists regarding what devices are labelled RDTAs. For example, one distributor may advertise a device as only involving a tank,[13] while another distributor advertises a very similar—if not identical—device as an RDTA.[14] Further research is needed to discriminate merely semantic differences in terminology from distinctions with relevant implications.

Figure 1 This image was found on Imgur.com, an online image sharing community. It apparently was posted by a user of the Avocado 24, a device manufactured by Geekvape Technology.

To cite: Harrell PT, Eissenberg T. *Tob Control* Published Online First: [*please include* Day Month Year]. doi:10.1136/tobaccocontrol-2017-053817

Figure 2 This image was found on the webpage for Geekvape Technology, an organisation with offices in both China and USA. This image was located in an advertisement for the Medusa RDTA under a heading of 'Main Features' and a subheading of 'Drip refill system'.

We know little about the prevalence of dripping and essentially nothing about the frequency of ADD use. A survey of high school students in Connecticut found that about a quarter of those who had ever used e-cigarettes also reported dripping.[3] However, the item assessing dripping was criticised for its potential inability to discriminate between direct dripping and ADD.[15] Surveillance efforts will require improved measures to allow for discrimination between different types of 'e-cigarettes'.

There are at least two separate issues in need of further research. One involves how e-cigarette users refer to available devices. Some of this research, involving focus groups or Internet surveillance, is ongoing[16 17] but is in need of further updates, particularly in relation to dripping. A second issue involves understanding whether different types of devices are distinct from one another in a way that alters health impact. For example, if 'dripping' devices differ dramatically in health impact from non-dripping devices, understanding the prevalence of dripping will take on greater urgency. Regardless, current measures appear inadequate due to the lack of universal and clear definitions of different e-cigarette systems. The resulting ambiguity is a challenge to research and regulatory efforts, as well as to consumers attempting to make informed decisions regarding product purchasing. Thus, there is an urgent need for further research and discussion on this topic.

Figure 3 This advertisement was found on the webpage for KangerTech, an e-cigarette brand based in China.

Contributors PTH wrote the original draft. TE provided feedback and suggestions. Both authors reviewed and approved the final manuscript.

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Competing interests PTH does not have any competing interests to declare. TE is a paid consultant in litigation against the tobacco industry and is named on a patent application for a device that measures the puffing behaviour of electronic cigarette users.

Provenance and peer review Not commissioned; externally peer reviewed.

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Automated dripping devices for vapers: RDTAs, bottomfeeders, squonk mods and dripboxes

Paul Truman Harrell and Thomas Eissenberg

Tob Control published online July 22, 2017

Notes

ONE person dies every FIVE seconds from smoking, reveals scientist

dailymail.co.uk/health/article-5807071/ONE-person-dies-FIVE-seconds-smoking-reveals-scientist.html

One person dies every five seconds from smoking, a scientist has revealed.

A total of three million people have died due to chronic obstructive pulmonary disease, a lung disorder caused by smoking, according to the most recent statistics from 2016.

This accounted for six per cent of global deaths.

Furthermore, the respiratory disease is expected to become the fourth-largest killer by 2020, behind heart diseases and cancer.

The shocking data was released during a seminar hosted by pulmonologist Syed Zafaryab Hussain, an expert in diseases related to breathing.

Dr Hussain used the findings to reiterate the dangers of smoking, warning that more people die from smoking than from terrorism, and that doctors must inform patients of the dangers.

Scientists have now revealed that a person dies every five seconds because of smoking

Scientists have now revealed that a person dies every five seconds because of smoking

A horrible habit

Dr Hussain presented the statistics at a seminar entitled: 'Hazards of Smoking and Chronic Obstructive Pulmonary Disease'. The seminar took place in Karachi, Pakistan.

Although more men than women smoke (about 40 per cent of the world's population, versus nine per cent), the number of women smoking has increased and has reached parity in some countries.

He said that there was now a greater responsibility for doctors to explain to patients the dangers of smoking and advise them on how they can quit.

Dr Hussain told the Express Tribune, a Pakistani newspaper, that carbon monoxide from smoking zaps oxygen from the body, which then leads to breathing difficulties.

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Furthermore, he believes that many young people are picking up the deadly habit as a 'fashion statement'.

Dr Hussain warned that alternate forms of smoking, like electrical cigarettes and sheesha, can result in a person developing chronic obstructive pulmonary disease as well.

Traditional methods of cooking, such as over an open fire are also dangerous, he added.

A colleague of Dr Hussain's, Dr Faisal Zuberi, warned about the dangers of passive smoke, and that sitting in a surrounding where there is smoke is akin to smoking '200 cigarettes'.

Three mil. people died from chronic obstructive pulmonary disease caused by smoking

In 2016, three million people died from COPD, which is a lung disorder caused by smoking

Global smoking statistics

Cigarettes are smoked by more than one billion people around the world - almost a fifth of the world population.

The majority of smokers are men: around 942 million, while 175 million women are smokers worldwide.

Smoking rates are decreasing in developed countries. For instance, in the United States, smoking rates dropped by 50 per cent betweern 1965 to 2006, according to the CDC.

More than 80 per cent of smokers now live in countries with low to middle incomes, and the country with the highest rate of smoking is China.

However, Timor-Leste - the eastern portion of an tiny Pacific island - has the highest prevalence of smokers in the world.

Dr Hussain said he was concerned about his native Pakistan, where 171,000 people died due to chronic obstructive pulmonary disease each year.

He said that anti-smoking laws made in Pakistan existed but had not been implemented.

WHAT IS COPD (CHRONIC OBSTRUCTIVE PULMONARY DISEASE)?

Chronic obstructive pulmonary disease (COPD) is the name for a group of lung conditions that cause breathing difficulties.

It includes:

- emphysema – damage to the air sacs in the lungs
- chronic bronchitis – long-term inflammation of the airways

COPD is a common condition that mainly affects middle-aged or older adults who smoke.

Many people don't realise they have it.

The breathing problems tend to get gradually worse over time and can limit your normal activities, although treatment can help keep the condition under control.

The main symptoms of COPD are:

- increasing breathlessness, particularly when you're active
- a persistent chesty cough with phlegm – some people may dismiss this as just a "smoker's cough"
- frequent chest infections
- persistent wheezing

Without treatment, the symptoms usually get slowly worse. There may also be periods when they get suddenly worse, known as a flare-up or exacerbation.

See your GP if you have persistent symptoms of COPD, particularly if you're over 35 and smoke or used to smoke.

Source: NHS

Smoking's effect on your body

A recent study found that smoking cigarettes damages the muscles in your body, as well.

The smoke directly reduces the number of blood vessels in leg muscles and limits the amount of oxygen and nutrients they can receive.

This study, conducted by researchers from California, Brazil and Japan, is the first to show the direct impact of smoking on the muscles.

For the study, the team exposed mice to smoke from tobacco cigarettes for eight weeks, either by inhalation or by injecting mice with a solution bubbled with smoke.

In the study, the team found a 34 percent decrease in the capillary-to-muscle fiber ratio of calf muscles in mice exposed to smoke.

Capillaries are the smallest blood vessels in the body. A high capillary-to-fiber ratio allows blood to more fully permeate muscle tissue.

However, the study shows that because blood vessels have been diminished, the rate of blood flow to muscles is reduced - depriving them of oxygen and nutrients.

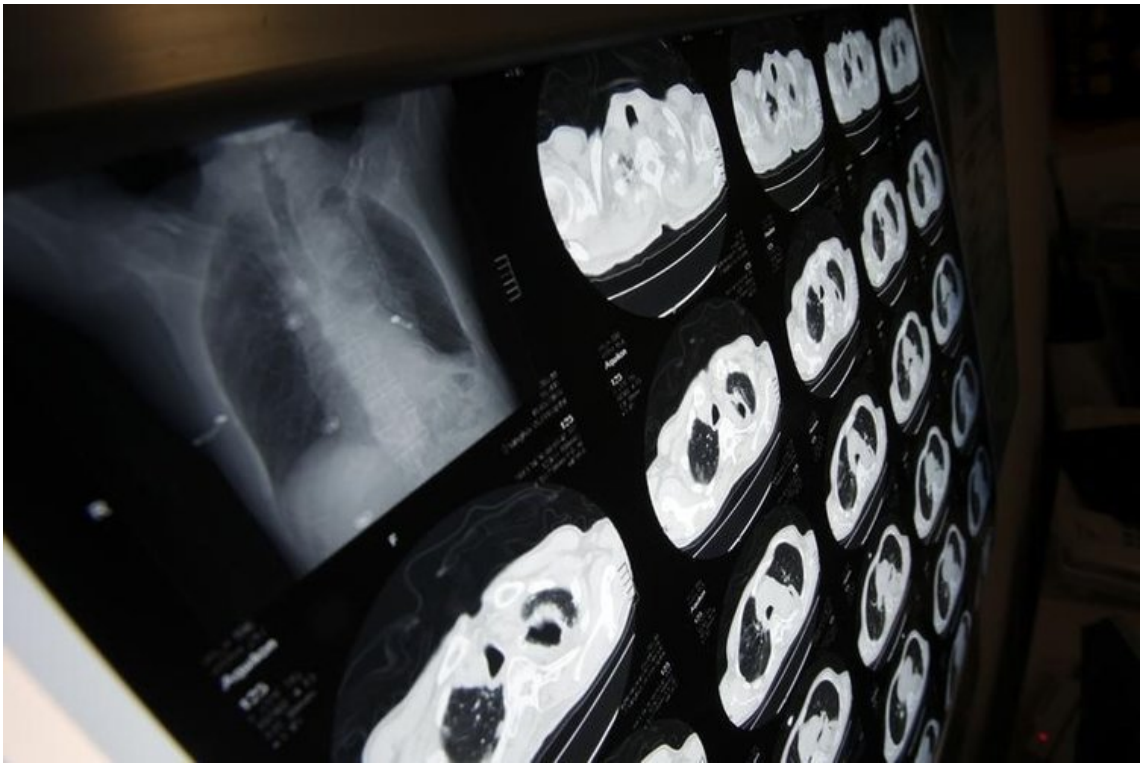
And when muscles are deprived of these two substances to use for energy, they are weakened and unable to perform a great amount of physical activity.

Previous studies have shown that smoking makes muscles weaker because lungs become inflamed by cigarette use, restricting your ability to exercise and perform activities.

A lung condition is the third leading cause of death in the US, and 'no one's talking about it'

businessinsider.com/copd-chronic-obstructive-pulmonary-disease-is-a-leading-cause-of-death-2017-11

Lydia Ramsey Nov. 28, 2017, 10:02 AM



A X-ray of a patient with a lung tumour caused by smoking is seen at Ruijin Hospital in Shanghai
Thomson Reuters

- **Chronic obstructive pulmonary disease, or COPD, is the third leading cause of death in the US behind heart disease and cancer.**
- **While the condition is prevalent, it doesn't get as much attention as other leading causes of death like cancer.**
- **There aren't as many resources being used to research and develop new approaches to treat the condition, which makes tackling the condition challenging.**

When you think about the leading causes of death in the US, it's likely that cancer and heart conditions pop into your head first.

Cancer and heart disease are indeed the two leading causes of death in the US, but they're talked about far more than the third leading cause of death: chronic obstructive pulmonary disease, or COPD.

The condition makes it difficult to breathe, leading to coughing and shortness of breath as it progresses. There are about 16 million people diagnosed with the condition in the US. But,

according to Cheryl MacDiarmid, the senior vice president of primary care at pharma giant GlaxoSmithKline, it doesn't get as much attention as other deadly diseases.

"It's the third leading cause of death in the US, and no one's talking about it," MacDiarmid said.

That's in part because of the nature of the disease, MacDiarmid. Cigarette smoking is the leading cause of COPD. About a quarter of the people who get COPD haven't smoked, and in those cases, environmental factors like polluted air could be involved as well as certain genetic risk factors.

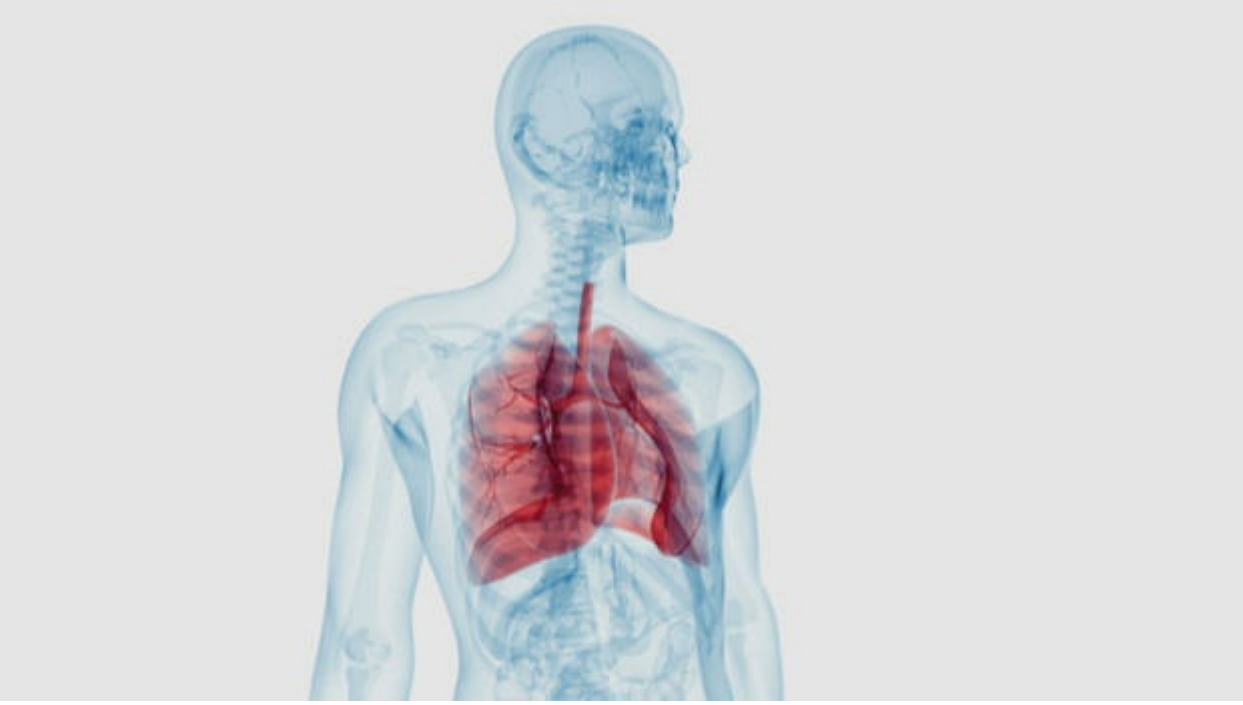
Treatments for respiratory conditions like COPD are a key part of GSK's prescription drug business, and the company's one of the only major drugmakers still working to develop treatments for COPD as companies shift their attention toward cancer.

There's also a lot less basic research going into COPD compared to other top killers. While the National Institute of Health budgeted $6 billion for cancer and more than $1.3 billion for heart disease research in 2017, it budgeted just $100 million for COPD.

That's a problem that's only increasing as Baby Boomers who may have smoked at one point in their life get older, MacDiarmid said. While we do know a lot more about COPD and how to treat it than we might have a decade ago, there is still a need to do basic research and find better ways to treat the condition.

COPD facts from the COPD Foundation

CBS News November 26, 2017, 7:30 AM



Chronic Obstructive Pulmonary Disease affects more than 6% of the U.S. population.

CBS News

From the COPD Foundation:

What is COPD?

Chronic Obstructive Pulmonary Disease (COPD) is an umbrella term used to describe progressive lung diseases, including refractory (non-reversible) asthma, some forms of bronchiectasis, chronic bronchitis and emphysema. It is characterized by increasing breathlessness.

COPD can develop for years without noticeable shortness of breath, with symptoms only developing during the later stages of the disease. Talk to your doctor as soon as you notice any of these symptoms, and ask about taking a spirometry test, which measures how well your lungs are working.

What are the signs and symptoms of COPD?

- Increased breathlessness
- Frequent coughing (with and without sputum)
- Wheezing
- Tightness in the chest

How common is COPD?

COPD affects an estimated 30 million individuals in the U.S., and more than half of them exhibit symptoms but have not been diagnosed. Early screening can identify COPD before major loss of lung function occurs.

Who should get tested for COPD?

Anyone with the following should get tested:

- A history of smoking
- Long-term exposure to air pollutants (including pollution and second-hand smoke)
- Chronic coughing with or without sputum
- Wheezing
- Shortness of breath that has become worse over time
- Cannot keep up with people your own age

Online Screener

You can start with the COPD Foundation's 5-question Risk Screener, then talk to your doctor about taking a spirometry test. Early screening can identify COPD before major loss of lung function occurs.

Risk factors and causes of COPD

The top three risk factors for developing COPD are:

Smoking - COPD most often occurs in people 40 years of age and older who have a history of smoking, or have had long-term exposure to second-hand smoke. While not everybody who smokes gets COPD, most of the individuals who have COPD have smoked at some point in their lives.

Environmental Factors - Long-term contact with harmful pollutants in the workplace or the home (fumes, dust and chemicals) can also cause the development of COPD. Heavy or long-term contact with secondhand smoke or other lung irritants may also cause COPD.

Genetic Factors - Alpha-1 Antitrypsin-related COPD is caused by a deficiency of the Alpha-1 Antitrypsin protein in the bloodstream. Without that protein, white blood cells can harm the lungs, and lung deterioration occurs. The World Health Organization and the American Thoracic Society recommends that every individual diagnosed with COPD be tested for Alpha-1. For more information about AATD and how to get tested, visit the Alpha-1 Foundation Website or call 1-877-2 CURE-A1.

The COPDGene Study has more information about research into other genetic causes of Chronic Obstructive Pulmonary Disease.

See also:

RJR Burned for $25M in Punitives, $46.5M Total, in Couple's COPD Tobacco Suit

Posted by Arlin Crisco on Apr 21, 2015 8:09:00 PM

Tweet

Gary Paige argues that changes to R.J. Reynolds should not mitigate against punitive damages in a suit by his clients, Thomas and Bettye Ryan. Jurors ultimately awarded $25 million in punitives, bringing the total award to $46.5 million in the Engle progeny case. Click here to watch gavel-to-gavel coverage on demand.

Fort Lauderdale, FL—Jurors found R.J. Reynolds liable for $25 million in punitive damages early Tuesday afternoon in a couple's suit against the tobacco manufacturer for the respiratory disease they contend was caused by the company's cigarettes and fraud. Ryan v. R.J. Reynolds Tobacco Co.

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The punitive verdict came four days after the six-member jury awarded $21.5 million in compensatories in Thomas and Bettye Ryan's Engle progeny suit against Reynolds for its concealment of smoking's health effects. The Ryans claim Thomas Ryan's chronic obstructive pulmonary disease, diagnosed in 1997, was caused by the company's concealment, which fueled a nicotine addiction that led him to smoke up to four packs a day for more than 40 years.

During closings Tuesday morning, attorneys debated how much the tobacco maker's changes in leadership and marketing since the 1990s mitigated against punishing it for its participation in a decades-long conspiracy to hide the health effects of smoking. King & Spalding's W. Ray Persons, representing Reynolds, described the tobacco maker today as a "changed company," with new corporate leadership and a focus on educating the public regarding the dangers of cigarettes and ways to quit smoking completely.

"If you want to quit, they'll sell you something to help you quit smoking and get away from tobacco products altogether," Persons said. "How much more can you do than provide somebody with a product that enables them to quit using your product?"

However, Gordon & Doner's Gary Paige, representing the Ryans, argued that the tobacco manufacturer's corporate makeover did not weigh against imposing punitive damages. Referring to the company's sale of a moist tobacco product called SNUS that is sold as an alternative to cigarettes, Paige told jurors, "They're going to migrate the smokers, all the smokers, to SNUS, a nicotine-delivery device that causes mouth cancer.... That's their great transformation."

Jurors took less than two hours to reach their punitive verdict, which was more than the $21.5 million in punitives that Paige and The Alvarez Law Firm's Alex Alvarez requested during closings. The decision on punitives brought the trial's total award to $46.5 million.

Neither the parties' attorneys nor Reynolds representatives could be immediately reached for comment.

Arlin Crisco can be reached at acrisco@cvn.com.

Related information:

Alex Alvarez, of The Alvarez Law Firm, and Gary Paige, of Gordon & Doner, represented Thomas and Bettye Ryan. W. Ray Persons, of King & Spalding, represented R.J. Reynolds.

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BREAKING: RJR Thumped with $14M Verdict & Possible Punitives for COPD that Forced Lung Transplant

blog.cvn.com/case-against-rjr-over-smokers-lung-transplant-goes-to-jury

Posted by Arlin Crisco on Feb 2, 2018 12:27:41 PM

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This article has been updated to reflect Friday's jury verdict.

Fort Lauderdale, FL—R.J. Reynolds Friday was found liable for nearly $14 million in compensatory damages, plus potential punitives, after jurors found the tobacco giant responsible for the respiratory disease that forced a South Florida smoker to undergo a lung transplant. Schlefstein v. R.J. Reynolds, 2008-CV-022558.

The award, reached after more than six hours of deliberations, includes $13.5 million for Dawn Schlefstein's pain and suffering stemming from her respiratory disease and the lung transplant that it required, as well as $465,000 for her related medical expenses.

The 17th Circuit Court jury in Broward County handed down the award after concluding Schlefstein suffered from nicotine addiction that led her to smoke and ultimately caused her respiratory disease.

Dawn Schlefstein was a regular smoker by the time she was 16, continuing to smoke a pack or more of cigarettes a day for at least 30 years, until she was diagnosed with chronic obstructive pulmonary disease, or COPD, in 1995. Despite quitting, the disease became so serious she ultimately underwent a left lung transplant in 2001.

Schlefstein, 63, died in 2009 for reasons unrelated to smoking, but, her family claims Reynolds, maker of the cigarettes she smoked, caused her emphysema, by conspiring to hide the dangers of its product for much of her life.

Friday's verdict also found against Reynolds on the family's fraud and conspiracy claims. Punitive proceedings will begin Monday.

The Alvarez Law Firm's Alex Alvarez, requested about $12.4 million in compensatories, plus a finding that punitives were warranted, during Thursday's closing arguments.

The case is one of thousands stemming from *Engle v. Liggett Group Inc.*, a Florida state court class-action lawsuit originally filed in 1994. After a trial victory for the class members, the state's supreme court ultimately decertified the class, but ruled that so-called Engle progeny cases may be tried individually. Engle progeny plaintiffs are entitled to the benefit of the jury's findings in the original verdict, including the determination that tobacco companies had placed a dangerous, addictive product on the market and hid the dangers of smoking, if they prove the smoker at the heart of the case suffered from nicotine addiction that was the legal cause of a smoking-related disease such as emphysema.

The cause of Schlefstein's respiratory disease turned into a key point of dispute during the 11-day trial. The defense contended Schlefstein's COPD was likely caused by something other than smoking, such as a genetic condition. During Thursday's closings, King & Spalding's Kathryn Lehman told jurors Schlefstein developed COPD at an unusually young age, even considering her smoking history. She also noted Schlefstein ultimately developed COPD in her formerly healthy, transplanted lung, despite the fact that she had quit smoking long before the transplant.

Lehman told jurors plaintiff's expert pulmonologist, Dr. Richard Kradin, concluded that, if Schlefstein hadn't smoked since her lung transplant, the COPD found in that lung could not have come from cigarettes. "His very words undermine the possibility, they prevent the plaintiff, they close the door, the admission from plaintiff's own expert is the reason that plaintiff cannot meet their burden of proof," Lehman said, arguing the cause of COPD in Schlefstein's transplanted lung was likely the same as the cause of her original respiratory disease.

But Gordon & Doner's Gary Paige, representing Schlefstein's family, told jurors the weight of medical evidence proved Schlefstein's smoking led to the COPD that required her transplant. "There's no doubt about it, she has no other exposures," Paige said in his closing argument Wednesday.

Paige noted that, because of the relatively early onset of Schlefstein's COPD, she was tested multiple times for Alpha-1 antitrypsin deficiency, or A1-A, one genetic disease that often causes COPD. However, the deficiency was never detected. "You will not find one doctor anywhere, outside of court or inside of court, nobody who is trained to diagnose emphysema, nobody in the entire world, ever has said that she has Alpha-1 antitrypsin deficiency," Paige said. "There's no medical doctor to refute it and no reason to refute it."

Email Arlin Crisco at acrisco@cvn.com.

Related Information

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Topics: Products Liability, tobacco, Engle Progeny, Florida, Schlefstein v. R.J. Reynolds

E-cigarettes are Poor Substitutes for Conventional Smoking in COPD Patients

copdnewstoday.com/2017/10/19/e-cigarettes-are-not-beneficial-for-chronic-obstructive-pulmonary-disease-patients

Ana Belo van Wijk, PhD October 20, 2017

E-cigarettes are not at all beneficial for chronic obstructive pulmonary disease (COPD) patients trying to quit smoking or to mitigate the health consequences of nicotine, according to a new study.

The study reporting the findings was published in the *Journal of General Internal Medicine* and is titled "Electronic Cigarette Use in U.S. Adults at Risk for or with COPD: Analysis from Two Observational Cohorts."

The use of e-cigarettes is becoming increasingly popular. However, because their availability is so recent, there is very little information on long-term effects of vaping.

Now, researchers at the UNC School of Medicine analyzed data gathered in two COPD-focused group studies, the COPDGene study and SPIROMICS, originally designed to understand the causes of COPD.

"We've seen a dramatic increase in the use of e-cigs in the United States, and it's unclear what the potential consequences are among smokers at-risk or with COPD," M. Bradley Drummond, MD, MHS, director of the Obstructive Lung Diseases Clinical and Translational Research Center at the UNC School of Medicine, said in a press release.

"But there is virtually no information available on older individuals at-risk or with COPD. So we've leveraged the data that has already been gathered from two existing COPD-focused [groups] as a way to begin to address this lack of information." Drummond added.

The study's goal was to determine the use pattern of e-cigarettes, and if this type of device had any beneficial effects on the health of older adults at risk for or with COPD.

To their surprise, researchers found that replacing conventional cigarettes with e-cigarettes did not offer the health benefits that COPD patients were expecting.

“We expected to see that folks who quit combustibles would have decreased symptoms because of their decreased tobacco use, but that wasn’t the case.” Drummond said.

“Individuals who had tried e-cigarettes as a way to reduce their use of conventional cigarettes were actually less likely to reduce their use or quit combustible cigarettes than those who had never tried e-cigarettes,” Drummond added.

Furthermore, patients using both e-cigarettes (vaping) and conventional cigarettes had the worst outcome in the study.

“The data suggests that these dual users are consuming even more nicotine than those who exclusively use conventional cigarettes.” Drummond said.

Researchers will continue to monitor e-cigarette use consequences in COPD patients in order to have clearer and more robust information for COPD patients.

“We can’t study these things fully in two or three years,” Drummond said. “We need 10 or more years to get the fullest picture possible.”

Nonetheless, preliminary results in this 3-year study showed there are no beneficial effects of e-cigarettes for COPD patients.

“Nowhere in these data did we see a potential benefit of e-cigarette use.” Drummond concluded.

Electronic Cigarettes (E-cigarettes)

drugabuse.gov/publications/drugfacts/electronic-cigarettes-e-cigarettes

What are electronic cigarettes?

Photo by Mandie Mills, CDC

Electronic cigarettes, also known as e-cigarettes, e-vaporizers, or electronic nicotine delivery systems, are battery-operated devices that people use to inhale an aerosol, which typically contains nicotine (though not always), flavorings, and other chemicals. They can resemble traditional tobacco cigarettes *(cig-a-likes)*, cigars, or pipes, or even everyday items like pens or USB memory sticks. Other devices, such as those with fillable tanks, may look different. Regardless of their design and appearance, these devices generally operate in a similar manner and are made of similar components. More than 460 different e-cigarette brands are currently on the market.[1] Some common nicknames for e-cigarettes are:

- e-cigs
- e-hookahs
- hookah pens
- vapes
- vape pens
- mods (customizable, more powerful vaporizers)

How do e-cigarettes work?

Most e-cigarettes consist of four different components, including:

- a cartridge or reservoir, which holds a liquid solution (*e-liquid* or *e-juice*) containing varying amounts of nicotine, flavorings, and other chemicals
- a heating element (atomizer)
- a power source (usually a battery)
- a mouthpiece that the person uses to inhale

In many e-cigarettes, puffing activates the battery-powered heating device, which vaporizes the liquid in the cartridge. The person then inhales the resulting aerosol or vapor (called *vaping*).

E-cigarette Use in Teens

E-cigarettes are popular among teens and are now the most commonly used form of tobacco among youth in the United States. Their easy availability, alluring advertisements, various e-liquid flavors, and the belief that they're safer than cigarettes have helped make them appealing to this age group. Further, a study of high school students found that one in

four teens reported using e-cigarettes for *dripping*, a practice in which people produce and inhale vapors by placing e-liquid drops directly onto heated atomizer coils. Teens reported the following reasons for dripping: to create thicker vapor (63.5 percent), to improve flavors (38.7 percent), and to produce a stronger throat hit—a pleasurable feeling that the vapor creates when it causes the throat to contract (27.7 percent).[2] More research is needed on the risks of this practice.

In addition to the unknown health effects, early evidence suggests that e-cigarette use may serve as an introductory product for preteens and teens who then go on to use other tobacco products, including cigarettes, which are known to cause disease and premature death. A study showed that students who had used e-cigarettes by the time they started 9th grade were more likely than others to start smoking cigarettes and other smokable tobacco products within the next year.[3] Another study supports these findings, showing that high school students who used e-cigarettes in the last month were about 7 times more likely to report that they smoked cigarettes when asked approximately 6 months later, as compared to students who said they didn't use e-cigarettes. Notably, the reverse was not true—students who said they smoked cigarettes were no more likely to report use of e-cigarettes when asked approximately 6 months later. Like the previous study, these results suggest that teens using e-cigarettes are at a greater risk for smoking cigarettes in the future.[4] However, more research is still needed to understand if experimenting with e-cigarettes leads to regular use of smokable tobacco.

Under U.S. Food and Drug Administration (FDA) regulations designed to protect the health of young Americans, minors can no longer buy e-cigarettes in stores or online (see "Government Regulation of E-cigarettes"). The FDA now regulates the manufacture, import, packaging, labeling, advertising, promotion, sale, and distribution of e-cigarettes. This includes components and parts of e-cigarettes but excludes accessories.[5]

Government Regulation of E-cigarettes

In 2016, the FDA established a rule for e-cigarettes and their liquid solutions. Because e-cigarettes contain nicotine derived from tobacco, they are now subject to government regulation as tobacco products, including the requirement that both in-store and online purchasers be at least 18 years of age (see "E-cigarette Use in Teens"). For more information about this ruling, visit the FDA's webpage, The Facts on the FDA's New Tobacco Rule.

How do e-cigarettes affect the brain?

The nicotine in e-liquids is readily absorbed from the lungs into the bloodstream when a person uses an e-cigarette. Upon entering the blood, nicotine stimulates the adrenal glands to release the hormone epinephrine (adrenaline). Epinephrine stimulates the central nervous system and increases blood pressure, breathing, and heart rate. As with most addictive substances, nicotine activates the brain's reward circuits and also increases levels of a chemical messenger in the brain called *dopamine*, which reinforces rewarding behaviors. Pleasure caused by nicotine's interaction with the reward circuit motivates some people to use nicotine again and again, despite risks to their health and well-being.

What are the health effects of e-cigarettes? Are they safer than tobacco cigarettes?

Some research suggests that e-cigarettes might be less harmful than cigarettes when people who regularly smoke switch to them as a complete replacement. But nicotine in any form is a highly addictive drug. Research suggests it can even prime the brain's reward system, putting vapers at risk for addiction to other drugs.[6]

Also, e-cigarette use exposes the lungs to a variety of chemicals, including those added to e-liquids, and other chemicals produced during the heating/vaporizing process.[7] A study of some e-cigarette products found the vapor contains known carcinogens and toxic chemicals, as well as potentially toxic metal nanoparticles from the device itself. The study showed that the e-liquids of certain cig-a-like brands contain high levels of nickel and chromium, which may come from the nichrome heating coils of the vaporizing device. Cig-a-likes may also contain low levels of cadmium, a toxic metal also found in cigarette smoke that can cause breathing problems and disease.[8] Additionally, another study found that there was significantly greater toxicant exposure in adolescent e-cigarette users compared with their nonusing peers. In most cases, these harmful chemicals were present whether the product contained nicotine or flavorings.[9] More research is needed on the health consequences of repeated exposure to these chemicals. More research is needed on the health consequences of repeated exposure to these chemicals.

Health Effects for Teens

The teen years are critical for brain development, which continues into young adulthood. Young people who use nicotine products in any form, including e-cigarettes, are uniquely at risk for long-lasting effects. Because nicotine affects the development of the brain's reward system, continued e-cigarette use can not only lead to nicotine addiction, but it also can make other drugs such as cocaine and methamphetamine more pleasurable to a teen's developing brain.[10]

Nicotine also affects the development of brain circuits that control attention and learning. Other risks include mood disorders and permanent problems with impulse control—failure to fight an urge or impulse that may harm oneself or others.[10]

Can e-cigarettes help a person quit smoking?

Some people believe e-cigarettes may help lower nicotine cravings in those who are trying to quit smoking. However, e-cigarettes are not an FDA-approved quit aid, and there is no conclusive scientific evidence on the effectiveness of e-cigarettes for long-term smoking cessation. It should be noted that there are seven FDA-approved quit aids that are proven safe and can be effective when used as directed.

E-cigarettes haven't been thoroughly evaluated in scientific studies. For now, not enough data exists on the safety of e-cigarettes, how the health effects compare to traditional cigarettes, and if they are helpful for people trying to quit smoking.

Points to Remember

- Electronic cigarettes are battery-operated devices that people use to inhale an aerosol, which typically contains nicotine (though not always), flavorings, and other chemicals. In many e-cigarettes, puffing activates the battery-powered heating device, which vaporizes the liquid in the cartridge or reservoir. The person then inhales the resulting aerosol or vapor (called *vaping*).
- E-cigarettes are popular among teens. Under U.S. Food and Drug Administration (FDA) regulations designed to protect the health of young Americans, minors can no longer buy e-cigarettes in stores or online.
- Nicotine stimulates the adrenal glands to release the hormone epinephrine (adrenaline) and increases the levels of a chemical messenger in the brain called *dopamine*. Pleasure caused by nicotine's interaction with the brain's reward system motivates some people to use nicotine again and again, despite possible risks to their health and well-being.
- Research so far suggests that e-cigarettes are less harmful than cigarettes when people who regularly smoke switch to them as a complete replacement. But e-cigarettes can still damage a person's health.
- E-cigarettes can lead to nicotine addiction and increased risk for addiction to other drugs.
- E-cigarette use also exposes the lungs to a variety of chemicals, including those added to e-liquids, and other chemicals produced during the heating/vaporizing process.
- More research is needed to determine if e-cigarettes may be as effective as smoking cessation aids already approved by the FDA.

Learn More

For more information about e-cigarettes, visit:

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BMJ Open

Is prevalence of e-cigarette and nicotine replacement therapy use among smokers associated with average cigarette consumption in England? A time-series analysis

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ABSTRACT

Objectives Many smokers use e-cigarettes and licensed nicotine replacement therapy (NRT), often in an attempt to reduce their cigarette consumption. We estimated how far changes in prevalence of e-cigarette and NRT use while smoking were accompanied by changes in cigarette consumption at the population level.

Design Repeated representative cross-sectional population surveys of adults aged 16+ years in England.

Methods We used Autoregressive Integrated Moving Average with Exogeneous Input (ARIMAX) modelling of monthly data between 2006 and 2016 from the Smoking Toolkit Study. Prevalence of e-cigarette use and NRT use in current smokers, and specifically for smoking reduction and temporary abstinence, were input variables. Mean daily cigarette consumption was the dependent variable. Analyses involved adjustment for mass media expenditure and tobacco-control policies.

Results No statistically significant associations were found between changes in use of e-cigarettes (β −0.012, 95% CI −0.026 to 0.002) or NRT (β 0.015, 95% CI −0.026 to 0.055) while smoking and daily cigarette consumption. Neither did we find clear evidence for an association between e-cigarette use (β −0.010, 95% CI −0.025 to 0.005 and β 0.011, 95%–0.027 to 0.004) or NRT use (β 0.006, 95%–0.030 to 0.043 and β 0.022, 95%–0.020 to 0.063) specifically for smoking reduction and temporary abstinence, respectively, and changes in daily cigarette consumption.

Conclusion If use of e-cigarettes and licensed NRT while smoking acted to reduce cigarette consumption in England between 2006 and 2016, the effect was likely very small at a population level.

Strengths and limitations of this study

- This is the first time series study to assess the population-level impact of the use of nicotine replacement therapy and e-cigarettes for harm reduction on cigarette consumption.
- This study uses a large representative sample of the population in England and considers both smoking reduction and temporary abstinence.
- A wide range of confounders are adjusted for including population-level interventions.
- In countries with weaker tobacco control, or stricter regulation of using products for harm reduction, different effects may be observed.
- Data are observational and so strong conclusions regarding cause and effect cannot be made.

INTRODUCTION

Randomised controlled trials have shown that use of non-tobacco nicotine-containing products (eg, nicotine replacement therapy; NRT) are efficacious for harm-reduction attempts.[1] Harm reduction is defined as any attempt to reduce the harm from smoking without an intention to quit completely, such as, the use of NRT for smoking reduction (ie, during attempts to cut down) or during periods of temporary abstinence (ie, during periods of time when one is unable to smoke).[1] Outside of the clinical setting where little behavioural support is provided, the use of NRT during attempts to cut down smoking appears to increase smoker's propensity to quit, but does not result in significantly large reductions in cigarette consumption.[2–4] Explanations for this include the lack of behavioural support and possible poor compliance with the medical regimen.[5 6]

In recent years, there has been an increase in the overall use of nicotine-containing products for harm reduction, with a growth in e-cigarettes more than offsetting a decline in the use of NRT.[7–9] Previous studies suggest that e-cigarettes which contain nicotine reduce cravings more effectively than NRT,[7 10 11] have better adherence rates[7 12] and deliver clinically significant levels of nicotine into the blood, at least for some smokers.[10 11 13] Thus, although further studies are needed it is possible that e-cigarettes may be a more

effective aid for smoking reduction than licensed nicotine products.[14 15] However, it also remains possible that e-cigarettes will not result in clinically significant reductions in cigarette intake at a population level.

The aim of this study was to assess the association between changes in prevalence of e-cigarettes and NRT with changes in mean cigarette consumption per day using a time-series approach. Time-series analysis allows us to take into account underlying trends, the effect of other tobacco-control interventions, autocorrelation (whereby data collected at points closer in time tend to be more similar), and to consider possible lag effects of the independent variable on the dependent variable.[16] Where associations are found, they cannot unequivocally establish a causal association but can be indicative, as has been the case with estimating the effect of price of cigarettes on population consumption,[17] mass-media expenditure on use of specialist stop-smoking services[18] and introduction of varenicline to the market on prevalence of use of smoking cessation medication.[19] Where associations are not found, or they go in a direction opposite to that expected, this can also be informative.

Specifically, this paper assesses the association between mean cigarette consumption per day and:

1. Current e-cigarette use among smokers for any purpose, current use specifically for smoking reduction and current use specifically for temporary abstinence.
2. Current NRT use among smokers for any purpose, current use specifically for smoking reduction and current use specifically for temporary abstinence.

Sensitivity analyses will examine the effect of focusing only on daily e-cigarette and NRT use, given previous associations between extent of non-tobacco nicotine-containing product use and the effectiveness of harm-reduction attempts.[6]

METHODS

Design

We used Autoregressive Integrated Moving Average with Exogeneous Input (ARIMAX) modelling of monthly data between 2006 and 2016 primarily from the Smoking Toolkit Study. The smoking toolkit study (STS) is a monthly survey of a representative sample of the population in England aged 16+ years.[20] This has been collecting data on smoking patterns among smokers and recent ex-smokers since November 2006. Questions on the use of e-cigarettes among all smokers were introduced in May 2011 and as aids to a quit attempt among smokers attempting to stop in July 2009. The STS involves monthly household surveys using a random location sampling design, with initial random selection of grouped output areas (containing 300 households), stratified by ACORN (sociodemographic) characteristics (https://acorn.caci.co.uk/) and region. Interviewers then choose which houses within these areas are most likely to fulfil quotas based on the probability of individuals being at home in different regions and conduct face-to-face computer-assisted interviews with one member per household. Participants from the STS appear to be representative of the population in England, having similar sociodemographic composition as other large national surveys, such as the Health Survey for England.[20]

Measures

Explanatory variables

Daily and non-daily smokers were asked the following questions:

1. Which, if any, of the following are you currently using to help you cut down the amount you smoke?
2. Do you regularly use any of the following in situations when you are not allowed to smoke?
3. Can I check, are you using any of the following either to help you stop smoking, to help you cut down or for any other reason at all?

All three questions had the following response options: nicotine gum, nicotine replacement lozenges\tablets, nicotine replacement inhaler, nicotine replacement nasal spray, nicotine patch, electronic cigarette, nicotine mouth spray, other, none.

Current e-cigarette use was derived by an 'electronic cigarette' response to any of the three questions; e-cigarette use for smoking reduction by a response to the first question; and e-cigarette use for temporary abstinence by a response to the second question.

Current NRT use was derived by an NRT product response ('nicotine gum, nicotine replacement lozenges\tablets, nicotine replacement inhaler, nicotine replacement nasal spray, nicotine patch or nicotine mouth spray') to any of the three questions; NRT use for smoking reduction by an NRT product response to the first question; and NRT use for temporary abstinence by an NRT product response to the second question.

Data were not recorded on NRT use for temporary abstinence between November 2006 and January 2007 and was imputed using prevalence data from February 2007.

Data were only available on the prevalence of use of electronic cigarettes among smokers from April 2011 although use specifically during a recent quit attempt were available from July 2009. Thus, prevalence of electronic cigarette use among smokers between July 2009 and April 2011 was estimated from data on use during a quit attempt; use of electronic cigarettes among smokers between November 2006 and June 2009 was assumed to be 0.1% of smokers based on other surveys which found their use to be very rare before 2009.[21 22]

Daily NRT and e-cigarette users were classified as those who reported that they used the product(s) at least once per day in response to the question: How many times per day on average do you use your nicotine replacement product or products? This question was introduced in July 2010. Prior to this time, prevalence of daily NRT use was assumed to be 60% of all users,[6] while e-cigarette prevalence was computed as above using prevalence during a quit attempt or 0.1%.

Outcome variables

Smokers taking part in the STS were also asked how many cigarettes they smoke on average per day. Non-daily smokers were asked how many cigarettes they smoked per week which was then converted to a daily figure.

Co-variables

In England, tobacco mass media campaigns have been run as part of a national tobacco-control programme. Spending was almost completely suspended in 2010 and then reintroduced in 2011 at a much lower level. Previous studies have shown that such cuts were associated with a decreased use of smoking cessation support.[18 23] Thus, advertising expenditure will be adjusted for using data obtained from Public Health England. Data on mass media expenditure was available monthly from May 2008, and yearly prior to this period, and so a monthly average was assumed. For a number of months, spending was effectively zero and was imputed as 0.1 to allow the analysis to run.

A number of tobacco-control policies were adjusted for. These included the move in commissioning of stop-smoking services to local authorities in April 2013,[24] introduction of a smoking ban in July 2007,[25] licensing of NRT for harm reduction in December 2009,[26] the publication of National Institute for Health and Care Excellence guidance on harm reduction in June 2013[27] and change in the minimum age of sale of cigarettes in October 2007.[28] Price of cigarettes is correlated 0.99 with time and will thereby be taken into account by use of differencing (ie, using the differences between consecutive observation rather than observations themselves) to make the series stationary.

Analysis

The analysis plan was registered on the Open Science Framework prior to data analysis (https://osf.io/6swk3/). All data were analysed in R V.3.2.4[29] using ARIMAX modelling.[16 30 31] Data were weighted prior to the analyse to match the population in England using a rim (marginal) weighting technique. This involves an iterative sequence of weighting adjustments whereby separate nationally representative target profiles are set (for gender, working status, children in the household, age, social grade and region). This process is then repeated until all variables match the specified targets.[20]

Two waves of data were collected in March 2007 and March 2013. These waves were averaged. No data were collected in December 2008. Mean cigarette consumption, NRT use and e-cigarette use during this period were calculated as an average of the month before and the month after. For a few months (May 2012, July 2012, September 2012, November 2012, January 2013, March 2013), data on electronic cigarettes and NRT use among smokers were not recorded. For these months, the average of the previous and next month was imputed.

The Granger causality test suggested that there was some evidence for the violation of the assumption of weak exogeneity (ie, Y can depend on the lagged values of X but the reverse must not be true) between the input and the output series. However, caution has been advised when using this and similar tests on data across a long time series,[32 33] and there was no theoretical reason we could identify for a bidirectional relationship between e-cigarette use and cigarette consumption. It was assumed that the association was spurious and likely removed following adjustment for other covariates.

Both unadjusted and fully adjusted models are reported which regressed onto mean cigarette consumption per day: (1) use of e-cigarettes among current smokers; (2) use of e-cigarettes for smoking reduction; (3) use of e-cigarettes for temporary abstinence; (4) use of NRT for harm reduction; (5) use of NRT for temporary abstinence and (6) use of NRT for smoking reduction. Sensitivity analyses were conducted which constrained the analysis to only those reporting daily e-cigarette and NRT use. We followed a standard ARIMAX modelling approach.[16 34] The series were first log-transformed to stabilise the variance, and if required, first differenced and seasonally differenced. The autocorrelation and partial autocorrelation functions were then examined in order to determine the seasonal and non-seasonal moving average (MA) and autoregressive terms (AR). For example, AR(1) means that the value of a series at one point in time is the sum of a fraction of the value of the series at the immediately preceding point in time and an error component; while MA(1) means that the value of a series at one point in time is a function of a fraction of the error component of the series at the immediately preceding point in time and an error component at the current point in time. To identify the most appropriate transfer function (ie, lag) for the continuous explanatory variables, the sample cross-correlation function was checked for each ARIMAX model. Coefficients can be interpreted as estimates of the percentage change in cigarette consumption for every (a) percentage increase in use of e-cigarettes and NRT, (b) percentage increase in mass media expenditure and (c) implementation of tobacco-control policies.

Bayes factors (BFs) were derived for non-significant findings using an online calculator[35] to disentangle whether there is evidence for the null hypothesis of no effect (BF <1/3rd) or the data are insensitive (BF between 1/3rd and 3). A half-normal distribution was assumed with a percentage change in the outcomes of interest for every percentage increase in the input series of 0.009% based on the effect detectable with 80% power (see sample size). Sensitivity analyses were conducted using a much larger percentage change of 0.1. This was based on a meta-analysis assessing the efficacy of non-tobacco nicotine replacement products for harm reduction which reported that 21.8% of the experimental group had reduced consumption by more than 50% at final follow-up compared with 16.5% receiving placebo.[1] We therefore assumed that a 5% change in prevalence of NRT and e-cigarettes would be associated with a 0.5% change in overall cigarette consumption.

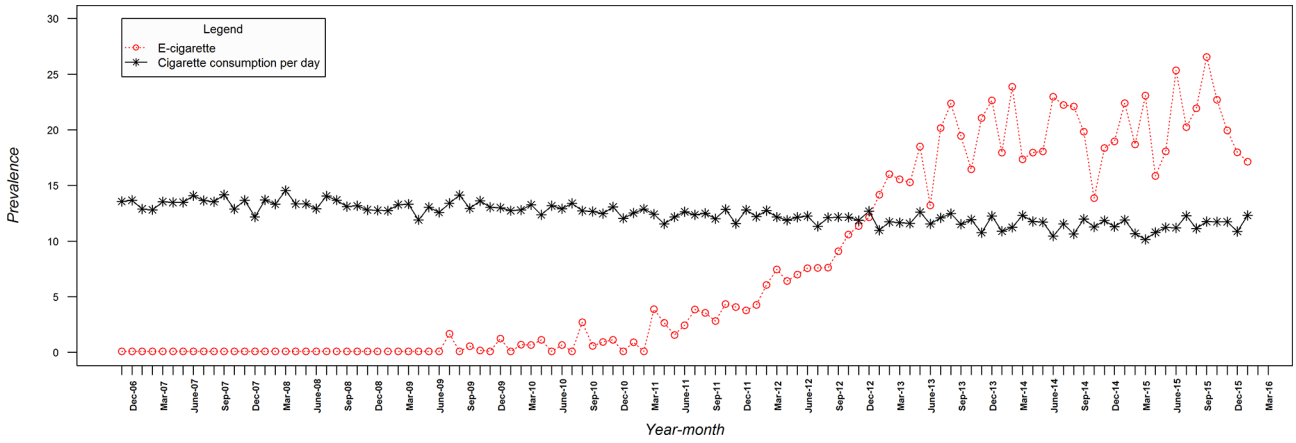

Figure 1 Monthly prevalence of cigarette consumption and e-cigarettes for harm reduction among smokers.

Strengthening the Reporting of Observational Studies in Epidemiology guidelines for the reporting of observational studies were followed throughout.[36]

Sample size

Simulation-based power analyses suggested that this study would have 80% power to detect a change in the output series of 0.009% for every 1% change in the input series, assuming 113 monthly data collection points, MA (1) autocorrelation,[37] a baseline proportion for the input series of 0.005,[9] a baseline mean (SD) for the output series of 12.3[38] and a total change over time for the input series of 30%.[38]

RESULTS

Sample characteristics

Data were collected on 199 483 adults aged 16+ years taking part in the STS who reported their smoking status between November 2006 and March 2016. Of these, 43 608 (20.8%, 95% CI 20.6 to 21.0) were current smokers. Fifty-two per cent (95% CI 52% to 53%) of the smokers were male and 60.4% (95% CI 60% to 60.1%) were in routine or manual positions or were unemployed. The average age of smokers in this study was 42.1 years (95% CI 42.0 to 42.1).

Main analysis

Figure 1 shows that cigarette consumption declined over the study period from 13.6 to 12.3 (mean 12.4, SD 0.92). This figure also shows that current use of e-cigarettes among smokers for harm reduction increased from negligible use in the last quarter of 2006 to 17.1% at the end of the study (mean 7.8%, SD 8.82). Figure 2 shows that there was also a decline in the use of NRT for harm reduction from 12.2% to 6% (mean 14.4%, SD 4.36). Online supplementary figures 1 and 2 show the changes in e-cigarette and NRT use for smoking reduction and temporary abstinence, respectively.

Tables 1, 2 and 3 show the results of the ARIMAX models assessing the association between cigarette consumption per day with (1) e-cigarette use among current smokers and NRT use for harm reduction; (2) e-cigarette and NRT use for smoking reduction and (3) e-cigarette and NRT use for temporary abstinence. The findings were inconclusive as to whether an association was present between use of e-cigarettes and NRT for any purpose and cigarette consumption.

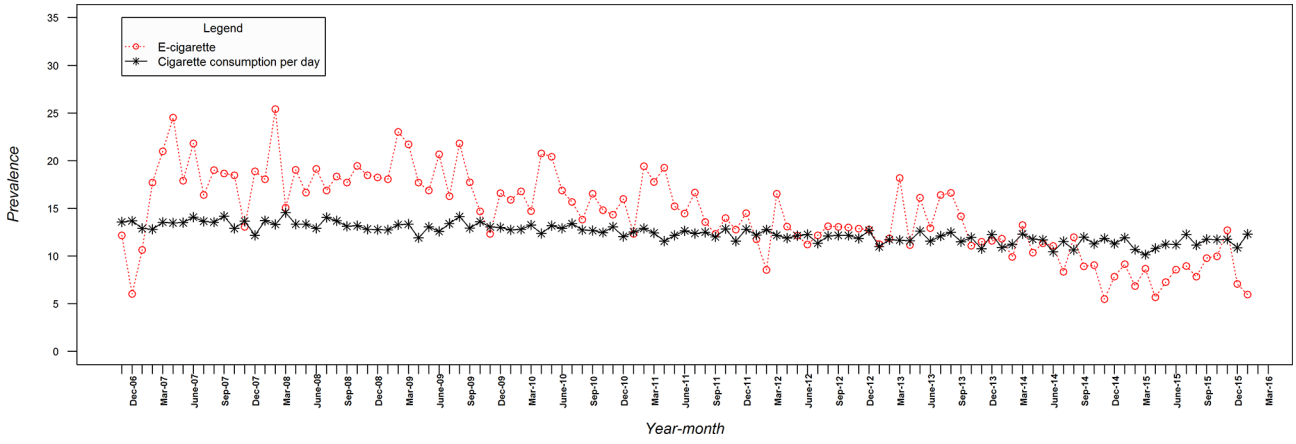

Figure 2 Monthly prevalence of cigarette consumption and nicotine replacement therapy use for harm reduction among smokers.

Table 1 Estimated percentage-point changes in mean cigarette consumption per day as a function of e-cigarette use and NRT use among smokers from November 2006 to March 2016, based on ARIMAX models

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Any current use of e- cigarettes (immediate impact)	–0.011 (–0.025 to 0.002) 0.097		–0.012 (–0.026 to 0.002) 0.091	–0.010 (–0.024 to 0.004) 0.149		–0.011 (–0.026 to 0.003) 0.130
NRT use for harm reduction (immediate impact)		0.012 (–0.028 to 0.053) 0.546	0.015 (–0.026 to 0.055) 0.475		0.003 (–0.019 to 0.025) 0.794	0.005 (–0.017 to 0.027) 0.672
Mass media expenditure (immediate impact)			<0.001 (–0.001 to 0.001) 0.984			<0.001 (–0.001 to 0.001) 0.880
	Total percentage change due to the exposure (95% CI) P values					
Smoking ban (pulse effect)			0.015 (–0.070 to 0.101) 0.724			0.013 (–0.072 to 0.099) 0.756
Increase in age-of-sale (pulse effect)			–0.041 (–0.126 to 0.044) 0.342			–0.043 (–0.128 to 0.042) 0.324
Move to local authority control (pulse effect)			–0.019 (–0.105 to 0.067) 0.662			–0.027 (–0.112 to 0.058) 0.533
Licensing for NRT for harm reduction (pulse effect)			0.021 (–0.067 to 0.110) 0.639			0.020 (–0.069 to 0.109) 0.661
NICE guidance on harm reduction (pulse effect)			–0.024 (–0.109 to 0.061) 0.578			–0.028 (–0.114 to 0.057) 0.512
Best fitting model	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}
Non-seasonal AR p value	NA	NA	NA	NA	NA	NA
Non-seasonal MA p value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Continued

Table 1 Continued

	All users of nicotine replacement		Only daily users of nicotine replacement	
	Percentage change per 1 % change in the exposure (95% CI) P values			
Seasonal AR p value	NA	NA	NA	NA
Seasonal MA p value	NA	NA	NA	NA
R^2	0.65	0.66	0.65	0.64	0.66
Bayes factor e-cigarette (0.009 (0.1))	2.44 (0.46)	2.68 (0.55)	1.95 (0.35)	2.12 (0.41)
Bayes factor NRT (0.009 (0.1))	0.77 (0.14)	0.74 (0.13)	0.69 (0.09)	0.63 (0.08)

An AR(1) means that the value of a series at one point in time is the sum of a fraction of the value of the series at the immediately preceding point in time and an error component; an MA(1) means that the value of a series at one point in time is a function of a fraction of the error component of the series at the immediately preceding point in time and an error component at the current point in time.
AR, autoregressive; ARIMAX, Autoregressive Integrated Moving Average with Exogeneous Input; MA, moving average; NA, not applicable; NICE, National Institute for Health and Care Excellence; NRT, nicotine replacement therapy.

BFs were between one-third and three when assuming a 0.009% change in cigarette consumption for every percentage change in the input series, suggesting the data are insensitive to detect very small reductions in cigarette consumption. Most BFs were less than one-third, when assuming a 0.1% change in cigarette consumption for every percentage change in the input series, suggesting evidence for the null hypothesis that NRT use and e-cigarette use among smokers has not resulted in large reductions in cigarette intake.

Sensitivity analysis

Current daily use of e-cigarettes among smokers for harm reduction increased from negligible use in the last quarter of 2006 to 11.1% at the end of the study (mean 4.5%, SD 4.91). There was also an increase in e-cigarette use specifically for temporary abstinence (from 0.1% to 8.4%; mean 3.5% SD 3.81) and smoking reduction (from 0.1% to 8.3%; mean 3.3% SD 3.64).

In contrast, there was a decline in the use of NRT for harm reduction from 7.3% to 2.9% (mean 6.5%, SD 2.35) and a decline in NRT use specifically for temporary abstinence (from 7.3% to 1.8%; mean 4.7% SD 2.29) and smoking reduction (from 6.8% to 2.6%; mean 5.8%, SD 2.46).

Tables 1, 2 and 3 also show the results of the sensitivity analyses restricted to those smokers using NRT or e-cigarettes daily. The findings were inconclusive as to whether or not an association was present between the daily use of e-cigarettes and NRT for any purpose and cigarette consumption. BFs suggested the data are insensitive to detect very small reductions in cigarette consumption, but there is evidence for the null hypothesis that NRT use and e-cigarette use among smokers have not resulted in large reductions in cigarette intake.

DISCUSSION

To our knowledge, this is the first empirical study to estimate the population association between the use of e-cigarettes and NRT among current smokers on cigarette consumption per day, using a time-series approach. There was evidence that there was no substantial association between the rise in use of e-cigarettes and decline in NRT use and changes in cigarette consumption per day.

Strengths and limitations

A strength of the study is the use of a large representative sample of the population in England, stratification of results by daily use, and the consideration of both temporary abstinence and smoking reduction. Previous studies have shown that reductions in cigarette intake are dependent on the extent of NRT use and differ as a function of the specific harm-reduction behaviour, that is, an attempt to cut down or restraining from smoking during periods of brief abstinence.[2 6]

The study had a number of limitations. First, caution should be taken when interpreting estimates of the

Table 2 Estimated percentage point changes in mean cigarette consumption per day as a function of e-cigarette use and NRT use among smokers for cutting down from November 2006 to March 2016, based on ARIMAX models

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Use of e-cigarettes for cutting down (immediate impact)	–0.010 (–0.024 to 0.005) 0.191		–0.010 (–0.025 to 0.005) 0.191	–0.008 (–0.023 to 0.006) 0.256		–0.009 (–0.024 to 0.006) 0.229
NRT use for cutting down (immediate impact)		0.002 (–0.033 to 0.037) 0.917	0.006 (–0.030 to 0.043) 0.732		–0.002 (–0.016 to 0.013) 0.825	–0.002 (–0.017 to 0.013) 0.786
Mass media expenditure (immediate impact)			<0.001 (–0.001 to 0.001) 0.885			<0.001 (–0.001 to 0.001) 0.860
	Total percentage change due to the exposure (95% CI) P values					
Smoking ban (pulse effect)			0.014 (–0.072 to 0.099) 0.755			0.012 (–0.073 to 0.097) 0.782
Increase in age-of-sale (pulse effect)			–0.043 (–0.128 to 0.042) 0.323			–0.042 (–0.127 to 0.043) 0.329
Move to local authority control (pulse effect)			–0.025 (–0.110 to 0.061) 0.571			–0.029 (–0.115 to 0.056) 0.499
Licensing for NRT for harm reduction (pulse effect)			0.018 (–0.072 to 0.108) 0.694			0.015 (–0.074 to 0.103) 0.747
NICE guidance on harm reduction (pulse effect)			–0.028 (0.058 to <0.001) 0.529			–0.027 (–0.112 to 0.059) 0.541
Best fitting model	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}
Non-seasonal AR p values	NA	NA	NA	NA	NA	NA
Non-seasonal MA p values	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Continued

Table 2 Continued

	All users of nicotine replacement		Only daily users of nicotine replacement	
	Percentage change per 1 % change in the exposure (95% CI) P values			
Seasonal AR p values	NA	NA	NA	NA
Seasonal MA p values	NA	NA	NA	NA
R^2	0.64	0.65	0.64	0.65
Bayes factor e-cigarette (0.009 (0.1))	1.87 (0.34)	1.79 (0.32)	1.46 (0.23)	1.61 (0.27)
Bayes factor NRT (0.009 (0.1))	0.86 (0.16)	0.81 (0.15)	0.76 (0.10)	0.76 (0.10)

An AR(1) means that the value of a series at one point in time is the sum of a fraction of the value of the series at the immediately preceding point in time and an error component; an MA(1) means that the value of a series at one point in time is a function of a fraction of the error component of the series at the immediately preceding point in time and an error component at the current point in time.
AR, autoregressive; ARIMAX, Autoregressive Integrated Moving Average with Exogeneous Input; MA, moving average; NA, not applicable; NICE, National Institute for Health and Care Excellence; NRT, nicotine replacement therapy.

covariates, that is, impact of some of the tobacco-control policies, as interrupted explanatory variables with short time-periods prior to their introduction in ARIMAX-type models often give inaccurate estimates of the SEs.[28] Thus, although the increase in age-of-sale has been previously associated with a decline in smoking prevalence,[24] the short lead-in period may have masked any true association.[27] Second, the STS required participants to recall their average daily cigarette intake which is likely to have been somewhat inaccurate. Third, the findings may not generalise to other countries. England has a strong tobacco-control climate and relatively liberal attitude towards harm reduction and e-cigarette use. In countries with weaker tobacco control, or stricter regulation of using products for harm reduction, different effects may be observed. Fourth, although we are unaware of any other major population-level interventions or other events during the study period, we cannot rule out residual confounding. Fifth, participants were not asked questions regarding potentially important features of the e-cigarette (eg, nicotine content, flavouring, device type) or frequency and duration of use. It is likely that these factors may play a role in their effectiveness and should be considered in future studies.[15 39] Finally, as data were not collected on current e-cigarette use prior to April 2011, prevalence was estimated from use during a quit attempt or from previous studies.[21 22] This was necessary to ensure that the time series was long enough for an ARIMAX analysis and is an appropriate approach when data are missing completely at random.[16 40] As prevalence was low and relatively stable during this period, it is unlikely to have impacted on the reported results.

Implications of findings

The findings are in line with previous studies which show that reductions in cigarette consumption observed in clinical trials of NRT for harm reduction do not appear to generalise beyond the closely controlled trial setting.[1 2] It was hypothesised that e-cigarettes may be associated with population mean cigarette intake given that they reduce cravings more effectively than NRT,[7 10 11] have better adherence rates[7 12] and deliver clinically significant levels of nicotine into the blood.[10 11 11 13]

The finding that e-cigarette use was not associated with reductions in consumption at a population level is consistent with previous real-world studies at the individual level. These have found little change in consumption among ever e-cigarette users[41] and that only a minority of daily users manage to reduce by a substantial amount which is not likely to be detected at a population level.[42] The findings of a recent pragmatic controlled trial, whereby 60% of participants using e-cigarettes had managed to reduce by over 50% by 6 months' follow-up, suggests that the lack of effectiveness at a population level may not be the consequence of poor behavioural support.[11]

Of course, it remains plausible that e-cigarettes may still be associated with a small effect on mean population cigarette consumption,[15] and that a reduction in harm from

Table 3 Estimated percentage point changes in mean cigarette consumption per day as a function of e-cigarette use and NRT use among smokers for temporary abstinence from November 2006 to March 2016, based on ARIMAX models

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Use of e-cigarettes for temporary abstinence (immediate impact)	–0.010 (–0.024 to 0.005) 0.150		–0.011 (–0.027 to 0.004) 0.146	–0.010 (–0.024 to 0.004) 0.159		–0.011 (–0.026 to 0.003) 0.135
NRT use for temporary abstinence (immediate impact)		0.023 (–0.016 to 0.062) 0.241	0.022 (–0.020 to 0.063) 0.303		0.006 (–0.015 to 0.028) 0.563	0.006 (–0.016 to 0.028) 0.585
Mass media expenditure (immediate impact)			<0.001 (–0.001 to 0.001) 0.873			<0.001 (–0.001 to 0.001) 0.942
	Total percentage change due to the exposure (95% CI) P values					
Smoking ban (pulse effect)			0.017 (–0.069 to 0.103) 0.696			0.014 (–0.071 to 0.099) 0.750
Increase in age-of-sale (pulse effect)			–0.036 (–0.122 to 0.050) 0.415			–0.040 (–0.125 to 0.044) 0.350
Move to local authority control (pulse effect)			–0.016 (–0.102 to 0.071) 0.721			–0.026 (–0.111 to 0.060) 0.556
Licensing for NRT for harm reduction (pulse effect)			0.023 (–0.067 to 0.114) 0.615			0.019 (–0.070 to 0.108) 0.670
NICE guidance on harm reduction (pulse effect)			–0.021 (–0.106 to 0.065) 0.638			–0.030 (–0.116 to 0.055) 0.483
Best fitting model	ARIMAX(0,1,1)(0,0,0)[12]	ARIMAX(0,1,1)(0,0,0)[12]	ARIMAX(0,1,1)(0,0,0)[12]	ARIMAX(0,1,1)(0,0,0)[12]	ARIMAX(0,1,1)(0,0,0)[12]	ARIMAX(0,1,1)(0,0,0)[12]
Non-seasonal AR P values	NA	NA	NA	NA	NA	NA

Continued

Table 3 Continued

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Non-seasonal MA P values	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Seasonal AR P values	NA	NA	NA	NA	NA	NA
Seasonal MA P values	NA	NA	NA	NA	NA	NA
R^2	0.65	0.65	0.65	0.65	0.64	0.65
Bayes factor e-cigarette (0.009 (0.1))	1.01 (0.59)		1.94 (0.38)	1.97 (0.35)		2.15 (0.41)
Bayes factor NRT (0.009 (0.1))		0.15 (0.02)	0.69 (0.11)		1.05 (0.18)	0.61 (0.08)

An AR(1) means that the value of a series at one point in time is the sum of a fraction of the value of the series at the immediately preceding point in time and an error component; an MA(1) means that the value of a series at one point in time is a function of a fraction of the error component of the series at the immediately preceding point in time and an error component at the current point in time.
AR, autoregressive; ARIMAX, Autoregressive Integrated Moving Average with Exogeneous Input; MA, moving average; NA, not applicable; NICE, National Institute for Health and Care Excellence; NRT, nicotine replacement therapy.

smoking at a population level could be seen through their promotion of quit attempts[37] or by reducing smoke intake from each cigarette.[5]

Conclusion

In conclusion, the increased prevalence of e-cigarettes use among smokers in England has not been associated with a detectable change in cigarette consumption per day. The decline in the use of NRT has also not been associated with a change in mean cigarette intake. If use of e-cigarettes and licensed NRT while smoking act to reduce cigarette consumption, the effect is probably small.

Contributors EB, JB, SM and RW designed the study. EB wrote the first draft and conducted the analyses. All authors commented on this draft and contributed to the final version.

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Patient consent Obtained.

Ethics approval Ethical approval for the Smoking Toolkit Study was granted by the UCL Ethics Committee (ID 0498/001).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement For access to the data please contact the lead author, EB (e.beard@ucl.ac.uk).

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THE AMERICAN JOURNAL of MEDICINE®

E-Cigarette, a Shipwreck! a Scandal?

To the Editor:

Primack et al[1] must be commended for their prospective cohort study of 1506 never-smoking young adults (18-30 years old) showing that cigarette smoking was initiated by 48% of e-cigarette users (vs 10% of nonusers, adjusted odds ratio = 6.8). However, their conclusion ". . . supports policy and educational interventions designed to decrease use of e-cigarettes among non-smokers" is not adequate.

First, this finding is the worst news, as it has not been expected, this population being highly resilient to cigarette smoking. It comes after a series confirming commonsense warnings against this gateway to addiction: vaping is great for shooting up even more when combining nicotine plus flavors. The most recent news was that e-cigarette use is initiated far earlier than smoking cigarettes.[2]

Second, almost no policy has yet been set serial red flags over a decade: a) e-cigarette companies have been rapidly bought by Big Tobacco; b) the social marketing began as soon as 2010, when Johnny Depp used e-cigarettes in "The Tourist."[3] Worse, in mid-2017, the US Food and Drug Administration delayed for several years the key regulation of e-cigarettes, including flavored products.[4] Last, proposing education when the standard is not the social norm is not only poorly effective but also counterproductive, as it is pointing the usual finger of blame.

The solution is simple: a ban, as in Finland; not only a marketing ban but also a prohibition of nicotine cartridge sales, as nicotine is a prescription drug there, requiring an authorization. This is wise: no one can ignore that the tobacco industry was happy in the 1990s when anticipating the over-the-counter sales of nicotine replacement therapy, because without proper psychological support and dose adjustment, this treatment has little effectiveness.[5]

Prosecutions may be considered too. For example, against those who misrepresented observational data to advocate for e-cigarettes as a cessation tool,[6] or the French High Council for Public Health, which issued a statement in 2016 claiming, first of all: "(e-cigarettes) can be considered as a help to stop or reduce smoking by smokers,"[7] flying in the face of the 2014 World Health Organization statement prohibiting manufacturers and third parties from making health claims for e-cigarettes, including that e-cigarettes are smoking cessation aids.[8] Even more, as in France, no adequate monitoring of e-cigarettes use has been implemented.

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Authorship: The author is solely responsible for the content of this manuscript.

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Aldehydes are the predominant forces inducing DNA damage and inhibiting DNA repair in tobacco smoke carcinogenesis

Weng, Mao-Wen; Lee, Hyun-Wook; Park, Sung-Hyun; Hu, Yu; Wang, Hsing-Tsui; Chen, Lung-Chi; Rom, William N; Huang, William C; Lepor, Herbert; Wu, Xue-Ru; Yang, Chung S; Tang, Moon-Shong

Tobacco smoke (TS) contains numerous cancer-causing agents, with polycyclic aromatic hydrocarbons (PAHs) and nitrosamines being most frequently cited as the major TS human cancer agents. Many lines of evidence seriously question this conclusion. To resolve this issue, we determined DNA adducts induced by the three major TS carcinogens: benzo(*a*)pyrene (BP), 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanoe (NNK), and aldehydes in humans and mice. In mice, TS induces abundant aldehyde-induced Î³-hydroxy-propano-deoxyguanosine (Î³-OH-PdG) and Î±-methyl-Î³-OH-PdG adducts in the lung and bladder, but not in the heart and liver. TS does not induce the BP- and NNK-DNA adducts in lung, heart, liver, and bladder. TS also reduces DNA repair activity and the abundance of repair proteins, XPC and OGG1/2, in lung tissues. These TS effects were greatly reduced by diet with polyphenols. We found that Î³-OH-PdG and Î±-methyl-Î³-OH-PdG are the major adducts formed in tobacco smokers' buccal cells as well as the normal lung tissues of tobacco-smoking lung cancer patients, but not in lung tissues of nonsmokers. However, the levels of BP- and NNK-DNA adducts are the same in lung tissues of smokers and nonsmokers. We found that while BP and NNK can induce BPDE-dG and O^6-methyl-dG adducts in human lung and bladder epithelial cells, these inductions can be inhibited by acrolein. Acrolein also can reduce DNA repair activity and repair proteins. We propose a TS carcinogenesis paradigm. Aldehydes are major TS carcinogens exerting dominant effect: Aldehydes induce mutagenic PdG adducts, impair DNA repair functions, and inhibit many procarcinogens in TS from becoming DNA-damaging agents.

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E-cigarette smoke damages DNA and reduces repair activity in mouse lung, heart, and bladder as well as in human lung and bladder cells

Lee, Hyun-Wook; Park, Sung-Hyun; Weng, Mao-Wen; Wang, Hsiang-Tsui; Huang, William C; Lepor, Herbert; Wu, Xue-Ru; Chen, Lung-Chi; Tang, Moon-Shong

E-cigarette smoke delivers stimulant nicotine as aerosol without tobacco or the burning process. It contains neither carcinogenic incomplete combustion byproducts nor tobacco nitrosamines, the nicotine nitrosation products. E-cigarettes are promoted as safe and have gained significant popularity. In this study, instead of detecting nitrosamines, we directly measured DNA damage induced by nitrosamines in different organs of E-cigarette smoke-

exposed mice. We found mutagenic O6-methyldeoxyguanosines and Î³-hydroxy-1,N2 -propano-deoxyguanosines in the lung, bladder, and heart. DNA-repair activity and repair proteins XPC and OGG1/2 are significantly reduced in the lung. We found that nicotine and its metabolite, nicotine-derived nitrosamine ketone, can induce the same effects and enhance mutational susceptibility and tumorigenic transformation of cultured human bronchial epithelial and urothelial cells. These results indicate that nicotine nitrosation occurs in vivo in mice and that E-cigarette smoke is carcinogenic to the murine lung and bladder and harmful to the murine heart. It is therefore possible that E-cigarette smoke may contribute to lung and bladder cancer, as well as heart disease, in humans.
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ISSN: 1091-6490
CID: 2933742

Oncotarget. 2017:8(41):70406-70421.DOI: 10.18632/oncotarget.19710

Acrolein induces mtDNA damages, mitochondrial fission and mitophagy in human lung cells

Wang, Hsiang-Tsui; Lin, Jing-Heng; Yang, Chun-Hsiang; Haung, Chun-Hao; Weng, Ching-Wen; Maan-Yuh Lin, Anya; Lo, Yu-Li; Chen, Wei-Shen; Tang, Moon-Shong
Acrolein (Acr), a highly reactive unsaturated aldehyde, can cause various lung diseases including asthma, chronic obstructive pulmonary disease (COPD), and lung cancer. We have found that Acr can damage not only genomic DNA but also DNA repair proteins causing repair dysfunction and enhancing cells' mutational susceptibility. While these effects may account for Acr lung carcinogenicity, the mechanisms by which Acr induces lung diseases other than cancer are unclear. In this study, we found that Acr induces damages in mitochondrial DNA (mtDNA), inhibits mitochondrial bioenergetics, and alters mtDNA copy number in human lung epithelial cells and fibroblasts. Furthermore, Acr induces mitochondrial fission which is followed by autophagy/ mitophagy and Acr-induced DNA damages can trigger apoptosis. However, the autophagy/ mitophagy process does not change the level of Acr-induced mtDNA damages and apoptosis. We propose that Acr-induced mtDNA damages trigger loss of mtDNA via mitochondrial fission and mitophagy. These processes and mitochondria dysfunction induced by Acr are causes that lead to lung diseases.
PMCID:5642564
PMID: 29050289
ISSN: 1949-2553
CID: 2742292

Oncotarget. 2016:7(49):80450-80464.DOI: 10.18632/oncotarget.12608

Acrolein preferentially damages nucleolus eliciting ribosomal stress and apoptosis in human cancer cells

Wang, Hsiang-Tsui; Chen, Tzu-Ying; Weng, Ching-Wen; Yang, Chun-Hsiang; Tang, Moon-Shong

Acrolein (Acr) is a potent cytotoxic and DNA damaging agent which is ubiquitous in the environment and abundant in tobacco smoke. Acr is also an active cytotoxic metabolite of the anti-cancer drugs cyclophosphamide and ifosfamide. The mechanisms via which Acr exerts its anti-cancer activity and cytotoxicity are not clear. In this study, we found that Acr induces cytotoxicity and cell death in human cancer cells with different activities of p53. Acr preferentially binds nucleolar ribosomal DNA (rDNA) to form Acr-deoxyguanosine adducts, and induces oxidative damage to both rDNA and ribosomal RNA (rRNA). Acr triggers ribosomal stress responses, inhibits rRNA synthesis, reduces RNA polymerase I binding to the promoter of rRNA gene, disrupts nucleolar integrity, and impairs ribosome biogenesis and polysome formation. Acr causes an increase in MDM2 levels and phosphorylation of MDM2 in A549 and HeLa cells which are p53 active and p53 inactive, respectively. It enhances the binding of ribosomal protein RPL11 to MDM2 and reduces the binding of p53 and E2F-1 to MDM2 resulting in stabilization/activation of p53 in A549 cells and degradation of E2F-1 in A549 and HeLa cells. We propose that Acr induces ribosomal stress which leads to activation of MDM2 and RPL11-MDM2 binding, consequently, activates p53 and enhances E2F-1 degradation, and that taken together these two processes induce apoptosis and cell death.
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ISSN: 1949-2553
CID: 2278562

Oncotarget. 2015:6(32):33226-33236.DOI: 10.18632/oncotarget.5429

Cigarette side-stream smoke lung and bladder carcinogenesis: inducing mutagenic acrolein-DNA adducts, inhibiting DNA repair and enhancing anchorage-independent-growth cell transformation

Lee, Hyun-Wook; Wang, Hsiang-Tsui; Weng, Mao-Wen; Chin, Chiu; Huang, William; Lepor, Herbert; Wu, Xue-Ru; Rom, William N; Chen, Lung-Chi; Tang, Moon-Shong
Second-hand smoke (SHS) is associated with 20-30% of cigarette-smoke related diseases, including cancer. Majority of SHS (>80%) originates from side-stream smoke (SSS). Compared to mainstream smoke, SSS contains more tumorigenic polycyclic aromatic hydrocarbons and acrolein (Acr). We assessed SSS-induced benzo(a)pyrene diol epoxide (BPDE)- and cyclic propano-deoxyguanosine (PdG) adducts in bronchoalveolar lavage (BAL), lung, heart, liver, and bladder-mucosa from mice exposed to SSS for 16 weeks. In SSS exposed mice, Acr-dG adducts were the major type of PdG adducts formed in BAL ($p < 0.001$), lung ($p < 0.05$), and bladder mucosa ($p < 0.001$), with no significant accumulation of Acr-dG adducts in heart or liver. SSS exposure did not enhance BPDE-DNA adduct formation in any of these tissues. SSS exposure reduced nucleotide excision repair ($p < 0.01$) and base excision repair ($p < 0.001$) in lung tissue. The levels of DNA repair proteins, XPC and hOGG1, in lung tissues of exposed mice were significantly ($p < 0.001$ and $p < 0.05$) lower than the levels in lung tissues of control mice. We found that Acr can transform human bronchial epithelial and urothelial cells in vitro. We propose that induction of mutagenic Acr-DNA adducts, inhibition of DNA repair, and induction of cell transformation are three mechanisms by which SHS induces lung and bladder cancers.
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PMID: 26431382
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CID: 1790072

Oncotarget. 2014:5(11):3526-3540.DOI: 10.18632/oncotarget.1954

Acrolein- and 4-Aminobiphenyl-DNA adducts in human bladder mucosa and tumor tissue and their mutagenicity in human urothelial cells

Lee, Hyun-Wook; Wang, Hsiang-Tsui; Weng, Mao-Wen; Hu, Yu; Chen, Wei-Sheng; Chou, David; Liu, Yan; Donin, Nicholas; Huang, William C; Lepor, Herbert; Wu, Xue-Ru; Wang, Hailin; Beland, Frederick A; Tang, Moon-Shong

Tobacco smoke (TS) is a major cause of human bladder cancer (BC). Two components in TS, 4-aminobiphenyl (4-ABP) and acrolein, which also are environmental contaminants, can cause bladder tumor in rat models. Their role in TS related BC has not been forthcoming. To establish the relationship between acrolein and 4-ABP exposure and BC, we analyzed acrolein-deoxyguanosine (dG) and 4-ABP-DNA adducts in normal human urothelial mucosa (NHUM) and bladder tumor tissues (BTT), and measured their mutagenicity in human urothelial cells. We found that the acrolein-dG levels in NHUM and BTT are 10-30 fold higher than 4-ABP-DNA adduct levels and that the acrolein-dG levels in BTT are 2 fold higher than in NHUM. Both acrolein-dG and 4-ABP-DNA adducts are mutagenic; however, the former are 5 fold more mutagenic than the latter. These two types of DNA adducts induce different mutational signatures and spectra. We found that acrolein inhibits nucleotide excision and base excision repair and induces repair protein degradation in urothelial cells. Since acrolein is abundant in TS, inhaled acrolein is excreted into urine and accumulates in the bladder and because acrolein inhibits DNA repair and acrolein-dG DNA adducts are mutagenic, we propose that acrolein is a major bladder carcinogen in TS.
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PMID: 24939871
ISSN: 1949-2553
CID: 1036762

Journal of biological chemistry. 2013:288(30):21678-21687.DOI: 10.1074/jbc.M113.476630

Cigarette smoke component acrolein modulates chromatin assembly by inhibiting histone acetylation

Chen, Danqi; Fang, Lei; Li, Hongjie; Tang, Moon-Shong; Jin, Chunyuan

Chromatin structure and gene expression are both regulated by nucleosome assembly. How environmental factors influence histone nuclear import and the nucleosome assembly pathway, leading to changes in chromatin organization and transcription, remains unknown. Acrolein (Acr) is an alpha,beta-unsaturated aldehyde, which is abundant in the environment, especially in cigarette smoke. It has recently been implicated as a potential major carcinogen of smoking-related lung cancer. Here we show that Acr forms adducts with histone proteins in vitro and in vivo and preferentially reacts with free histones rather than with nucleosomal histones. Cellular fractionation analyses reveal that Acr exposure specifically inhibits acetylations of N-terminal tails of cytosolic histones H3 and H4,

modifications that are important for nuclear import and chromatin assembly. Notably, Acr exposure compromises the delivery of histone H3 into chromatin and increases chromatin accessibility. Moreover, changes in nucleosome occupancy at several genomic loci are correlated with transcriptional responses to Acr exposure. Our data provide new insights into mechanisms whereby environmental factors interact with the genome and influence genome function.
PMCID:3724627
PMID: 23770671
ISSN: 0021-9258
CID: 383082

Cancer research. 2013:73(8 1 1).DOI: 10.1158/1538-7445.AM2013-120

Detection of acrolein-derived cyclic DNA adducts in human cells by monoclonal antibodies [Meeting Abstract]

Pan, Jishen; Awoyemi, Bisola; Xuan, Zhuoli; Vohra, Priya; Wang, Hsiang-Tsui; Dyba, Marcin; Greenspan, Emily; Fu, Ying; Creswell, Karen; Zhang, Lihua; Berry, Deborah; Tang, Moon-Shong; Chung, Fung-Lung
ISI:000331220600037
ISSN: 0008-5472
CID: 853322

Journal of biological chemistry. 2012:287(15):12379-12386.DOI: 10.1074/jbc.M111.329623

Effect of carcinogenic acrolein on DNA repair and mutagenic susceptibility

Wang HT; Hu Y; Tong D; Huang J; Gu L; Wu XR; Chung FL; Li GM; Tang MS
Acrolein (Acr), a ubiquitous environmental contaminant, is a human carcinogen. Acr can react with DNA to form mutagenic alpha- and gamma-hydroxy-1, N2-cyclic propano-2-deoxyguanosine adducts (alpha-OH-Acr-dG and gamma-OH-Acr-dG). We demonstrate here that Acr-dG adducts can be efficiently repaired by the nucleotide excision repair (NER) pathway in normal human bronchial epithelia (NHBE) and lung fibroblasts (NHLF). However, the same adducts were poorly processed in cell lysates isolated from Acr-treated NHBE and NHLF, suggesting that Acr inhibits NER. In addition, we show that Acr treatment also inhibits base excision repair (BER) and mismatch repair (MMR). While Acr does not change the expression of XPA, XPC, hOGG1, PMS2 or MLH1 genes, it causes a reduction of XPA, XPC, hOGG1, PMS2 and MLH1 proteins; this effect, however, can be neutralized by the proteasome inhibitor, MG132. Acr treatment further enhances both bulky and oxidative DNA damage-induced mutagenesis. These results indicate that Acr not only damages DNA, but can also modify DNA repair proteins and further causes degradation of these modified repair proteins. We propose that these two detrimental effects contribute to Acr mutagenicity and carcinogenicity
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PMID: 22275365
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CID: 150550

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Acrolein induced DNA damage, mutagenicity and effect on DNA repair

Tang, Moon-Shong; Wang, Hsiang-Tsui; Hu, Yu; Chen, Wei-Sheng; Akao, Makoto; Feng, Zhaohui; Hu, Wenwei

Acrolein (Acr) is a ubiquitous environmental contaminant; it also can be generated endogenously by lipid peroxidation. Acr contains a carbonyl group and an olefinic double bond; it can react with many cellular molecules including amino acids, proteins and nucleic acids. In this review article we focus on updating information regarding: (i) Acr-induced DNA damage and methods of detection, (ii) repair of Acr-DNA damage, (iii) mutagenicity of Acr-DNA adducts, (iv) sequence specificity and methylation effect on Acr-DNA adduct formation and (v) the role of Acr in human cancer. We have found that Acr can inhibit DNA repair and induces mutagenic Acr-dG adducts and that the binding spectrum of Acr in the p53 gene in normal human bronchial epithelial cells is similar to the p53 mutational spectrum in lung cancer. Since Acr-DNA adduct has been identified in human lung tissue and Acr causes bladder cancer in human and rat models, we conclude that Acr is a major lung and bladder carcinogen, and its carcinogenicity arises via induction of DNA damage and inhibition of DNA repair

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PMID: 21714128
ISSN: 1613-4133
CID: 137067

E-Cigarette Vapors, Flavorings, Trigger Lung Cell Stress

Newsroom

Wednesday, February 11, 2015

Do electronic cigarettes help people quit smoking? As the debate continues on that point, a new University of Rochester study suggests that e-cigarettes are likely a toxic replacement for tobacco products.

Emissions from e-cigarette aerosols and flavorings damage lung cells by creating harmful free radicals and inflammation in lung tissue, according to the UR study published in the journal *PLOS ONE.* Irfan Rahman, Ph.D., professor of Environmental Medicine at the UR School of Medicine and Dentistry, led the research, which adds to a growing body of scientific data that points to dangers of e-cigarettes and vaping.

The investigation suggests the harm begins when the e-cigarette's heating element is activated. The heating element is designed to turn a liquid solution (known as an e-liquid or "juice") into an aerosol that mimics cigarette smoke. The inhaled vapors contain heavy metals and other possible carcinogens in the form of nanoparticles – tiny particulate matter that can reach farther into lung tissue, cell systems, and blood stream.

Rahman's study also shows that some flavored e-juices (particularly cinnamon) create more stress and toxicity on lung tissue. Researchers observed in the laboratory that human lung cells exposed to e-cigarette aerosols released various inflammation biomarkers. Mice exposed to e-cigarettes with classic tobacco flavoring also demonstrated signs of pulmonary inflammation.

"Several leading medical groups, organizations, and scientists are concerned about the lack of restrictions and regulations for e-cigarettes," Rahman said. "Our research affirms that e-cigarettes may pose significant health risks and should be investigated further. It seems that every day a new e-cigarette product is launched without knowing the harmful health effects of these products."

Rahman's laboratory also recently reported in the journal *Environmental Pollution* that toxic metals and oxidants from e-cigarettes raise safety concerns as well as potential pollution hazards from second-hand exposures and disposal of e-cigarette waste. Another recent

study connected e-cigarette vapors to a higher risk of respiratory infections in young people.

In a joint statement issued January 8, 2015, the two leading cancer organizations in the United States – the American Association for Cancer Research and American Society for Clinical Oncology – said that e-cigarettes should be subject to the same Food and Drug Administration (FDA) restrictions as tobacco until more is known about possible adverse health effects. Insufficient data also exists on the value of the tool for smoking cessation. The biggest concern is for e-cigarette users under age 18. Health experts believe e-cigarettes entice some young people to start smoking and will make it socially acceptable again. E-liquid flavorings marketed to kids and teens include fruit, dessert, and candy, and are widely available at convenience stores, gas stations, and online. Manufacturers contend it's a safer alternative to cigarettes, and consumers have pushed sales in the U.S. beyond $1 billion.

A trend known as "dripping" allows e-cig users to drip an e-liquid directly onto the cigarette's heating element instead of using a refillable chamber to hold the e-liquids. The smoker inhales the aerosols and gets a stronger hit, while also being able to more easily switch between flavors, brands or nicotine content. The UR study found that dripping e-liquids or e-juices to produce vapors likely generates a larger dose of toxins to the lungs.

Rahman's study notes that manufacturers typically don't disclose all materials and chemicals used to make e-cigarettes and e-juices. Without that information or long-term use studies, consumers have limited information about the potential dangers for human health and the environment, he said.

Funding for the study came from The National Institute of Drug Abuse and a National Heart Lung and Blood Institute training grant. Study collaborators include: first author Chad Lerner, Ph.D., postdoctoral fellow in the Rahman laboratory; Scott McIntosh, Ph.D., associate professor of Public Health Sciences at UR, Deborah J. Ossip, Ph.D., professor of Public Health Sciences at UR; Alison Elder, Ph.D., associate professor of Environmental Medicine at UR; and Risa Robinson, Ph.D., professor at the Kate Gleason College of Engineering at Rochester Institute of Technology.

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Flavored Electronic Cigarettes Linked to Possible Cardiovascular Disease

bumc.bu.edu/busm/2018/06/14/flavored-electronic-cigarettes-linked-to-possible-cardiovascular-disease

Could flavored electronic cigarettes (e-cigarettes) cause bodily harm?

There has been a rapid rise in e-cigarette use, partially due to flavoring additives in tobacco products and perception of less harm than traditional combustible cigarettes. Numerous studies have been done on the risks of e-cigarettes to lungs, but the risk to blood vessels and how flavorings can affect the body are largely unknown.

The dangers of combustible cigarettes on the cardiovascular system has been known for decades, however, e-cigarettes have only been around since the early 2000s. Studies to determine whether e-cigarettes are dangerous to blood vessels have been done, but no study has looked directly at the flavored additives toxicity to blood vessels until now.

Researchers at BUSM looked at short-term effects of flavoring chemicals used in tobacco products like e-cigarettes on endothelial cells, cells that line the blood vessels. The researchers noticed that when blood vessels were exposed to flavoring additives, normally released chemicals to promote blood flow were decreased and increased inflammation, indicators of short-term toxicity. They also found that endothelial cells from smokers showed the same toxicity as those treated with flavoring chemicals.

“Our findings show that flavoring additives themselves were directly toxic to blood vessels and have adverse effects that may have relevance to cardiovascular toxicity long-term similar to combustible cigarettes,” explained corresponding author Jessica Fetterman, PhD assistant professor of medicine at BUSM.

These findings appear in the journal *Arteriosclerosis, Thrombosis, and Vascular Biology*.

Flavorings in Tobacco Products Induce Endothelial Cell Dysfunction

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Objective—Use of alternative tobacco products including electronic cigarettes is rapidly rising. The wide variety of flavored tobacco products available is of great appeal to smokers and youth. The flavorings added to tobacco products have been deemed safe for ingestion, but the cardiovascular health effects are unknown. The purpose of this study was to examine the effect of 9 flavors on vascular endothelial cell function.

Approach and Results—Freshly isolated endothelial cells from participants who use nonmenthol- or menthol-flavored tobacco cigarettes showed impaired A23187-stimulated nitric oxide production compared with endothelial cells from nonsmoking participants. Treatment of endothelial cells isolated from nonsmoking participants with either menthol (0.01 mmol/L) or eugenol (0.01 mmol/L) decreased A23187-stimulated nitric oxide production. To further evaluate the effects of flavoring compounds on endothelial cell phenotype, commercially available human aortic endothelial cells were incubated with vanillin, menthol, cinnamaldehyde, eugenol, dimethylpyrazine, diacetyl, isoamyl acetate, eucalyptol, and acetylpyrazine (0.1–100 mmol/L) for 90 minutes. Cell death, reactive oxygen species production, expression of the proinflammatory marker IL-6 (interleukin-6), and nitric oxide production were measured. Cell death and reactive oxygen species production were induced only at high concentrations unlikely to be achieved in vivo. Lower concentrations of selected flavors (vanillin, menthol, cinnamaldehyde, eugenol, and acetylpyridine) induced both inflammation and impaired A23187-stimulated nitric oxide production consistent with endothelial dysfunction.

Conclusions—Our data suggest that short-term exposure of endothelial cells to flavoring compounds used in tobacco products have adverse effects on endothelial cell phenotype that may have relevance to cardiovascular toxicity. **(*Arterioscler Thromb Vasc Biol*. 2018;38:00-00. DOI: 10.1161/ATVBAHA.118.311156.)**

Key Words: endothelial cells ■ eugenol ■ inflammation ■ nitric oxide ■ tobacco

Electronic cigarettes (e-cigarettes) came on the market in 2003, and since that time, their popularity has increased dramatically. The majority of adult e-cigarette users are current or former combustible cigarette smokers, which has garnered interest on whether e-cigarettes may aid in smoking cessation or be a harm-reduction tool in smokers.[1–3] In addition, e-cigarette use by youth is rising rapidly with ≈16% of high school students having used an e-cigarette in the past 30 days, whereas 37% of high schoolers reported ever use of an e-cigarette in 2015.[4–7] Importantly, studies have shown that youth who try e-cigarettes are at a 3- to 5-fold greater risk for combustible cigarette smoking, suggesting that e-cigarettes are serving as a gateway to other tobacco product use.[6,8] Further, e-cigarettes are marketed and perceived as being safer than combustible cigarettes because of the limited number of ingredients in the electronic liquid (primarily nicotine, propylene glycol/glycerin, and often contain flavorings).

Although combustible cigarettes are prohibited from containing characterizing flavors, with the exception of menthol, other tobacco products including e-cigarettes, cigars, little cigars, cigarillos, smokeless tobacco, and hookah are unrestricted regarding flavoring addition. Electronic liquids are available in a wide variety of flavorings with ≈7000 on the market with menthol, sweet, and fruity electronic liquids being the most popular.[9] The flavorings used in tobacco products, including electronic liquids, greatly increase the appeal of tobacco products and mask the harshness associated with use.[9–13] In 2014, of the high school students who reported use of a tobacco product, an estimated 73% reported using a flavored tobacco product,[10] and among youth, flavorings are cited as a primary reason for use of alternative tobacco products, including e-cigarettes, hookah, and cigars.[10,14,15] Although the majority of the morbidity and mortality burden of combustible cigarette smoking is attributable to cardiovascular disease, the

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Nonstandard Abbreviations and Acronyms	
DHE	dihydroethidium
e-cigarettes	electronic cigarettes
eNOS	endothelial NO synthase
HAEC	human aortic endothelial cell
ICAM-1	intercellular adhesion molecule-1
IL-6	interleukin-6

effects of tobacco product flavorings on the cardiovascular system are largely unknown.

The cardiovascular system is exposed to circulating toxins, and measures of vascular function are rapidly altered in response to environmental exposures. The endothelium plays a key role in maintaining vascular homeostasis, which has been shown to be disrupted by several cardiovascular risk factors, including combustible cigarette smoking.[16–18] Endothelial dysfunction not only precedes the development of atherosclerosis but also predictive of worse outcomes, including myocardial infarction and cardiac death.[19,20] Combustible cigarette smoking has been shown to induce endothelial dysfunction characterized by increased oxidative stress, a loss of nitric oxide signaling, inflammation, oxidative stress, and a prothrombotic phenotype.[16–18] Several studies in endothelial cells suggest that acrolein, an aldehyde found in combustible cigarette smoke and e-cigarette aerosol, induces inflammation and oxidative stress.[21–23] A recent study showed that flow-mediated vasodilation was impaired in young, healthy tobacco naïve individuals and combustible cigarette smokers 30 minutes after the use of an e-cigarette, suggesting that acute e-cigarette use impairs endothelial function.[24] However, the mechanisms underlying e-cigarette–induced vascular injury are largely unknown, and whether tobacco product flavorings induce endothelial dysfunction is unclear.

In this study, we developed an in vitro screening panel to identify whether flavorings added to tobacco products are toxic to endothelial cells and, if so, what levels induce toxicity. We selected a panel of measures of endothelial function, including measures of cell death, oxidative stress, inflammation, and nitric oxide bioavailability. Under pathological conditions, endothelial cells undergo cell death, have increased oxidative stress, decrease production or lose bioavailable nitric oxide, and become proinflammatory. We tested the vascular endothelial cell toxicity of common flavoring compounds in tobacco products across many different chemical classes. The flavorings vanillin, cinnamaldehyde, eugenol, acetylpyridine, and menthol impaired A23187-induced nitric oxide production and increased expression of the proinflammatory mediator, IL-6 (interleukin-6), suggesting that these flavors are harmful to the endothelium (Table 1).

Materials and Methods

Data available upon request from the authors.

Study Participants

We enrolled age- and sex-matched nonsmokers who do not use any tobacco products, nonmenthol cigarette smokers, and menthol cigarette smokers. All participants enrolled had no risk factors (diabetes mellitus, smoking, hypertension, dyslipidemia) or known cardiovascular disease. All participants provided written consent, and all study protocols were approved by the Boston Medical Center Institutional Review Board.

Flow-Mediated Vasodilation

Endothelial function was evaluated using flow-mediated vasodilation in which hyperemic flow stimulates endothelial nitric oxide production and subsequent vasodilation. As previously described, hyperemic flow was induced by proximal forearm cuff occlusion of the upper arm for 5 minutes, and a Toshiba SSH-140A ultrasound system was used to measure brachial artery diameter at baseline and 1 minute after the 5-minute occlusion.[25] The commercially available software, Brachial Analyzer version 3.2.3 (Medical Imaging Applications), was used to assess flow-mediated dilation data. Flow-mediated vasodilation is expressed as percent dilation.

Venous Endothelial Cell Biopsy

Venous endothelial cells were freshly isolated from nonsmokers, nonmenthol cigarette smokers, and menthol cigarette smokers without cardiovascular disease, as previously described.[26–28] A 0.018-inch J-wire (Arrow International, Reading, PA) was inserted through a 20 or 22 gauge catheter in a vein of the forearm and used to gently rub the inside of the vessel. After removal, the J-wire was rinsed several times with red blood cell lysis and dissociation buffer. The sample was then centrifuged and cells applied to poly-L-lysine–coated slides (Sigma, St Louis, MO). Nitric oxide production and bioavailability were then assessed immediately after isolation as outlined below.

Cell Culture Conditions and Tobacco Flavorings Exposures

Commercially available (Lonza Inc, Walkersville, MD) human aortic endothelial cells (HAECs) were cultured from passage 4 to 7 (EGM-2 [endothelial cell growth medium] complete media, Lonza). When the cells were near confluent, serum was withdrawn for 4 hours, and the cells were exposed to a flavoring compound diluted in media (phenol red–free EGM-2, Lonza) for 90 minutes at 37°C before measurement of apoptosis, oxidative stress, inflammation, and nitric oxide production as outlined below. Controls were vehicle matched to flavoring. All flavors are food safe grade, production lot consistent, and obtained from Sigma-Aldrich (St Louis, MO; Table I in the online-only Data Supplement for catalog numbers).

The flavoring compounds were heated at temperatures achieved using e-cigarette tank devices to test the potential toxicity of thermal degradation productions. A drop-tube furnace consisting of a quartz tube was configured in a vertical position and set to temperatures 200°C±50°C or 700°C±50°C. Vanillin, menthol, or eugenol were added dropwise into the heated area of the furnace where the flavoring compound was quickly aerosolized. The aerosol then moved through a glass impinge for collection in an ethanol solution (55% in PBS). Test concentrations of thermal product solutions were determined from the volume of flavoring compound initially added to the furnace before heating and collection. All cell exposures to the aerosolized flavoring compounds were compared with ethanol vehicle control.

Measurement of Nitric Oxide Bioavailability

HAECs were grown on 8-well slides, and after a 90-minute flavoring exposure, the cells were incubated with 3 µmol/L 4,5-diaminofluorescein diacetate (Calbiochem) for 30 minutes. After 2 washes with Hanks' balanced salt solution, cells were stimulated with 1 µmol/L A23187 (Sigma) for 15 minutes and fixed with 2% paraformaldehyde. Mean fluorescence intensity (excitation of 498 nm) of individual cells (20 cells per condition) was measured on a fluorescence microscope (Nikon Eclipse TE2000). Data are expressed as percent increase in 4,5-diaminofluorescein diacetate fluorescence stimulated by A23187 compared with unstimulated cells.

Quantification of Cell Death

HAECs were grown on 8-well slides, incubated with flavoring compounds for 90 minutes, fixed with 2% paraformaldehyde, and stored at −80°C. A commercially available TUNEL assay (terminal deoxynucleotidyl transferase dUTP nick-end labeling; Roche) was performed,

Table 1. Tobacco Product Flavorings Tested

Tobacco Product Flavoring	Class	Subgroup	Characterizing Flavor
Eugenol	Alcohols, phenols	Phenol	Clove
Vanillin	Aldehyde	Aromatic aldehyde	Vanilla
Cinnamaldehyde	Aldehyde	Aromatic aldehyde	Cinnamon
Menthol	Alcohols, phenols	Cyclic terpene	Mint, cooling effect
2,5-dimethylpyrazine	Pyrazine	Alkyl pyrazine	Strawberry
Diacetyl	Ketone	Diketone	Butter
Isoamyl acetate	Ester	Aliphatic esters	Banana
Eucalyptol	Ether	Ether	Spicy, cooling effect
Acetylpyridine	Pyridine	Pyridine	Burnt

and cells were imaged on a fluorescence microscope (Nikon Eclipse TE2000) for fluorescein and DAPI (4',6-diamidino-2-phenylindole; Vector Laboratories). DNAse 1 (Sigma) was used as a positive control for apoptosis. A minimum of 50 cells were quantitated for each condition. Data are presented as % TUNEL-positive cells.

Assessment of Oxidative Stress

HAECs were grown on 96-well plates and, after flavoring exposure, were incubated with dihydroethidium (DHE, 10 µmol/L, Thermo Fisher) for 30 minutes. Cells were washed 3× to remove DHE with Hanks' balanced salt solution. Fluorescence was measured on a plate reader with an excitation of 518 nm and emission of 606 nm (Molecular Devices). Antimycin A (50 µmol/L; Sigma) treatment for 30 minutes was used as a positive control. Data are presented as fold change in DHE fluorescence compared with vehicle control.

Quantification of IL-6 and ICAM-1 (Inflammatory) Activation

HAECs were grown on 6-well plates and were incubated an additional 90 minutes in media after flavoring exposure, allowing for a total time of 180 minutes for changes in RNA expression. Cells were scraped into Qiazol (Qiagen), frozen, thawed, chloroform (1/5 of the Qiazol volume) extracted, and shaken for 15 seconds. After a 5-minute incubation at room temperature, the samples were centrifuged at 12 000*g* for 15 minutes at 4°C. The aqueous phase was collected and RNA was extracted with a kit (miRNeasy Micro Kit, Qiagen) according to the manufacturer's instructions. RNA was eluted in 14 µL of water and quantified with a Nanodrop spectrophotometer (Thermo Fisher, average of 200 ng RNA/µL). cDNA synthesis of mRNA was performed with a cDNA reverse transcription kit (Quanta Bio, Beverly, MA). Reverse transcription-quantitative polymerase chain reaction was performed with a Viia7 (Applied Biosystems) thermal cycler using TaqMan Master Mix and TaqMan primers for IL-6 and ICAM-1 (intercellular adhesion molecule-1; Thermo Fisher). The $2^{-\Delta Ct}$ was calculated from threshold Ct values using GAPDH as a reference gene. Data are expressed as relative quantification to matched control.

Statistical Analysis

Statistical analyses were performed using SPSS version 24.0 (IBM Corp, Armonk, NY). Data are expressed as mean±SD, unless otherwise indicated. We evaluated each measure for normality using the Shapiro–Wilk test. For between group comparisons, variables with normal distribution were compared using a 1-way ANOVA using post hoc Dunnett 2-sided tests with contrasts to control (vehicle alone) or χ^2 testing for continuous or categorical data, respectively. For variables that were not normally distributed, we used Kruskal–Wallis tests. For 2-group comparisons before and after treatment, we used paired *t* tests, and for variables not normally distributed, we used Wilcoxon signed-rank tests. A $P<0.05$ was considered to be statistically significant.

Results

In a healthy endothelium, stimulation with eNOS (endothelial NO synthase) agonists, such as A23187, induces an increase in nitric oxide which in vivo results in vasodilation and is indicative of cardiovascular health.[19,29] Venous endothelial cells were freshly isolated by venous biopsy from nonsmokers (n=9), nonmenthol cigarette smokers (n=6), and menthol cigarette

Table 2. Clinical Characteristics

	Nonsmokers (n=9)	Nonmenthol Cigarette Smokers (n=6)	Menthol Cigarette Smokers (n=6)
Age, y	29±4	40±10	39±14
Female sex, n (%)	5 (55)	2 (33)	2 (33)
Black race, n (%)	6 (66)	5 (83)	5 (83)
Body mass index, kg/m^2	26.3±2.9	28.9±7.3	26.9±4.4
Systolic blood pressure, mm Hg	115±11	123±6	128±23
Diastolic blood pressure, mm Hg	65±6	73±9	77±10
Heart rate, bpm	59±6	64±9	57±8
Packs per day, n		0.7±0.2	1.4±0.7
Pack years		21±10	27±22

Data are expressed as mean±SD.

smokers (n=6) of similar age and sex (Table 2). Nonmenthol and menthol cigarette smokers had a similar number of packs smoked per day (0.7±0.2 versus 1.4±0.7; *P*=0.4) and pack years (21±10 versus 27±22; *P*=0.7). As part of larger, on-going study of vascular function and smoking, we evaluated flow-mediated vasodilation in the patients recruited for endothelial cell biopsy. We found a trend for lower flow-mediated vasodilation between the smoking groups and nonsmokers (Figure I in the online-only Data Supplement; *P*=0.12 between groups).

Freshly isolated endothelial cells collected from nonmenthol and menthol cigarette smokers had lower nitric oxide production in response to A23187 stimulation compared with cells from nonsmokers (*P*=0.003 nonsmokers versus nonmenthol cigarette smokers; *P*=0.012 nonsmokers versus menthol cigarette smokers; Figure 1A). The impairment in A23187-stimulated nitric oxide production was similar between nonmenthol cigarette smokers and menthol cigarette smokers (*P*=0.86; Figure 1A). The absence of a difference in A23187-stimulated nitric oxide production is likely because of the overwhelming toxicity of the many components of tobacco smoke that are already maximally impairing nitric oxide bioavailability. Consistent with this, we observed that the treatment of endothelial cells from nonmenthol cigarette smokers with 0.01 mmol/L menthol did not further impair nitric oxide production in response to A23187 (2.1±2.4 versus −2.6±5.1; *P*=0.5). Treatment of freshly isolated endothelial cells from healthy participants with 0.01 mmol/L menthol (Figure 1B) or 0.01 mmol/L eugenol (Figure 1C) impaired nitric oxide production in response to A23187 stimulation. These findings suggest that flavoring compounds induce endothelial cell dysfunction in human cells similarly to the abnormal function in active cigarette smokers.

To further characterize the acute effects of several flavoring compounds on a broad set of endothelial phenotypes, we studied commercially available endothelial cells. Several tobacco product flavorings and doses induced cell death measured by TUNEL assay (Figure 2). Specifically, all flavorings tested induced cell death at the highest concentration tested (10–100 mmol/L). Cinnamaldehyde precipitated out of solution at concentrations >10 mmol/L; therefore, all experiments were performed at 10 mmol/L or lower concentrations. Cinnamaldehyde, eugenol, dimethylpyrazine, isoamyl acetate, and eucalyptol treatment at 10 mmol/L increased cell death compared with vehicle control. Treatment of HAECs with 1 mmol/L dimethylpyrazine also increased cell death, suggesting that endothelial cells are especially sensitive to dimethylpyrazine exposure.

Oxidative stress was assessed using the fluorescent dye DHE after treatment of HAECs with flavorings across several concentrations (Figure 3). As expected, the positive control, antimycin A, increased the levels of oxidants as measured by an increase in DHE fluorescence. Vanillin and eugenol increased oxidative stress at the highest concentration tested (10 mmol/L vanillin, 10 mmol/L eugenol), whereas all other flavorings tested had no effect on oxidative stress. The concentrations of vanillin and eugenol that increased oxidative stress were also the same concentrations that caused cell death, suggesting significant damage to endothelial cells at these levels. The concentrations of flavorings for all additional assays tested were performed at concentrations below the dose observed to induce cell death.

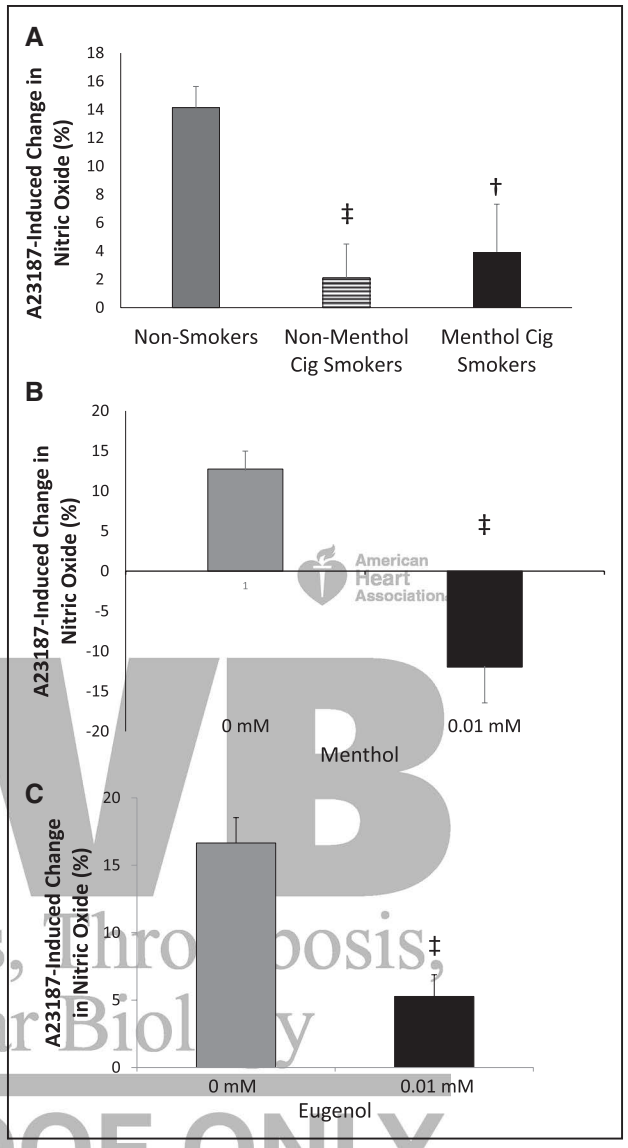

Figure 1. Menthol and eugenol impair nitric oxide production in freshly isolated endothelial cells from human participants. Endothelial cells from menthol (n=6) and nonmenthol cigarette smokers (n=6) had a lower change in nitric oxide measured by 4,5-diaminofluorescein diacetate (DAF-2DA) fluorescence in response to A23187 stimulation compared with endothelial cells from nonsmokers (n=9, ‡*P*<0.01, †*P*<0.05; **A**). Treatment of endothelial cells freshly isolated from healthy participants with 0.01 mmol/L menthol (**B**) or eugenol (**C**) decreased DAF-2DA fluorescence in response to A23187 stimulation (n=5, ‡*P*<0.01 for menthol; n=5, ‡*P*<0.01 for eugenol). Data are expressed as mean±SEM.

Expression of a proinflammatory mediator, IL-6, was quantified in HAECs 3 hours after exposure to flavoring compounds (Figure 4). Vanillin, cinnamaldehyde, eugenol, and acetylpyridine increased IL-6 expression at most concentrations tested, even in the 0.001 to 0.01 mmol/L range. Menthol increased IL-6 expression at 10 and 100 mmol/L but not at the lower concentrations (0.01–1 mmol/L). Dimethylpyrazine, diacetyl, isoamyl acetate, and eucalyptol had no effect on IL-6 expression in HAECs. Expression of the adhesion molecule, ICAM-1, was quantified in HAECs after a 3-hour exposure to flavoring compounds (Figure II in the online-only Data Supplement). Vanillin at a concentration of 10 mmol/L increased ICAM-1

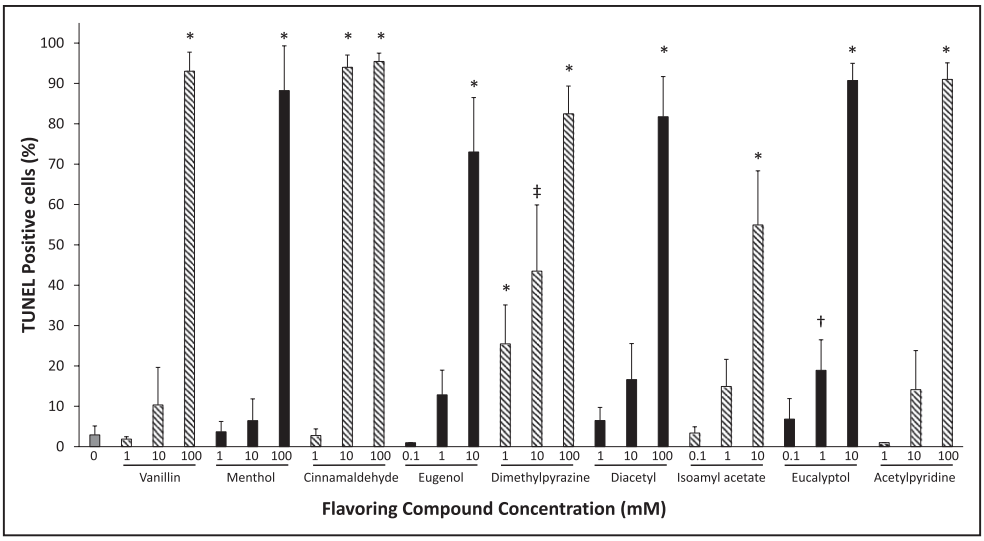

Figure 2. Tobacco flavoring compounds induce cell death. The percentage of cells staining positive for DNA strand breaks (TUNEL positive [terminal deoxynucleotidyl transferase dUTP nick-end labeling]) after a 90 min incubation with varying concentrations of flavor compounds were detected using immunofluorescence (n=3–4, *P<0.001, ‡P<0.01, †P<0.05 compared with vehicle control). Data are expressed as mean±SEM.

expression in HAECs whereas other concentrations and flavoring compounds had no effect on ICAM-1 expression.

HAECs treated with the selected flavorings vanillin, menthol, cinnamaldehyde, eugenol, or acetylpyridine displayed a loss of nitric oxide production in response to A23187 stimulation at all the tested concentrations of tobacco product flavoring (Figure 5). In HAECs exposed to varying concentrations of eugenol for 90 minutes, phosphorylation of eNOS at its activation site, Serine 1177, in response to A23187 was impaired (Figure III in the online-only Data Supplement), suggesting that eugenol-induced decrease in nitric oxide bioavailability is due, in part, to an impairment in eNOS activation. Further, HAECs were treated with vanillin, eugenol, and menthol that had been aerosolized at temperatures designed to simulate those achieved using e-cigarette devices (200°C and 700°C) for 90 minutes and then A23187-stimulated nitric oxide was assessed. Treatment of HAECs with vanillin aerosolized at 200°C but not 700°C decreased nitric oxide production in response to A23187 stimulation (Figure 6). HAECs treated with eugenol at 200°C and 700°C impaired nitric oxide production in response to A23187 stimulation while aerosolized menthol treatment had no effect (Figure 6). Collectively, these data suggest that heating of the flavoring compounds alters their toxicity.

Discussion

Our study provides evidence that flavoring additives in tobacco products induce acute alterations in endothelial function. Treatment of endothelial cells from nonsmokers with menthol and eugenol resulted in a loss of nitric oxide signaling, recapitulating the phenotype observed in endothelial cells

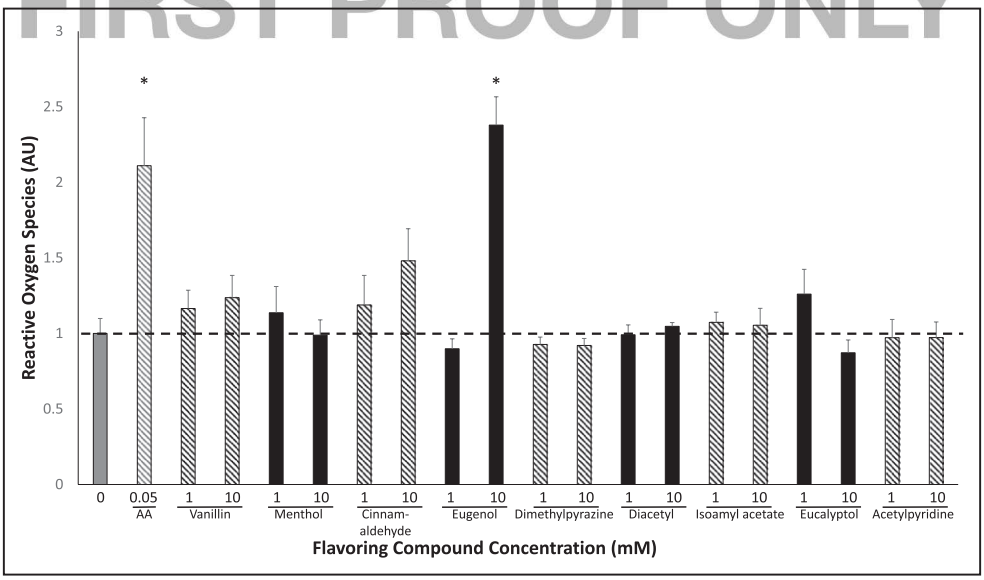

Figure 3. Tobacco flavoring compounds increase oxidative stress. Oxidative stress was measured by quantifying the fluorescent dye dihydroethidium after exposure of human aortic endothelial cells to flavoring compounds at varying concentrations (n=3, *P<0.001). Antimycin A (AA), a stimulus for mitochondrial oxidant generation, served as a positive control. Data are expressed as mean±SEM.

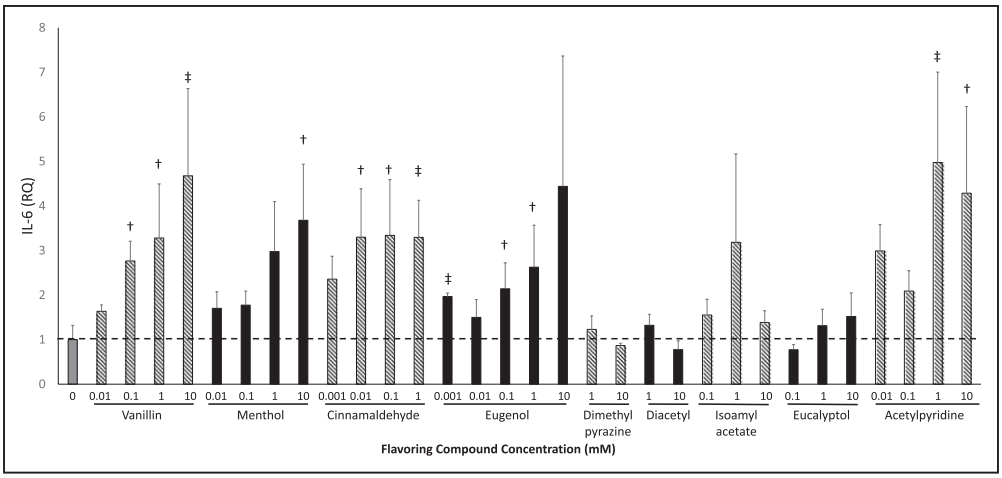

Figure 4. Tobacco flavoring compounds increase endothelial cell inflammation. IL-6 (interleukin-6) expression was quantified using reverse transcription-quantitative polymerase chain reaction 3 h after initial flavoring exposure in human aortic endothelial cells. All data are expressed as the relative quantification compared with vehicle alone treated cells (n=3–6, ‡*P*<0.01, †*P*<0.05). Data are expressed as mean±SEM.

from nonmenthol and menthol cigarette smokers. We found a similar degree of impairment in nitric oxide bioavailability in endothelial cells from nonmenthol and menthol cigarette smokers, which is consistent with prior literature showing that nonmenthol and menthol cigarette smokers have a similar degree of cardiovascular risk.[30–34] We then systematically assessed the impact of several flavoring compounds, in the absence of combustion products, on a panel of measures of endothelial function, including nitric oxide production, oxidative stress, inflammation, and cell death. The unique chemical characteristics of each flavoring compound led to variable changes in different outcomes whereas at some concentrations, all tobacco product flavoring compounds induced cell death. Oxidative stress was induced by the flavoring compounds but at concentrations that are likely supraphysiological. Notably, the flavorings vanillin, cinnamaldehyde, eugenol, and acetylpyridine impaired A23187-induced nitric oxide production and increased expression of the proinflammatory mediator, IL-6, across all concentrations tested, suggesting that the endothelium is particularly sensitive to these flavors. Menthol also increased IL-6 expression at the higher concentrations tested (10 and 100 mmol/L) and impaired nitric oxide production in response to A23187 at doses as low as 0.01 mmol/L. Treatment of HAECs with flavoring additives vanillin and eugenol aerosolized at temperatures achieved using e-cigarettes, impaired nitric oxide production in response to A23187 stimulation whereas aerosolized of menthol had no effect on nitric oxide production. The impairment in nitric oxide bioavailability observed after treatment with native and aerosolized flavoring additives suggests that the heating process alters the flavoring-induced endothelial

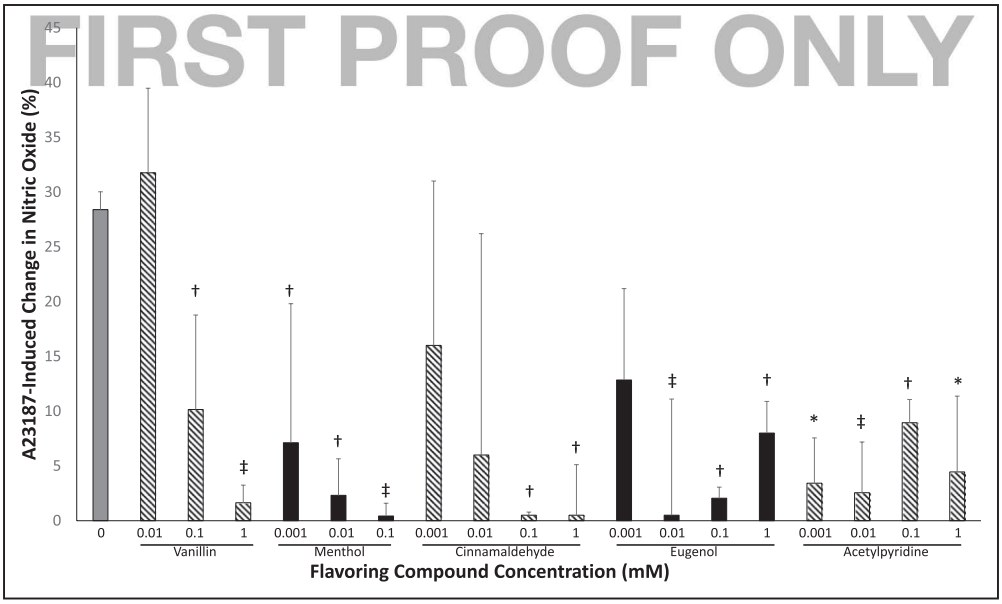

Figure 5. Tobacco flavoring compounds impair nitric oxide production in human aortic endothelial cells (HAECs). Nitric oxide production (4,5-diaminofluorescein diacetate [DAF-2DA] fluorescence) in response to A23187 stimulation was decreased in HAECs treated with flavoring compounds (n=3, **P*<0.001, ‡*P*<0.01, †*P*<0.05 compared with untreated control). Data are presented as percent change in DAF-2DA fluorescence in response to A23187 stimulation. Data are expressed as mean±SEM.

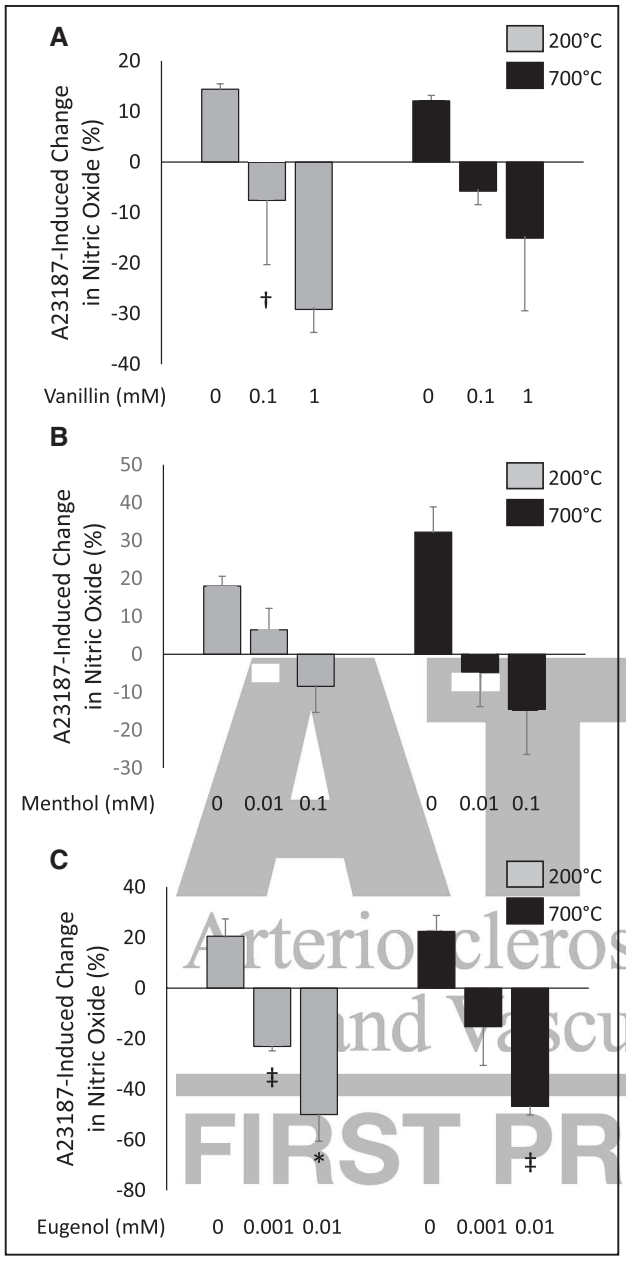

Figure 6. Differential effects of aerosolizing tobacco flavoring compounds on A23187-stimulated nitric oxide production in human aortic endothelial cells (HAECs). Treatment of HAECs with vanillin aerosolized at 200°C impaired A23187-stimulated nitric oxide production (4,5-diaminofluorescein diacetate [DAF-2DA] fluorescence), but this impairment was not observed with vanillin aerosolized at 700°C (n=3, †P<0.05 compared with untreated vehicle control, **A**). HAECs treated with menthol aerosolized at 200°C or 700°C had no effect on A23187-stimulated nitric oxide production (n=3, **B**). Treatment of HAECs with eugenol aerosolized at 200°C and 700°C impaired nitric oxide production in response to A23187 stimulation (n=3, *P<0.001, ‡P<0.01, compared with vehicle control, **C**). Data are presented as percent change in DAF-2DA fluorescence in response to A23187 stimulation. Data are expressed as mean±SEM.

dysfunction for some flavors but not others. Collectively, our data suggest that acute exposure to flavoring additives used in tobacco products induce characteristics of endothelial dysfunction at potentially physiologically relevant concentrations.

Although several studies have investigated the toxicity of tobacco product flavorings on pulmonary epithelial cells, few studies have assessed flavoring toxicity on the vascular endothelium. In human umbilical vein endothelial cells, treatment with vapor extract from different e-cigarette devices for 24 to 48 hours decreased endothelial cell viability and proliferation and altered endothelial cell morphology to varying degrees across the products, but to less of an extent that combustible cigarette smoke extract.[35] Among the e-cigarette products used to generate the vapor extracts, all contained flavorings, but the authors did not provide product information.[35] Thus, differentiating which flavored products were toxic on endothelial cells in this study was not possible.[35] In another study, e-cigarette condensate treatment of rodent pulmonary endothelial cell lines increased monolayer permeability, decreased cellular metabolic activity, and reduced cellular proliferation.[36] Interestingly, exposure to e-cigarette condensate without nicotine had a similar effect on endothelial barrier function as the e-cigarette condensate with nicotine, suggesting the effects of e-cigarette condensate are independent of nicotine.[36] In healthy nonsmokers and combustible cigarette smokers, use of an e-cigarette with unflavored electronic liquid impaired flow-mediated vasodilation, a measure of endothelial function and nitric oxide bioavailability, and increased measures of oxidative stress.[24] However, measures of oxidative stress (serum Nox2 [NADPH oxidase 2]-derived peptide and 8-isoPGF2α [8-iso-prostaglandin F2 alpha]) and nitric oxide bioavailability were less impacted by a single e-cigarette use compared with smoking a single combustible cigarette, suggesting that e-cigarettes could be a reduced harm tobacco product.[24] Hence, several studies have tested the toxicity of e-cigarette generated vapor on endothelial cell phenotype, but few have determined whether the flavor additives induce endothelial cell toxicity.

We measured the acute effects of flavoring compounds used in tobacco products on a select panel of measures of endothelial cell function in vitro to rapidly screen for flavor toxicity. Moreover, acute endothelium dysfunction is often observed immediately after smoking (cigarettes and e-cigarettes) and is recognized as a predictor of increased cardiovascular risk and disease.[19,20,24,37] We found differential effects of the flavoring compounds on nitric oxide bioavailability, cell death, oxidative stress, and IL-6 expression that may be related to their different chemical properties. All of the flavoring compounds tested impaired nitric oxide production, which may be the result of reactive oxygen species scavenging nitric oxide and reduced eNOS activation. Nitric oxide is a cardioprotective signaling molecule that inhibits vascular inflammation and thrombosis and plays a key role in regulating vascular tone.[19,29] The loss of nitric oxide signaling is known to promote a proinflammatory and prothrombotic endothelium, resulting in vascular dysfunction and atherosclerotic plaque formation.[19,38] The flavoring compounds that impaired nitric oxide production also upregulated IL-6 which is consistent with oxidative stress, a known stimulus of inflammatory signaling pathways. Treatment of freshly isolated endothelial cells from nonsmokers with menthol or eugenol recapitulated the loss of nitric oxide bioavailability observed in endothelial cells from nonmenthol and menthol cigarette smokers, suggesting an effect of menthol exposure separate from cigarette smoke. Our studies are strengthened

by the application of only the flavoring compounds to the cells, allowing us to isolate the effects of individual flavors on endothelial function. Other pathways may be impacted in endothelial cells by flavoring compound exposure, and the mechanisms are yet to be explored.

Our study has many limitations. We incubated endothelial cells with tobacco product flavoring compounds suspended in media without heating or addition of other typical electronic liquid constituents, such as the solvents propylene glycol and glycerol. Heating or combustion of the flavoring compounds likely alters the compounds, making them more or less toxic.[39] Consistent with this hypothesis, aerosolization of select flavoring compounds, vanillin and eugenol, did not alter their effects on nitric oxide bioavailability. However, aerosolization of menthol reduced menthol's inhibition of A23187-induced nitric oxide production. Similarly, we studied only the acute effects of flavoring compounds on endothelial cell function, and the effects associated with chronic use of flavored tobacco products need to be addressed. In addition, the in vitro effects may be different than the in vivo effects observed after flavored tobacco product use. The impairment in nitric oxide production in the endothelial cells from menthol cigarette smokers may not be directly attributable to the presence of menthol and is likely the result of the combined effects of multiple constituents in menthol cigarette smoke. This is consistent with the epidemiological evidence, showing that both menthol and nonmenthol cigarettes increase cardiovascular risk to a similar extent.[30–34] A study evaluating the pharmacokinetics of menthol estimated the daily exposure of menthol to be ≈80 µmol for an individual who smokes 20 mentholated cigarettes and estimated an absorption of ≈20% of the menthol in a combustible cigarette.[40] In our study, at a dose comparable to this estimated daily exposure, we found that treatment of endothelial cells from healthy, nonsmokers with 10 µmol/L menthol impaired A23187-stimulated nitric oxide production, suggesting that the concentrations evaluated in vitro are likely to be achieved in vivo. However, further work is needed to evaluate the levels of flavoring compounds and their metabolites in the circulation after use of flavored tobacco products.

We provide evidence that flavoring additives to tobacco products impair stimulated nitric oxide production and inflammation suggestive of endothelial dysfunction across a range of concentrations likely to be achieved in vivo. All flavorings tested impaired A23187-induced nitric oxide production, suggesting that measures of eNOS activation and nitric oxide production are sensitive measures of endothelial cell toxicity in vitro. The toxicity data generated herein, using a variety of common flavorings, provide quantitative support for the regulatory prohibition or the establishment of limitations on allowable levels of these flavorings in electronic liquids and other tobacco products. Future studies will focus on how the toxicity of the flavorings is altered with heating and characterization of the levels obtained in the circulation after use of an e-cigarette.

Sources of Funding

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Disclosures

None.

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Highlights

- The cardiovascular health effects of flavoring additives used in tobacco products, including electronic cigarettes, have not yet been studied.
- Our data suggest that short-term exposure of endothelial cells to flavoring compounds used in tobacco products have adverse effects on endothelial cell phenotype that may have relevance to cardiovascular toxicity.
- The toxicity data generated herein, using a variety of common flavorings, provide quantitative support for the regulatory prohibition or the establishment of limitations on allowable levels of these flavorings in electronic liquids and other tobacco products.
- Future studies will focus on how the toxicity of the flavorings is altered with heating and characterization of the levels obtained in the circulation after use of an electronic cigarette.

Arteriosclerosis, Thrombosis, and Vascular Biology

JOURNAL OF THE AMERICAN HEART ASSOCIATION

Flavorings in Tobacco Products Induce Endothelial Cell Dysfunction

Jessica L. Fetterman, Robert M. Weisbrod, Bihua Feng, Reena Bastin, Shawn T. Tuttle, Monica Holbrook, Gregory Baker, Rose Marie Robertson, Daniel J. Conklin, Aruni Bhatnagar and Naomi M. Hamburg

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Supplemental Data for: Flavorings in Tobacco Products Induce Endothelial Cell Dysfunction

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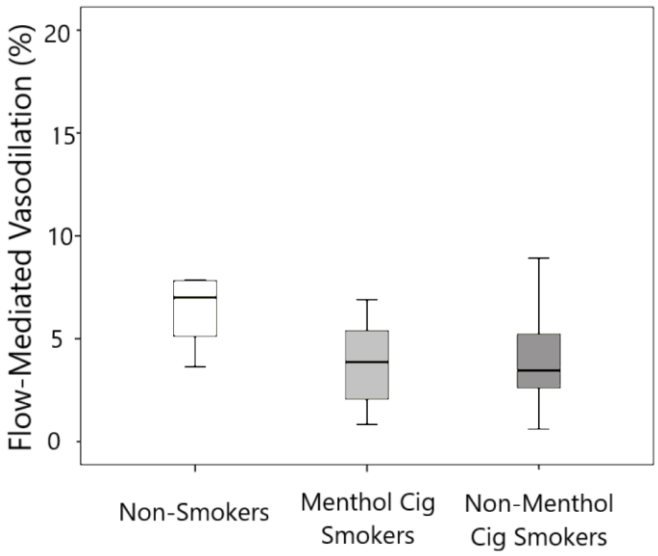
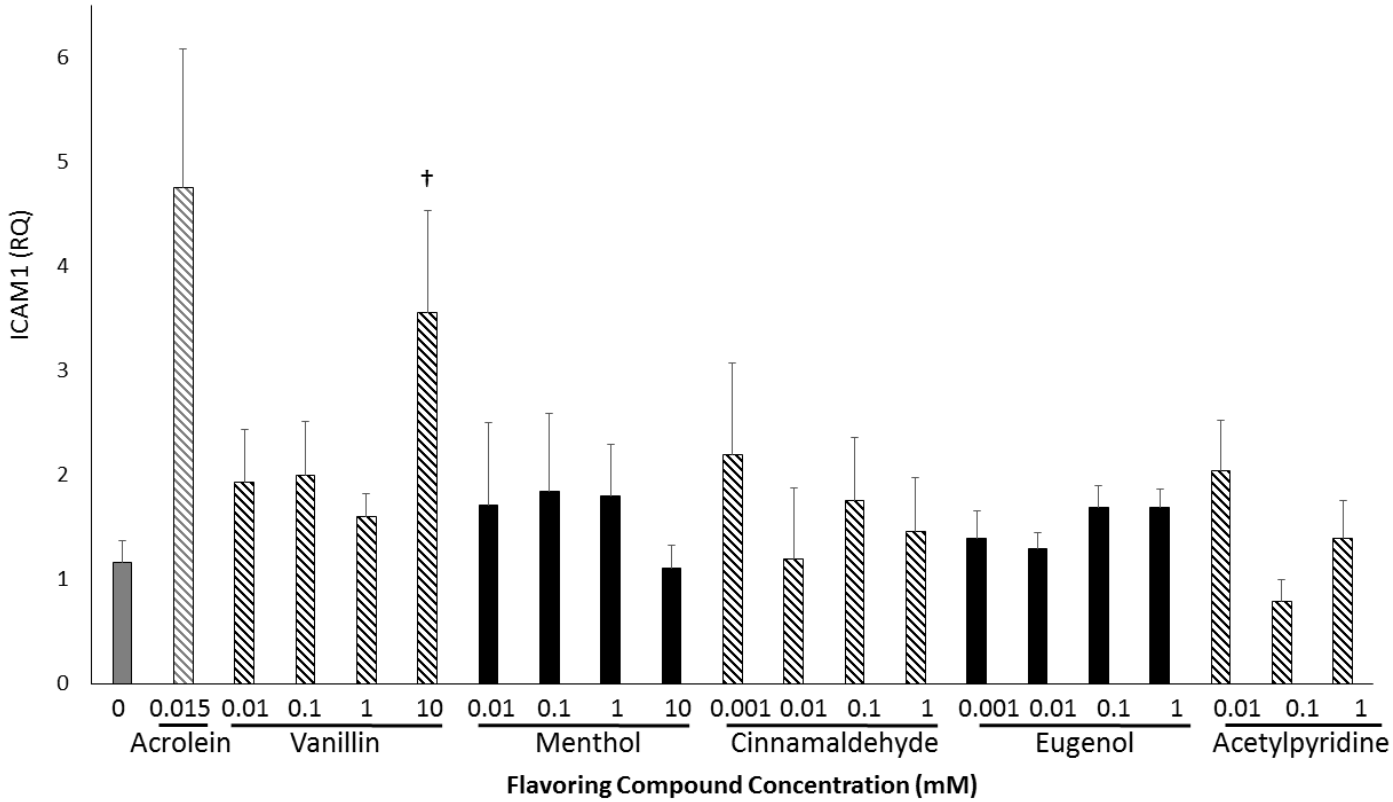
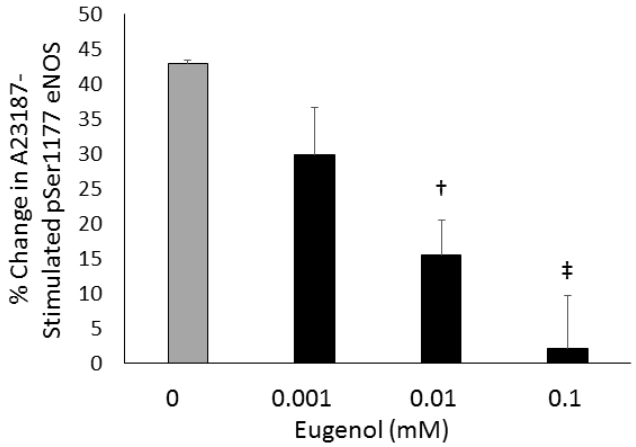


Supplemental Figure I: Flow-mediated vasodilation was numerically lower in menthol (n=5) and non-menthol (n=5) cigarette smokers compared to non-smokers (n = 8; *P*=0.12 between groups). Data are expressed as Mean ± standard deviation.



Supplemental Figure II: Flavoring compound treatment had no effect on ICAM1 expression. Treatment of HAECs with flavoring compounds for 90 minutes had no effect on ICAM1 expression with the exception of 10mM vanillin which, increased ICAM1 expression compared to untreated control (†P<0.05). Treatment of HAECs with the positive control acrolein trended towards an increase in ICAM1 expression compared to untreated cells (P=0.06). Data are expressed as relative quantification (RQ) compared to untreated control (N=3-4).



Supplemental Figure III: Eugenol treatment impairs eNOS activation. Treatment of HAECs with varying doses of eugenol for 90 minutes impaired eNOS phosphorylation at its activation site, Serine 1177 in response to A23187 stimulation (n = 3, ‡P<0.01, †P<0.05 compared to untreated control). Data are presented as percent change in phosphorylation of eNOS at its Serine 1177 site in response to A23187 stimulation and are expressed as the Mean ± SEM.

Supplemental Table I. Major Resources

Flavoring Compounds	**Vendor**	**Catalog #**
Vanillin	Sigma-Aldrich	V1104
Menthol	Sigma-Aldrich	63660
Eugenol	Sigma-Aldrich	E51791
Cinnamaldehyde	Sigma-Aldrich	W228613
2,5-dimethylpyrazine	Sigma-Aldrich	175420
Diacetyl (2,3-butanedione)	Sigma-Aldrich	B85307
Isoamyl acetate	Sigma-Aldrich	112674
Eucalyptol	Sigma-Aldrich	C80601
Acetylpyridine	Sigma-Aldrich	W325104
Endothelial Phenotype Measures		
0.018" J-wire for Endothelial Biopsy	Fisher Scientific	NC0147469
Human aortic endothelial cells	Lonza	CC-2535
DAF-2DA	Calbiochem	251505
A23187	Sigma-Aldrich	C7522
TUNEL	Sigma-Aldrich	11684809910
DAPI	Vector Laboratories	H-1200
Dihydroethidium (DHE)	ThermoFisher	D23107
IL-6 TaqMan Primers	ThermoFisher	Hs00985639_m1
ICAM TaqMan Primers	ThermoFisher	HS99999152_m1
GAPDH TaqMan Primer	ThermoFisher	4331182

E-cigarette flavorings foster cardiovascular dysfunction

mdedge.com/ecardiologynews/article/168097/cardiology/e-cigarette-flavorings-foster-cardiovascular-dysfunction

Flavorings used in e-cigarettes have a negative impact on endothelial cells that may play a role in cardiovascular toxicity.

Flavored tobacco products are popular among current smokers, including youth, and the flavorings have been deemed ingestible, but their impact on heart health has not been studied, wrote Jennifer Fetterman, PhD, of Boston University, and her colleagues. The report was published in Arteriosclerosis, Thrombosis, and Vascular Biology.

The researchers studied nine types of flavorings used in alternative tobacco products to assess their impact on cardiovascular health.

The first part of the study comprised a population of nine nonsmokers, six nonmenthol cigarette smokers, and six menthol cigarette smokers without cardiovascular disease. The researchers isolated venous endothelial cells from each participant.

Overall, cells from both nonmenthol and menthol cigarette smokers had significantly lower nitric oxide production compared with nonsmokers (P = .003 and P = .012, respectively). In addition, the flavoring compounds menthol and eugenol impaired nitric oxide production in the cells of healthy individuals.

“Increased inflammation and a loss of nitric oxide are some of the first changes to occur leading up to cardiovascular disease and events like heart attacks and stroke, so they are considered early predictors of heart disease,” Dr. Fetterman said in a statement, adding that the “findings suggest that these flavoring additives may have serious health consequences.”

Carpe89/ThinkStock

To characterize the acute effects of flavoring compounds, the researchers also acquired commercially available endothelial cells and exposed them to nine flavorings: eugenol (clove), vanillin (vanilla), cinnamaldehyde (cinnamon), menthol (mint), 2,5-dimethylpyrazine (strawberry), diacetyl (butter), isoamyl acetate (banana), eucalyptol (mint), and acetylpyridine (burnt).

All nine flavorings induced cell death at the highest concentration tested, ranging from 10 to 100 mmol/L).

The study findings were limited by several factors, primarily a lack of data on how heating the flavorings in the in vitro part of the study might have affected toxicity in the body, the researchers noted.

“Future studies will focus on how the toxicity of the flavorings is altered with heating and characterization of the levels obtained in the circulation after use of an e-cigarette,” they said.

However, data support the need for regulation and limits on the level of flavorings used in e-cigarettes and other tobacco products, they emphasized.
“These findings suggest that flavoring compounds induce endothelial cell dysfunction in human cells similarly to the abnormal function in active cigarette smokers,” the researchers noted.

The study was funded by the National Heart, Lung, and Blood Institute; Food and Drug Administration Center for Tobacco Products; and the American Heart Association. The researchers had no financial conflicts to disclose.

SOURCE: Fetterman J et al. Arterioscler Thromb Vasc Biol. 2018. doi: 10.1161/ATVBAHA.118.311156.

E-Cig Flavors Found to be Toxic When Inhaled

Sara E. Teller

June 22, 2018

SHARE

Photo by Cianna Jolie on Unsplash

Researchers examined the impact of nine flavorings commonly added to e-cigarettes, cigars, hookahs and other products and found that short-term exposure to these additives can be toxic to endothelial cell function. This means, that flavorings could impair blood vessel function over time and lead to heart damage. They impair nitric oxide production, which inhibits inflammation and clotting while regulating blood vessel enlargement in response to blood flow.

Vanillin (vanilla), cinnamaldehyde (cinnamon), eugenol (clove), and acetylpyridine (burnt flavor) impair A23187-induced nitric oxide production and increase expression of the proinflammatory mediator interleukin(IL)-6 across all concentrations tested, “suggesting that the endothelium is particularly sensitive to these flavors,” Jessica Fetterman, PhD, of Boston University School of Medicine, and her colleagues wrote of their findings.

There are more than 7,000 different flavors of e-cigarettes on the market. Although many of the flavorings used have been determined to be safe in food products, the long-term safety for inhalation into the lungs is not yet known.

“When we eat something, the stomach has a lot of mechanisms to detoxify, but the lungs and blood vessels are largely unprotected,” Fetterman said. “People aren’t meant to inhale a lot of stuff into their lungs other than air.”

In addition to examining vanillin, cinnamaldehyde, eugenol, and acetylpyridine, the researchers also investigated the impact of dacetyl (butter), dimethylpyrazine (strawberry), isoamyl acetate (banana), and eucalyptol (spicy cooling) on endothelial cell function. Isolated endothelial cells from participants who use non-menthol- or menthol-flavored tobacco cigarettes showed impaired A23187-stimulated nitric oxide production compared with those from nonsmokers.

Treatment of endothelial cells isolated from nonsmoking participants with either menthol (0.01 mmol/L) or eugenol (0.01 mmol/L) decreased A23187-stimulated nitric oxide production.

Photo by John Caroro on Unsplash

The researchers incubated commercially available human aortic endothelial cells with vanillin, menthol, cinnamaldehyde, eugenol, dimethylpyrazine, diacetyl, isoamyl acetate, eucalyptol, and acetylpyrazine (0.1–100 mmol/L) for 90 minutes. They then measured cell death, reactive oxygen species production, expression of IL-6, and nitric oxide production.

“Cell death and reactive oxygen species production were induced only at high concentrations unlikely to be achieved in vivo. Lower concentrations of selected flavors (vanillin, menthol, cinnamaldehyde, eugenol, and acetylpyridine) induced both inflammation and impaired A23187-stimulated nitric oxide production consistent with endothelial dysfunction,” according to the report.

Tobacco flavoring additives were found to restrict stimulated nitric oxide production and inflammation, “suggestive of endothelial dysfunction across a range of concentrations likely to be achieved in vivo.”

Fetterman said future studies are needed to better understand the short-term and long-term cardiovascular impact of exposure to inhaled tobacco product flavorings. The limitations of their procedure included that flavoring compounds were suspended in media without heating or the addition of other typical electronic liquid constituents, such as the solvents propylene glycol and glycerol. “Heating or combustion of the flavoring compounds likely alters the compounds, making them more or less toxic.”

Still, the study findings overall “provide quantitative support for the regulatory prohibition or the establishment of limitations on allowable levels of these flavorings in electronic liquids and other tobacco products.” The U.S. Food and Drug Administration is currently considering a ban on toxic flavors added to e-cigarettes and other tobacco products.

Sources:

E-Cigarette Flavorings May Harm Blood Vessels: Cell studies show short-term endothelial disruption with exposure

Not All Vape Flavors are Created Equal. K-Dawn’s Dr. Daliah Explains

Join the Discussion

Not All Vape Flavors are Created Equal. K-Dawn's Dr. Daliah Explains

kdwn.com/2018/06/15/not-vape-flavors-created-equal-k-dawns-dr-daliah-explains

June 16, 2018

June 15, 2018
A study published by the American Heart Association found nine different E-cig flavors to impair blood vessel function, which can impair heart health.

Endothelial cells, which delicately line blood and lymph vessels, were found to become inflamed at low concentrations of some vapor flavors. And at high concentrations of others, exibited cell death. Nitric oxide production, necessary for vessel dilation to improve blood flow, was impaired as well. These are often the same changes seen in early heart disease.

The 9 flavors (and the chemicals within) cited in the report to cause the endothelial inflammation and/or damage were:

- Mint (menthol)
- Vanilla (vanillin)
- Clove (eugenol)
- Cinnamon (cinnamaldehyde)
- Strawberry (dimethylpyrazine)
- Banana (isoamyl acetate)
- Butter (diacetyl)
- Eucalyptus/spicy cooling (eucalyptol)
- Burnt flavor (acetylpyridine)

Strawberry flavoring appeared to have the most adverse effect on the cells.

Now many other flavors were not included in this study, so its unknown how safe they may be.

For more on the study, read here.

An alternate study published last November looked at vaping flavors and their effects on heart muscle cells.

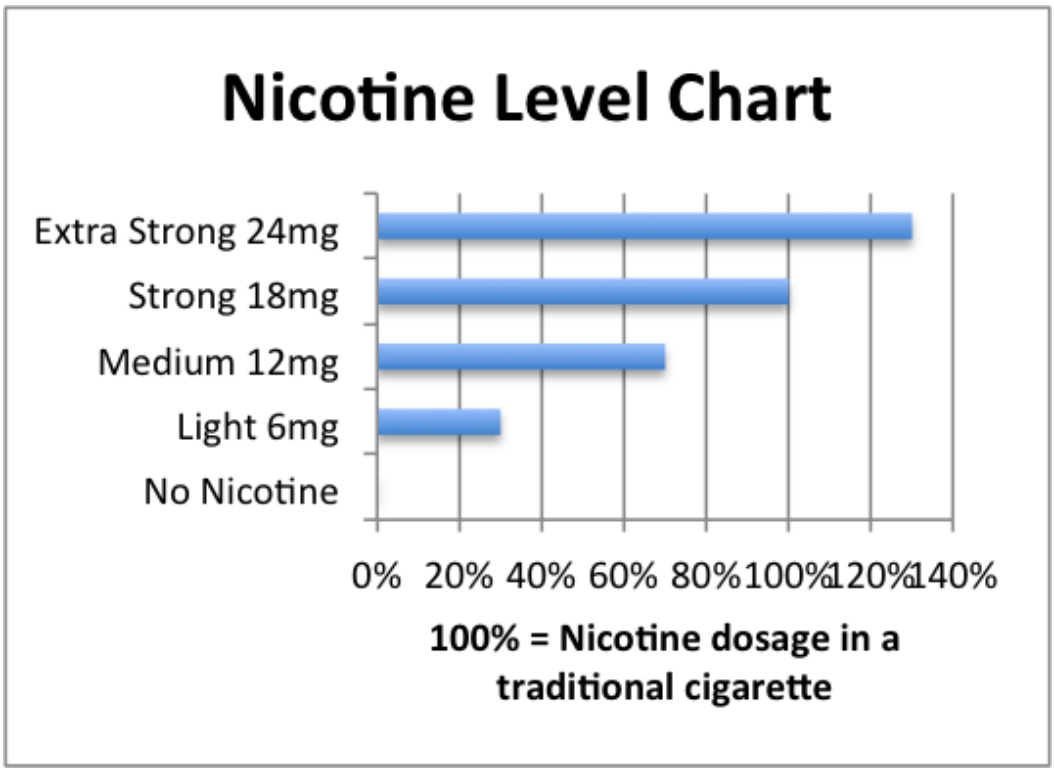
For more on this study, read here.

The moral? Just because we love the taste of something, doesn't mean its safe to inhale.

Vaping Linked to Heart Disease and Cancer

A study from New York University found the nicotine in electronic cigarettes to cause DNA damage similar to cigarette smoking.

Dr. Moon-shong Tang and his colleagues exposed mice to e-cig smoke during a three-month period, 5 days a week for three hours a day. They found these mice, compared to those breathing filtered air, to have DNA damage to cells in their bladders, lungs and hearts. The amount of nicotine inhaled was approximately 10mg/ml. That dose would be commonly consumed by many humans who vape.



They then looked at human bladder and lung cells and found tumor cells were able to grow more easily once exposed to nicotine and vaping chemicals.

Last May, researchers from Vanderbilt-Ingram Cancer Center in Nashville found e-cig smoke to increase one's risk of bladder cancer.

In 2015, the University of Minnesota identified chemicals commonly found in e-cig vapor to include:

- Formaldehyde (human carcinogen)
- Acetaldehyde (carcinogen related to alcohol drinking)
- Acrolein (highly irritating and toxic)
- Toluene (toxic) NNN, NNK (tobacco carcinogens related to nicotine)
- Metals (possible carcinogens and toxins)

Although electronic cigarette "juice" may appear safe, it could produce harmful chemicals once heated to become a vapor.

A lethal dose of nicotine for an adult ranges from 30-60 mg and varied for children (0.5-1.0 mg/kg can be a lethal dosage for adults, and 0.1 mg/kg for children). E-cigs, depending on their strengths (0 – 5.4%) could contain up to 54 mg of nicotine per cartridge (a 1.8% e -cig would contain 18mg/ml).

The topic of nicotine increasing one's vulnerability to cancer is nothing new as decades ago researchers found nicotine to affect the cilia (brush border) along the respiratory tree, preventing mucous production and a sweeping out of carcinogens trying to make their way down to the lungs.

More research needs to be performed but this recent report reminds us that exposing our delicate lung tissue and immune system to vaping chemicals may not be as safe as we think.

For more on the study read here.

Toxic metals found in vaping liquid

In February, one study reported that toxic levels of lead and other metals may leak from the heating coil element into the vapor inhaled during e-cig use.

Researchers at Johns Hopkins Bloomberg School of Public Health found these metals to include:

- lead
- nickel
- manganese
- chromium
- arsenic

We've known for some time that vaping fluid could contain chemicals that turn toxic once heated, but this study shed light on e-cig metal components causing metal leakage to the vapor making contact with delicate respiratory epithelium (lining).

Reported by Forbes, Rich Able, a medical device marketing consultant, stated the following, "the FDA does not currently test any of the most popular vaping and e-cigarette instruments being manufactured at unregulated factories in Asia that source low-grade parts, batteries, and materials for the production of these devices," suggesting that "the metal and parts composition of these devices must be stringently tested for toxic analytes and corrosive compounds."

These chemicals may act as neurotoxins, affecting our nervous system, cause tissue necrosis (cell death) and even multi-organ failure. Moreover they can affect how our immune system reacts to other chemicals as well as foreign pathogens, affecting our ability to fight other diseases.

Although studies have suggested e-cig vapor to be safer than tobacco smoke, not enough research has been done, in the relatively few years vaping has been around, looking at how heat-transformed chemicals and leaked metals affect our breathing, lungs and other organs once absorbed into the body.

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Daliah Wachs, MD, FAAFP

Category

Local News

Health Tip: Teens E-cigarette Users More Likely to Smoke: Study

consumer.healthday.com/cancer-information-5/electronic-cigarettes-970/health-tip-teens-e-cigarette-users-more-likely-to-smoke-study-734846.html

June 29, 2018

(HealthDay News) -- Students who use electronic cigarettes by the time they start ninth grade are more likely to start smoking traditional cigarettes and use other tobacco products within a year, according to a new study by the National Institutes of Health published in the *Journal of the American Medical Association*.

The study looked at 222 9th graders who had used e-cigarettes or tobacco and 2,308 students who didn't use any e-cigarettes or tobacco.

Within six months, 30.7 percent of those who had used e-cigarettes started using tobacco products, which included cigarettes, cigars or hookahs. By contrast, 8.1 percent of those who had never used an e-cigarette began using tobacco products, the study found.

BMJ Open

Is prevalence of e-cigarette and nicotine replacement therapy use among smokers associated with average cigarette consumption in England? A time-series analysis

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ABSTRACT

Objectives Many smokers use e-cigarettes and licensed nicotine replacement therapy (NRT), often in an attempt to reduce their cigarette consumption. We estimated how far changes in prevalence of e-cigarette and NRT use while smoking were accompanied by changes in cigarette consumption at the population level.

Design Repeated representative cross-sectional population surveys of adults aged 16+ years in England.

Methods We used Autoregressive Integrated Moving Average with Exogeneous Input (ARIMAX) modelling of monthly data between 2006 and 2016 from the Smoking Toolkit Study. Prevalence of e-cigarette use and NRT use in current smokers, and specifically for smoking reduction and temporary abstinence, were input variables. Mean daily cigarette consumption was the dependent variable. Analyses involved adjustment for mass media expenditure and tobacco-control policies.

Results No statistically significant associations were found between changes in use of e-cigarettes (β −0.012, 95% CI −0.026 to 0.002) or NRT (β 0.015, 95% CI −0.026 to 0.055) while smoking and daily cigarette consumption. Neither did we find clear evidence for an association between e-cigarette use (β −0.010, 95% CI −0.025 to 0.005 and β 0.011, 95%–0.027 to 0.004) or NRT use (β 0.006, 95%–0.030 to 0.043 and β 0.022, 95%–0.020 to 0.063) specifically for smoking reduction and temporary abstinence, respectively, and changes in daily cigarette consumption.

Conclusion If use of e-cigarettes and licensed NRT while smoking acted to reduce cigarette consumption in England between 2006 and 2016, the effect was likely very small at a population level.

Strengths and limitations of this study

- This is the first time series study to assess the population-level impact of the use of nicotine replacement therapy and e-cigarettes for harm reduction on cigarette consumption.
- This study uses a large representative sample of the population in England and considers both smoking reduction and temporary abstinence.
- A wide range of confounders are adjusted for including population-level interventions.
- In countries with weaker tobacco control, or stricter regulation of using products for harm reduction, different effects may be observed.
- Data are observational and so strong conclusions regarding cause and effect cannot be made.

INTRODUCTION

Randomised controlled trials have shown that use of non-tobacco nicotine-containing products (eg, nicotine replacement therapy; NRT) are efficacious for harm-reduction attempts.[1] Harm reduction is defined as any attempt to reduce the harm from smoking without an intention to quit completely, such as, the use of NRT for smoking reduction (ie, during attempts to cut down) or during periods of temporary abstinence (ie, during periods of time when one is unable to smoke).[1] Outside of the clinical setting where little behavioural support is provided, the use of NRT during attempts to cut down smoking appears to increase smoker's propensity to quit, but does not result in significantly large reductions in cigarette consumption.[2–4] Explanations for this include the lack of behavioural support and possible poor compliance with the medical regimen.[5 6]

In recent years, there has been an increase in the overall use of nicotine-containing products for harm reduction, with a growth in e-cigarettes more than offsetting a decline in the use of NRT.[7–9] Previous studies suggest that e-cigarettes which contain nicotine reduce cravings more effectively than NRT,[7 10 11] have better adherence rates[7 12] and deliver clinically significant levels of nicotine into the blood, at least for some smokers.[10 11 13] Thus, although further studies are needed it is possible that e-cigarettes may be a more

effective aid for smoking reduction than licensed nicotine products.[14 15] However, it also remains possible that e-cigarettes will not result in clinically significant reductions in cigarette intake at a population level.

The aim of this study was to assess the association between changes in prevalence of e-cigarettes and NRT with changes in mean cigarette consumption per day using a time-series approach. Time-series analysis allows us to take into account underlying trends, the effect of other tobacco-control interventions, autocorrelation (whereby data collected at points closer in time tend to be more similar), and to consider possible lag effects of the independent variable on the dependent variable.[16] Where associations are found, they cannot unequivocally establish a causal association but can be indicative, as has been the case with estimating the effect of price of cigarettes on population consumption,[17] mass-media expenditure on use of specialist stop-smoking services[18] and introduction of varenicline to the market on prevalence of use of smoking cessation medication.[19] Where associations are not found, or they go in a direction opposite to that expected, this can also be informative.

Specifically, this paper assesses the association between mean cigarette consumption per day and:

1. Current e-cigarette use among smokers for any purpose, current use specifically for smoking reduction and current use specifically for temporary abstinence.
2. Current NRT use among smokers for any purpose, current use specifically for smoking reduction and current use specifically for temporary abstinence.

Sensitivity analyses will examine the effect of focusing only on daily e-cigarette and NRT use, given previous associations between extent of non-tobacco nicotine-containing product use and the effectiveness of harm-reduction attempts.[6]

METHODS

Design

We used Autoregressive Integrated Moving Average with Exogeneous Input (ARIMAX) modelling of monthly data between 2006 and 2016 primarily from the Smoking Toolkit Study. The smoking toolkit study (STS) is a monthly survey of a representative sample of the population in England aged 16+ years.[20] This has been collecting data on smoking patterns among smokers and recent ex-smokers since November 2006. Questions on the use of e-cigarettes among all smokers were introduced in May 2011 and as aids to a quit attempt among smokers attempting to stop in July 2009. The STS involves monthly household surveys using a random location sampling design, with initial random selection of grouped output areas (containing 300 households), stratified by ACORN (sociodemographic) characteristics (https://acorn.caci.co.uk/) and region. Interviewers then choose which houses within these areas are most likely to fulfil quotas based on the probability of individuals being at home in different regions and conduct face-to-face computer-assisted interviews with one member per household. Participants from the STS appear to be representative of the population in England, having similar sociodemographic composition as other large national surveys, such as the Health Survey for England.[20]

Measures

Explanatory variables

Daily and non-daily smokers were asked the following questions:

1. Which, if any, of the following are you currently using to help you cut down the amount you smoke?
2. Do you regularly use any of the following in situations when you are not allowed to smoke?
3. Can I check, are you using any of the following either to help you stop smoking, to help you cut down or for any other reason at all?

All three questions had the following response options: nicotine gum, nicotine replacement lozenges\tablets, nicotine replacement inhaler, nicotine replacement nasal spray, nicotine patch, electronic cigarette, nicotine mouth spray, other, none.

Current e-cigarette use was derived by an 'electronic cigarette' response to any of the three questions; e-cigarette use for smoking reduction by a response to the first question; and e-cigarette use for temporary abstinence by a response to the second question.

Current NRT use was derived by an NRT product response ('nicotine gum, nicotine replacement lozenges\tablets, nicotine replacement inhaler, nicotine replacement nasal spray, nicotine patch or nicotine mouth spray') to any of the three questions; NRT use for smoking reduction by an NRT product response to the first question; and NRT use for temporary abstinence by an NRT product response to the second question.

Data were not recorded on NRT use for temporary abstinence between November 2006 and January 2007 and was imputed using prevalence data from February 2007.

Data were only available on the prevalence of use of electronic cigarettes among smokers from April 2011 although use specifically during a recent quit attempt were available from July 2009. Thus, prevalence of electronic cigarette use among smokers between July 2009 and April 2011 was estimated from data on use during a quit attempt; use of electronic cigarettes among smokers between November 2006 and June 2009 was assumed to be 0.1% of smokers based on other surveys which found their use to be very rare before 2009.[21 22]

Daily NRT and e-cigarette users were classified as those who reported that they used the product(s) at least once per day in response to the question: How many times per day on average do you use your nicotine replacement product or products? This question was introduced in July 2010. Prior to this time, prevalence of daily NRT use was assumed to be 60% of all users,[6] while e-cigarette prevalence was computed as above using prevalence during a quit attempt or 0.1%.

Outcome variables

Smokers taking part in the STS were also asked how many cigarettes they smoke on average per day. Non-daily smokers were asked how many cigarettes they smoked per week which was then converted to a daily figure.

Co-variables

In England, tobacco mass media campaigns have been run as part of a national tobacco-control programme. Spending was almost completely suspended in 2010 and then reintroduced in 2011 at a much lower level. Previous studies have shown that such cuts were associated with a decreased use of smoking cessation support.[18 23] Thus, advertising expenditure will be adjusted for using data obtained from Public Health England. Data on mass media expenditure was available monthly from May 2008, and yearly prior to this period, and so a monthly average was assumed. For a number of months, spending was effectively zero and was imputed as 0.1 to allow the analysis to run.

A number of tobacco-control policies were adjusted for. These included the move in commissioning of stop-smoking services to local authorities in April 2013,[24] introduction of a smoking ban in July 2007,[25] licensing of NRT for harm reduction in December 2009,[26] the publication of National Institute for Health and Care Excellence guidance on harm reduction in June 2013[27] and change in the minimum age of sale of cigarettes in October 2007.[28] Price of cigarettes is correlated 0.99 with time and will thereby be taken into account by use of differencing (ie, using the differences between consecutive observation rather than observations themselves) to make the series stationary.

Analysis

The analysis plan was registered on the Open Science Framework prior to data analysis (https://osf.io/6swk3/). All data were analysed in R V.3.2.4[29] using ARIMAX modelling.[16 30 31] Data were weighted prior to the analyse to match the population in England using a rim (marginal) weighting technique. This involves an iterative sequence of weighting adjustments whereby separate nationally representative target profiles are set (for gender, working status, children in the household, age, social grade and region). This process is then repeated until all variables match the specified targets.[20]

Two waves of data were collected in March 2007 and March 2013. These waves were averaged. No data were collected in December 2008. Mean cigarette consumption, NRT use and e-cigarette use during this period were calculated as an average of the month before and the month after. For a few months (May 2012, July 2012, September 2012, November 2012, January 2013, March 2013), data on electronic cigarettes and NRT use among smokers were not recorded. For these months, the average of the previous and next month was imputed.

The Granger causality test suggested that there was some evidence for the violation of the assumption of weak exogeneity (ie, Y can depend on the lagged values of X but the reverse must not be true) between the input and the output series. However, caution has been advised when using this and similar tests on data across a long time series,[32 33] and there was no theoretical reason we could identify for a bidirectional relationship between e-cigarette use and cigarette consumption. It was assumed that the association was spurious and likely removed following adjustment for other covariates.

Both unadjusted and fully adjusted models are reported which regressed onto mean cigarette consumption per day: (1) use of e-cigarettes among current smokers; (2) use of e-cigarettes for smoking reduction; (3) use of e-cigarettes for temporary abstinence; (4) use of NRT for harm reduction; (5) use of NRT for temporary abstinence and (6) use of NRT for smoking reduction. Sensitivity analyses were conducted which constrained the analysis to only those reporting daily e-cigarette and NRT use. We followed a standard ARIMAX modelling approach.[16 34] The series were first log-transformed to stabilise the variance, and if required, first differenced and seasonally differenced. The autocorrelation and partial autocorrelation functions were then examined in order to determine the seasonal and non-seasonal moving average (MA) and autoregressive terms (AR). For example, AR(1) means that the value of a series at one point in time is the sum of a fraction of the value of the series at the immediately preceding point in time and an error component; while MA(1) means that the value of a series at one point in time is a function of a fraction of the error component of the series at the immediately preceding point in time and an error component at the current point in time. To identify the most appropriate transfer function (ie, lag) for the continuous explanatory variables, the sample cross-correlation function was checked for each ARIMAX model. Coefficients can be interpreted as estimates of the percentage change in cigarette consumption for every (a) percentage increase in use of e-cigarettes and NRT, (b) percentage increase in mass media expenditure and (c) implementation of tobacco-control policies.

Bayes factors (BFs) were derived for non-significant findings using an online calculator[35] to disentangle whether there is evidence for the null hypothesis of no effect (BF <1/3rd) or the data are insensitive (BF between 1/3rd and 3). A half-normal distribution was assumed with a percentage change in the outcomes of interest for every percentage increase in the input series of 0.009% based on the effect detectable with 80% power (see sample size). Sensitivity analyses were conducted using a much larger percentage change of 0.1. This was based on a meta-analysis assessing the efficacy of non-tobacco nicotine replacement products for harm reduction which reported that 21.8% of the experimental group had reduced consumption by more than 50% at final follow-up compared with 16.5% receiving placebo.[1] We therefore assumed that a 5% change in prevalence of NRT and e-cigarettes would be associated with a 0.5% change in overall cigarette consumption.

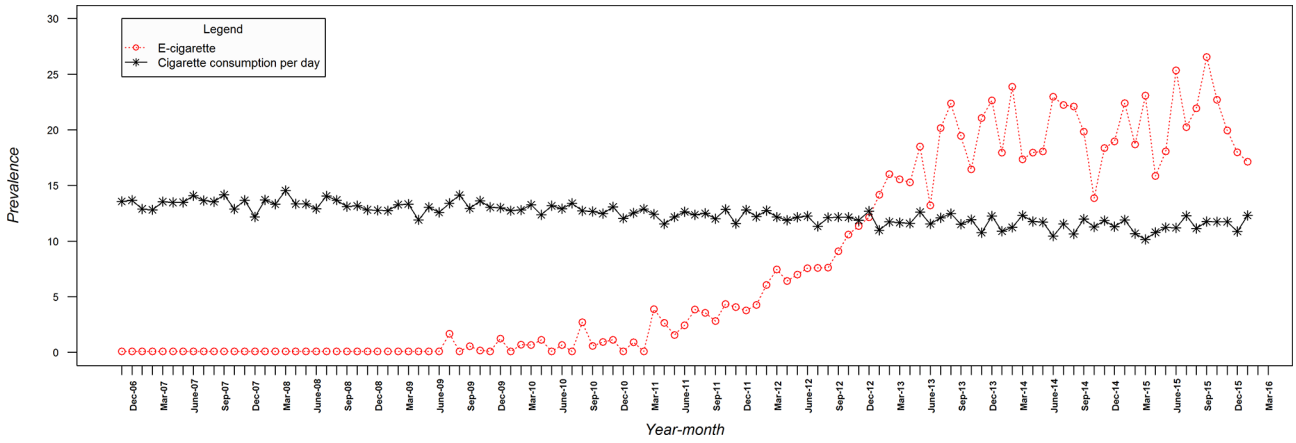

Figure 1 Monthly prevalence of cigarette consumption and e-cigarettes for harm reduction among smokers.

Strengthening the Reporting of Observational Studies in Epidemiology guidelines for the reporting of observational studies were followed throughout.[36]

Sample size

Simulation-based power analyses suggested that this study would have 80% power to detect a change in the output series of 0.009% for every 1% change in the input series, assuming 113 monthly data collection points, MA (1) autocorrelation,[37] a baseline proportion for the input series of 0.005,[9] a baseline mean (SD) for the output series of 12.3[38] and a total change over time for the input series of 30%.[38]

RESULTS

Sample characteristics

Data were collected on 199 483 adults aged 16+ years taking part in the STS who reported their smoking status between November 2006 and March 2016. Of these, 43 608 (20.8%, 95% CI 20.6 to 21.0) were current smokers. Fifty-two per cent (95% CI 52% to 53%) of the smokers were male and 60.4% (95% CI 60% to 60.1%) were in routine or manual positions or were unemployed. The average age of smokers in this study was 42.1 years (95% CI 42.0 to 42.1).

Main analysis

Figure 1 shows that cigarette consumption declined over the study period from 13.6 to 12.3 (mean 12.4, SD 0.92). This figure also shows that current use of e-cigarettes among smokers for harm reduction increased from negligible use in the last quarter of 2006 to 17.1% at the end of the study (mean 7.8%, SD 8.82). Figure 2 shows that there was also a decline in the use of NRT for harm reduction from 12.2% to 6% (mean 14.4%, SD 4.36). Online supplementary figures 1 and 2 show the changes in e-cigarette and NRT use for smoking reduction and temporary abstinence, respectively.

Tables 1, 2 and 3 show the results of the ARIMAX models assessing the association between cigarette consumption per day with (1) e-cigarette use among current smokers and NRT use for harm reduction; (2) e-cigarette and NRT use for smoking reduction and (3) e-cigarette and NRT use for temporary abstinence. The findings were inconclusive as to whether an association was present between use of e-cigarettes and NRT for any purpose and cigarette consumption.

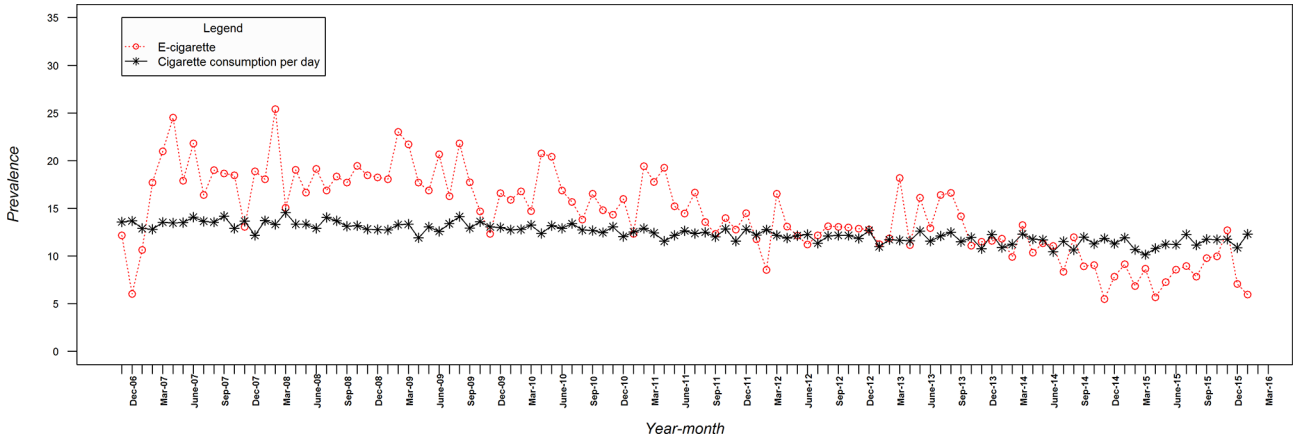

Figure 2 Monthly prevalence of cigarette consumption and nicotine replacement therapy use for harm reduction among smokers.

Table 1 Estimated percentage-point changes in mean cigarette consumption per day as a function of e-cigarette use and NRT use among smokers from November 2006 to March 2016, based on ARIMAX models

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Any current use of e- cigarettes (immediate impact)	–0.011 (–0.025 to 0.002) 0.097		–0.012 (–0.026 to 0.002) 0.091	–0.010 (–0.024 to 0.004) 0.149		–0.011 (–0.026 to 0.003) 0.130
NRT use for harm reduction (immediate impact)		0.012 (–0.028 to 0.053) 0.546	0.015 (–0.026 to 0.055) 0.475		0.003 (–0.019 to 0.025) 0.794	0.005 (–0.017 to 0.027) 0.672
Mass media expenditure (immediate impact)			<0.001 (–0.001 to 0.001) 0.984			<0.001 (–0.001 to 0.001) 0.880
	Total percentage change due to the exposure (95% CI) P values					
Smoking ban (pulse effect)			0.015 (–0.070 to 0.101) 0.724			0.013 (–0.072 to 0.099) 0.756
Increase in age-of-sale (pulse effect)			–0.041 (–0.126 to 0.044) 0.342			–0.043 (–0.128 to 0.042) 0.324
Move to local authority control (pulse effect)			–0.019 (–0.105 to 0.067) 0.662			–0.027 (–0.112 to 0.058) 0.533
Licensing for NRT for harm reduction (pulse effect)			0.021 (–0.067 to 0.110) 0.639			0.020 (–0.069 to 0.109) 0.661
NICE guidance on harm reduction (pulse effect)			–0.024 (–0.109 to 0.061) 0.578			–0.028 (–0.114 to 0.057) 0.512
Best fitting model	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}
Non-seasonal AR p value	NA	NA	NA	NA	NA	NA
Non-seasonal MA p value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Continued

Table 1 Continued

	All users of nicotine replacement		Only daily users of nicotine replacement	
	Percentage change per 1 % change in the exposure (95% CI) P values			
Seasonal AR p value	NA	NA	NA	NA
Seasonal MA p value	NA	NA	NA	NA
R^2	0.65	0.66	0.65	0.64	0.66
Bayes factor e-cigarette (0.009 (0.1))	2.44 (0.46)	2.68 (0.55)	1.95 (0.35)	2.12 (0.41)
Bayes factor NRT (0.009 (0.1))	0.77 (0.14)	0.74 (0.13)	0.69 (0.09)	0.63 (0.08)

An AR(1) means that the value of a series at one point in time is the sum of a fraction of the value of the series at the immediately preceding point in time and an error component; an MA(1) means that the value of a series at one point in time is a function of a fraction of the error component of the series at the immediately preceding point in time and an error component at the current point in time.
AR, autoregressive; ARIMAX, Autoregressive Integrated Moving Average with Exogeneous Input; MA, moving average; NA, not applicable; NICE, National Institute for Health and Care Excellence; NRT, nicotine replacement therapy.

BFs were between one-third and three when assuming a 0.009% change in cigarette consumption for every percentage change in the input series, suggesting the data are insensitive to detect very small reductions in cigarette consumption. Most BFs were less than one-third, when assuming a 0.1% change in cigarette consumption for every percentage change in the input series, suggesting evidence for the null hypothesis that NRT use and e-cigarette use among smokers has not resulted in large reductions in cigarette intake.

Sensitivity analysis

Current daily use of e-cigarettes among smokers for harm reduction increased from negligible use in the last quarter of 2006 to 11.1% at the end of the study (mean 4.5%, SD 4.91). There was also an increase in e-cigarette use specifically for temporary abstinence (from 0.1% to 8.4%; mean 3.5% SD 3.81) and smoking reduction (from 0.1% to 8.3%; mean 3.3% SD 3.64).

In contrast, there was a decline in the use of NRT for harm reduction from 7.3% to 2.9% (mean 6.5%, SD 2.35) and a decline in NRT use specifically for temporary abstinence (from 7.3% to 1.8%; mean 4.7% SD 2.29) and smoking reduction (from 6.8% to 2.6%; mean 5.8%, SD 2.46).

Tables 1, 2 and 3 also show the results of the sensitivity analyses restricted to those smokers using NRT or e-cigarettes daily. The findings were inconclusive as to whether or not an association was present between the daily use of e-cigarettes and NRT for any purpose and cigarette consumption. BFs suggested the data are insensitive to detect very small reductions in cigarette consumption, but there is evidence for the null hypothesis that NRT use and e-cigarette use among smokers have not resulted in large reductions in cigarette intake.

DISCUSSION

To our knowledge, this is the first empirical study to estimate the population association between the use of e-cigarettes and NRT among current smokers on cigarette consumption per day, using a time-series approach. There was evidence that there was no substantial association between the rise in use of e-cigarettes and decline in NRT use and changes in cigarette consumption per day.

Strengths and limitations

A strength of the study is the use of a large representative sample of the population in England, stratification of results by daily use, and the consideration of both temporary abstinence and smoking reduction. Previous studies have shown that reductions in cigarette intake are dependent on the extent of NRT use and differ as a function of the specific harm-reduction behaviour, that is, an attempt to cut down or restraining from smoking during periods of brief abstinence.[2 6]

The study had a number of limitations. First, caution should be taken when interpreting estimates of the

Table 2 Estimated percentage point changes in mean cigarette consumption per day as a function of e-cigarette use and NRT use among smokers for cutting down from November 2006 to March 2016, based on ARIMAX models

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Use of e-cigarettes for cutting down (immediate impact)	–0.010 (–0.024 to 0.005) 0.191		–0.010 (–0.025 to 0.005) 0.191	–0.008 (–0.023 to 0.006) 0.256		–0.009 (–0.024 to 0.006) 0.229
NRT use for cutting down (immediate impact)		0.002 (–0.033 to 0.037) 0.917	0.006 (–0.030 to 0.043) 0.732		–0.002 (–0.016 to 0.013) 0.825	–0.002 (–0.017 to 0.013) 0.786
Mass media expenditure (immediate impact)			<0.001 (–0.001 to 0.001) 0.885			<0.001 (–0.001 to 0.001) 0.860
	Total percentage change due to the exposure (95% CI) P values					
Smoking ban (pulse effect)			0.014 (–0.072 to 0.099) 0.755			0.012 (–0.073 to 0.097) 0.782
Increase in age-of-sale (pulse effect)			–0.043 (–0.128 to 0.042) 0.323			–0.042 (–0.127 to 0.043) 0.329
Move to local authority control (pulse effect)			–0.025 (–0.110 to 0.061) 0.571			–0.029 (–0.115 to 0.056) 0.499
Licensing for NRT for harm reduction (pulse effect)			0.018 (–0.072 to 0.108) 0.694			0.015 (–0.074 to 0.103) 0.747
NICE guidance on harm reduction (pulse effect)			–0.028 (0.058 to <0.001) 0.529			–0.027 (–0.112 to 0.059) 0.541
Best fitting model	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}	ARIMAX(0,1,1)(0,0,0)^{12}
Non-seasonal AR p values	NA	NA	NA	NA	NA	NA
Non-seasonal MA p values	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Continued

Table 2 Continued

	All users of nicotine replacement		Only daily users of nicotine replacement	
	Percentage change per 1 % change in the exposure (95% CI) P values			
Seasonal AR p values	NA	NA	NA	NA
Seasonal MA p values	NA	NA	NA	NA
R^2	0.64	0.65	0.64	0.65
Bayes factor e-cigarette (0.009 (0.1))	1.87 (0.34)	1.79 (0.32)	1.46 (0.23)	1.61 (0.27)
Bayes factor NRT (0.009 (0.1))	0.86 (0.16)	0.81 (0.15)	0.76 (0.10)	0.76 (0.10)

An AR(1) means that the value of a series at one point in time is the sum of a fraction of the value of the series at the immediately preceding point in time and an error component; an MA(1) means that the value of a series at one point in time is a function of a fraction of the error component of the series at the immediately preceding point in time and an error component at the current point in time.
AR, autoregressive; ARIMAX, Autoregressive Integrated Moving Average with Exogeneous Input; MA, moving average; NA, not applicable; NICE, National Institute for Health and Care Excellence; NRT, nicotine replacement therapy.

covariates, that is, impact of some of the tobacco-control policies, as interrupted explanatory variables with short time-periods prior to their introduction in ARIMAX-type models often give inaccurate estimates of the SEs.[28] Thus, although the increase in age-of-sale has been previously associated with a decline in smoking prevalence,[24] the short lead-in period may have masked any true association.[27] Second, the STS required participants to recall their average daily cigarette intake which is likely to have been somewhat inaccurate. Third, the findings may not generalise to other countries. England has a strong tobacco-control climate and relatively liberal attitude towards harm reduction and e-cigarette use. In countries with weaker tobacco control, or stricter regulation of using products for harm reduction, different effects may be observed. Fourth, although we are unaware of any other major population-level interventions or other events during the study period, we cannot rule out residual confounding. Fifth, participants were not asked questions regarding potentially important features of the e-cigarette (eg, nicotine content, flavouring, device type) or frequency and duration of use. It is likely that these factors may play a role in their effectiveness and should be considered in future studies.[15 39] Finally, as data were not collected on current e-cigarette use prior to April 2011, prevalence was estimated from use during a quit attempt or from previous studies.[21 22] This was necessary to ensure that the time series was long enough for an ARIMAX analysis and is an appropriate approach when data are missing completely at random.[16 40] As prevalence was low and relatively stable during this period, it is unlikely to have impacted on the reported results.

Implications of findings

The findings are in line with previous studies which show that reductions in cigarette consumption observed in clinical trials of NRT for harm reduction do not appear to generalise beyond the closely controlled trial setting.[1 2] It was hypothesised that e-cigarettes may be associated with population mean cigarette intake given that they reduce cravings more effectively than NRT,[7 10 11] have better adherence rates[7 12] and deliver clinically significant levels of nicotine into the blood.[10 11 11 13]

The finding that e-cigarette use was not associated with reductions in consumption at a population level is consistent with previous real-world studies at the individual level. These have found little change in consumption among ever e-cigarette users[41] and that only a minority of daily users manage to reduce by a substantial amount which is not likely to be detected at a population level.[42] The findings of a recent pragmatic controlled trial, whereby 60% of participants using e-cigarettes had managed to reduce by over 50% by 6 months' follow-up, suggests that the lack of effectiveness at a population level may not be the consequence of poor behavioural support.[11]

Of course, it remains plausible that e-cigarettes may still be associated with a small effect on mean population cigarette consumption,[15] and that a reduction in harm from

Table 3 Estimated percentage point changes in mean cigarette consumption per day as a function of e-cigarette use and NRT use among smokers for temporary abstinence from November 2006 to March 2016, based on ARIMAX models

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Use of e-cigarettes for temporary abstinence (immediate impact)	–0.010 (–0.024 to 0.005) 0.150		–0.011 (–0.027 to 0.004) 0.146	–0.010 (–0.024 to 0.004) 0.159		–0.011 (–0.026 to 0.003) 0.135
NRT use for temporary abstinence (immediate impact)		0.023 (–0.016 to 0.062) 0.241	0.022 (–0.020 to 0.063) 0.303		0.006 (–0.015 to 0.028) 0.563	0.006 (–0.016 to 0.028) 0.585
Mass media expenditure (immediate impact)			<0.001 (–0.001 to 0.001) 0.873			<0.001 (–0.001 to 0.001) 0.942
	Total percentage change due to the exposure (95% CI) P values					
Smoking ban (pulse effect)			0.017 (–0.069 to 0.103) 0.696			0.014 (–0.071 to 0.099) 0.750
Increase in age-of-sale (pulse effect)			–0.036 (–0.122 to 0.050) 0.415			–0.040 (–0.125 to 0.044) 0.350
Move to local authority control (pulse effect)			–0.016 (–0.102 to 0.071) 0.721			–0.026 (–0.111 to 0.060) 0.556
Licensing for NRT for harm reduction (pulse effect)			0.023 (–0.067 to 0.114) 0.615			0.019 (–0.070 to 0.108) 0.670
NICE guidance on harm reduction (pulse effect)			–0.021 (–0.106 to 0.065) 0.638			–0.030 (–0.116 to 0.055) 0.483
Best fitting model	ARIMAX(0,1,1)(0,0,0)[12]	ARIMAX(0,1,1)(0,0,0)[12]	ARIMAX(0,1,1)(0,0,0)[12]	ARIMAX(0,1,1)(0,0,0)[12]	ARIMAX(0,1,1)(0,0,0)[12]	ARIMAX(0,1,1)(0,0,0)[12]
Non-seasonal AR P values	NA	NA	NA	NA	NA	NA

Continued

Table 3 Continued

	All users of nicotine replacement			Only daily users of nicotine replacement		
	Percentage change per 1 % change in the exposure (95% CI) P values					
Non-seasonal MA P values	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Seasonal AR P values	NA	NA	NA	NA	NA	NA
Seasonal MA P values	NA	NA	NA	NA	NA	NA
R^2	0.65	0.65	0.65	0.65	0.64	0.65
Bayes factor e-cigarette (0.009 (0.1))	1.01 (0.59)		1.94 (0.38)	1.97 (0.35)		2.15 (0.41)
Bayes factor NRT (0.009 (0.1))		0.15 (0.02)	0.69 (0.11)		1.05 (0.18)	0.61 (0.08)

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AR, autoregressive; ARIMAX, Autoregressive Integrated Moving Average with Exogeneous Input; MA, moving average; NA, not applicable; NICE, National Institute for Health and Care Excellence; NRT, nicotine replacement therapy.

smoking at a population level could be seen through their promotion of quit attempts[37] or by reducing smoke intake from each cigarette.[5]

Conclusion

In conclusion, the increased prevalence of e-cigarettes use among smokers in England has not been associated with a detectable change in cigarette consumption per day. The decline in the use of NRT has also not been associated with a change in mean cigarette intake. If use of e-cigarettes and licensed NRT while smoking act to reduce cigarette consumption, the effect is probably small.

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Early assessment of China's 2015 tobacco tax increase

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Abstract In 2015, the Chinese government raised tobacco excise tax for the first time since 2009. Changing from previous practice, the State Tobacco Monopoly Administration raised its cigarette prices at the same time. We assessed the early impact of the 2015 tax increase on cigarette prices, sales volumes, tax revenue generation and the potential effect on prevalence of smoking in China. Between 2014 and 2016, the retail price of cigarettes increased on average by 11%, with the cheapest category of cigarette brands increasing by 20%. The average proportion of tax in the price of cigarettes rose from 51.7% to 55.7%. Annual cigarette sales decreased by 7.8%, from 127 to 117 billion packs. The increase in cigarette prices could be associated with a 0.2% to 0.6% decrease in the proportion of adults smoking, representing between 2.2 and 6.5 million fewer smokers. Tax revenues from cigarettes increased by 14%, from 740 to 842 billion Chinese yuan between 2014 and 2016, reflecting an extra 101 billion Chinese yuan in tax revenues for the government. The 2015 tax increase shows that tobacco taxation can provide measurable benefits to both public health and finance in China. The experience also highlights the potential for tobacco taxation to contribute to China's broader development targets, including the sustainable development goals and Healthy China 2030. Looking forward, this link to development can be facilitated through multisectoral research and dialogue to develop consistent cross-sectoral objectives for tobacco tax policy design and implementation.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

In China, tobacco use is contributing to the increase in noncommunicable diseases.[1] More than 1 million Chinese adults die annually from tobacco use and this number is estimated to increase in coming years.[2,3] In 2012, the United Nations (UN) addressed heightened concerns about the impact of noncommunicable diseases in a High-Level Meeting of the UN General Assembly. The Declaration from this meeting notes the "increased burden that noncommunicable diseases impose through impoverishment from long-term treatment costs, and from productivity losses that threaten household incomes and the economies of Member States."[4] Indeed, diseases caused by smoking account for around 3% of health expenditures in China, while out-of-pocket medical expenditures, due to smoking, impoverish more than 10 million Chinese households each year.[5,6]

In 2015, the UN adopted *Transforming our world: the 2030 agenda for sustainable development*,[7] which includes 17 goals that countries have agreed to achieve. Sustainable development goal (SDG) 3, that is, "ensure healthy lives and promoting well-being for all ages", includes target 3.4 to reduce by one third premature mortality from noncommunicable diseases by 2030.[7]

SDG 3 also includes target 3.a to strengthen country implementation of the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC).[7,8] China was an early adopter of the FCTC having ratified the Treaty in 2005. Since ratification, tobacco control efforts in China have accelerated with interventions including tighter controls on tobacco marketing, improved health warnings and bans on smoking in public places in several cities.

Tobacco taxation is a cornerstone of global tobacco control efforts, with Article 6 of the FCTC recognizing tax as an important and effective means of reducing the demand for tobacco. Taxation is recognized to be the single most effective tobacco control measure available and the guidelines for Article 6 implementation emphasizes that any comprehensive tobacco control strategy should include taxation.[8,9]

In 2015, China introduced its fourth major national tobacco tax reform since 1994. Many other large developing countries like Brazil, the Philippines, South Africa and Ukraine have raised tobacco taxes to help meet tobacco control objectives.[10] In Brazil, higher tobacco taxes contributed to almost half of the decrease in the proportion of adults smoking, from 34.4% in 1989 to 14.7% in 2013.[11,12] Similarly, in the Philippines, the so-called sin-tax reforms that began in 2012 was associated with a decrease in the proportion of adults smoking, from 27.9% in 2009 to 22.5% in 2015.[13]

Retrospective studies have shown the importance of tobacco taxation to public health outcomes. In the United States of America, for example, a study found that a 10% increase in cigarette taxes would decrease the number of deaths from respiratory cancers by 1.5%.[14] The French government has increased cigarette taxes substantially from the mid-1990s, with cigarette prices tripling in real terms by 2005. Among French males, rates of adult lung cancer deaths fell by 50% over the same period.[15,16]

Here we assess the immediate impact of the 2015 Chinese tobacco tax increase on cigarette prices, sales volumes and tax revenues across the different price categories of China's cigarette market. The study also explores the potential impact on smoking prevalence and considers the way forward for tax policy design in China.

Tax reform and cigarette pricing

Table 1 shows the excise system for cigarettes in China, before and after the tax increase in May 2015. The tax increase occurred at the wholesale level, with a specific excise of ¥ 0.10/pack being introduced together with a 6% increase in the existing *ad valorem* tax. Other indirect taxes on cigarettes, which remained unchanged, include value added tax (VAT) at 17%; an urban maintenance and construction tax and education surcharge (known as the C&E tax) of 12% applied on excise and VAT revenue; and a tobacco leaf

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Table 1. **Cigarette classification and excise tax structure in China, 2015**

Level, type of excise	Producer price range, ¥/pack[a]	Tax	
		Before 10 May 2015	From 10 May 2015
Producer			
Specific for all classes	> 0	0.06 ¥ /pack	0.06 ¥/pack
Ad valorem tax[b]			
Class I	> 10	56%	56%
Class II	7–10	56%	56%
Class III	3–7	36%	36%
Class IV	1.65–3	36%	36%
Class V	< 1.65	36%	36%
Wholesale			
Specific for all classes	> 0	No tax	0.10 ¥ pack
Ad valorem tax for all classes[b]	> 0	5%	11%

¥: yuan.
[a] One cigarette pack contains 20 sticks.
[b] The *ad valorem* excise rates are applied to the respective producer and wholesale price of each class.
Note: The conversion rate in 2016 was 1 United States dollar to ¥ 6.64.

tax of 20% on the value of leaf production. The definition of total tax on cigarettes in this article includes excise and these other indirect taxes, but excludes China's enterprise income tax. This exclusion is to be consistent with WHO's practice of excluding corporate income tax from the measure of taxes faced by the consumer.[10]

The 2015 tobacco tax increase coincided with an announcement from the State Tobacco Monopoly Administration that the wholesale price of all cigarette brands will increase by 6%. The monopoly is a state-owned monopoly that controls many aspects of China's tobacco industry, including the price and profit margins of cigarette producers, wholesalers and independent retailers. The monopoly, therefore, plays a pivotal role in determining how any tax increase is transmitted to the consumer via changes in price. The announcement was an important change from previous practice, because the monopoly did not increase cigarette prices following the last tobacco tax increase in 2009.[17,18] Thus, the 2015 tax reform was associated with some of new the tax burden being passed along to consumers. In addition, the monopoly directed its provincial branches to set retail prices to retain retail margins of at least 10% and they circulated a nationwide bulletin listing the advised retail price of all cigarettes.[19]

Economic theory suggests that a monopolist will tend to increase retail prices by more than the tax increase, so-called over-shift.[20] Since 2010, however, the monopoly has been implementing an optimization marketing strategy, requiring its cigarette manufacturers to focus on key brands that can compete with international brands, while maintaining cheap offerings in the market. This strategy serves to encourage smoking by poor people and uptake among new smokers. The monopoly has therefore increased the price of individual brands very infrequently, which in turn has contributed to an increase in cigarette affordability and consumption over time.[21] Thus, over-shifting of taxes may not be consistent with the monopoly's strategy, particularly with respect to the availability of cheap cigarettes.

Early outcome assessment

We used the WHO Tobacco Tax Simulation model to assess the impact of China's 2015 tax increase by each price category.[22,23] The model is originally a forecasting tool, but here we populated the model with actual price and sales volume data for the years 2014, 2015 and 2016. We obtained this data from the tobacco monopoly's annual bulletins.[24] One advantage of this model is that it details tax and price changes at different levels along the supply-chain, namely producers, wholesalers and retailers. This is relevant, because the government levies different taxes on these agents and applies a two-tiered excise system on producers.

The monopoly produces around 89 brand families with each of these families offering multiple variations in terms of price, packaging and quality. In 2015, there were some 870 different brands on the market, with retail prices ranging from 2.5–100.0 Chinese yuan (¥) per pack (equivalent to 0.4–16.1 United States dollars, US$). The monopoly categorizes the brands into five fixed price categories, from the most expensive brands in class I to the cheapest brands in class V, based on their producer price, known in China as the allocation price (Table 1).

We selected five brands to be representative of each price category with these brands having a large market share within their respective class. Since class I has a wide retail price span, we divided class I in to (A) and (B), where I(A) spans prices above ¥ 43/pack. To calculate the tax yield (i.e. tax per pack) and price in each class, we entered the allocation, wholesale and retail prices of these 6 brands into the tobacco tax simulation model. We calculated weighted average tax yields and prices for the entire market, using the market share of each class on a sales volume basis.

From the monopoly records, we obtained the total tax revenues for the entire cigarette market in 2014, 2015, and 2016.[24,25] However, as tax revenues by class were not available, we estimated the tax revenues for each class from the tobacco tax simulation model, then re-scaled them to match the monopoly's aggregate records in each year. Note the tax revenues predicted by the model in this manner were within 5% of the tax revenues reported by the monopoly. Therefore, any corrections were minor.

Cigarette consumption

In China, retail sales are a good indicator of cigarette consumption, because the domestic illicit market is small.[26] However, other factors can confound our ability to test the sensitivity of consumption to the 2015 tax increase. For example, the timeframe coincides with bans on smoking in public places in Beijing and several other cities, slower economic growth compared to earlier decades, as well as the residual effect of China's anti-extravagance campaign.[26] Also household survey data is lacking to quantify any impact on the proportion of smokers among China's population after the 2015 tax increase. Consequently, this study does not attempt to measure the elasticity of demand for cigarettes.

Instead, we used evidence from the literature to explore the potential impact of the 2015 tax increase on smoking. For example, recent studies have found that the price elasticity of demand for cigarettes in China is around –0.5.[27,28] This is similar to estimates from other developing countries, meaning that a 10% increase in

the price of cigarettes will reduce cigarette consumption by 5%.[29] This price elasticity reflects a combination of conditional demand, i.e. the amount consumed by smokers and number of people smoking. Evidence shows that about half of the reduction in cigarettes sales due to price increase is because people quit smoking and the remainder is a decrease in the amount of cigarettes consumed by continuing smokers.[29] Hence, the price prevalence elasticity of demand in developing countries is expected to be about −0.25.

Several studies have modelled the expected impact of cigarette tax increases by applying price prevalence elasticities of −0.1, −0.2 and −0.3 for high-, middle- and low-income countries respectively.[23,30,31] In this paper, we explore the potential impact of the 2015 tax increase on smoking prevalence by applying an elasticity range of between −0.1 and −0.3. That is, a 10% increase in the price of cigarettes will reduce smoking prevalence by 1–3% under the caveat that cigarettes do not become more affordable over time.

Early findings

Cigarette prices

The tax increase occurred at the wholesale level of the supply-chain and coincided with the monopoly's announcement that the wholesale price of all cigarettes would increase by 6%. This increase in the wholesale price of cigarettes matches the change in the *ad valorem* excise rate from 5% to 11%, indicating that the new specific rate of ¥ 0.1/pack was absorbed into industry wholesale margins, rather than being passed along to the consumer. Note the weighted average wholesale price increases by more than 6% (Table 2), reflecting a change in the composition (i.e. market share) of cigarette sales by class over time.

The impact of the tax increase on cigarette retail price varied across the classes, where the retail price of the cheapest class V brands increased by 20% (from ¥ 2.5 to ¥ 3.0) in nominal terms (Table 2). The increase for class V brands partly reflects the monopoly's notice that retail margins should be at least 10% for all brands and so the increase in class V brand's retail price of ¥ 0.5/pack included an increase in the retailers' profit margin of ¥ 0.2/pack. We interpret this as an incentive for retailers to continue stocking cheaper brands in support of the monopoly's optimization strategy. That is, cheaper brands are not as profitable as premium brands for retailers to stock, but the monopoly's strategy includes the continued availability of cheap brands.

Mid-priced class III brands account for almost half of the market and the retail price of these key brands increased by 5% (from ¥ 9.5 to ¥ 10.0 in nominal terms; Table 2). The price gap between class III and more expensive brands widened marginally. In contrast, the price gap between class III and cheaper class brands narrowed, though not by as much as would have been the case, had the new specific excise of ¥ 0.10/pack also been passed-through, that is included in the price increase. Overall, the average retail price of cigarettes increased by 11% in nominal terms (from ¥ 11.6 to ¥ 12.8), or by 7% after accounting for inflation.

Production and sales

Table 3 shows the aggregate market outcomes, including the reported production and sales volumes by class, and total cigarette tax revenues as reported by the monopoly, with the class breakdown of revenues being estimated by the WHO tobacco tax simulation model. The monopoly reported that annual cigarette retail sales volumes decreased by 8%, from 127 to 117 billion packs between 2014 and 2016, representing 10 billion fewer packs sold annually. Most of the decrease occurred in 2016, with this being the first full calendar year after the May 2015 tax increase. The decreases in both 2015 and 2016 constitute the first annual contractions in demand since 2001.[24]

Fig. 1 shows the pattern of cigarette production over the past decade, with the rapid growth in mid and high-priced brands reflecting the monopoly's optimization strategy. Between 2014 and 2016, the volume of class I and II cigarettes continued to expand at a modest pace, while other classes decreased. The sales of low-priced class III to V brands decreased the most, suggesting it was smokers from lower socioeconomic groups that reduced or quit smoking the most. However, it is difficult to fully assess the impact even with this disaggregated data, because the changes by class will reflect a mix of consumer switching between classes, reduced conditional demand and reduced smoking prevalence.

Table 2. **Cigarette pack prices and tax yields, China, 2014–2016**

Variable	Cigarette class[a]						Weighted average
	I(A)	I(B)	II	III	IV	V	
Average wholesale price, ¥/pack							
2014	36.0	20.6	11.6	8.3	4.5	2.3	10.3
2015	38.2	21.8	12.3	8.8	4.8	2.4	11.2
2016	38.2	21.8	12.3	8.8	4.8	2.4	11.2
Change (%)	2.2 (6)	1.2 (6)	0.7 (6)	0.5 (6)	0.3 (6)	0.1 (6)	0.9 (9)
Average retail price, ¥/pack							
2014	43.0	23.0	13.0	9.5	5.0	2.5	11.6
2015	45.0	25.0	14.0	10.0	5.5	3.0	12.8
2016	45.0	25.0	14.0	10.0	5.5	3.0	12.8
Change (%)	2.0 (5)	2.0 (9)	1.0 (8)	0.5 (5)	0.5 (10)	0.5 (20)	1.2 (11)
Average excise tax, ¥/pack							
2014	13.5	8.1	4.8	2.4	1.3	0.7	3.6
2015	15.6	9.4	5.6	3.0	1.7	1.0	4.4
2016	15.6	9.4	5.6	3.0	1.7	1.0	4.4
Change (%)	2.1 (16)	1.3 (16)	0.8 (16)	0.6 (24)	0.4 (27)	0.2 (31)	0.8 (24)
Average total tax,[b] ¥/pack							
2014	22.2	13.0	7.6	4.3	2.4	1.4	6.0
2015	24.9	14.7	8.6	5.0	2.9	1.7	7.1
2016	24.9	14.7	8.6	5.0	2.9	1.7	7.2
Change (%)	2.7 (12)	1.8 (13)	1.0 (13)	0.7 (17)	0.5 (20)	0.3 (25)	1.2 (19)

¥: yuan.

[a] Classification according to the State Tobacco Monopoly Administration. Class I has a wide retail price span, so we divided class I in to (A) and (B), where I(A) spans retail prices above 43 ¥ per pack. However, given that I(A) has a very small market share, we don't address this category in detail in this paper.

[b] Total tax includes excise and other indirect taxes on consumption, but excludes enterprise income tax.

Notes: One cigarette pack contains 20 sticks. The conversion rate in 2016 was 1 United States dollars to ¥ 6.64.

Table 3. **Annual production, retail sales and tax revenues of cigarettes, China 2014–2016**

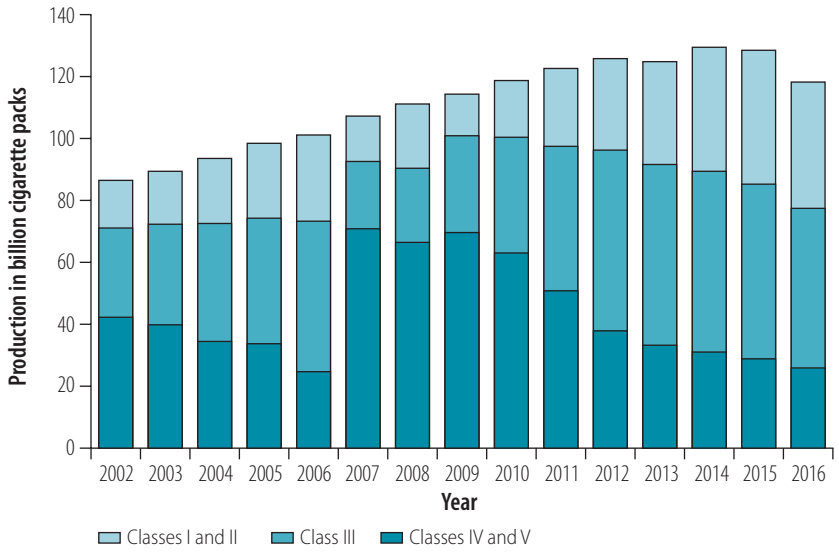
Variable	Cigarette class						Total market
	I(A)	I(B)	II	III	IV	V	
Production volume, billion packs							
2014	2	24	13	58	24	8	129
2015	2	25	15	56	22	7	128
2016	2	23	15	52	20	6	118
Change (%)	0 (–9)	–1 (–4)	2 (14)	–6 (–11)	–4 (–16)	–2 (–22)	–11 (–9)
Retail sales volume, billion packs							
2014	2	24	13	57	23	8	127
2015	2	25	15	55	21	7	124
2016	2	23	15	52	20	6	117
Change (%)	0 (–8)	–1 (–3)	2 (15)	–6 (–10)	–4 (–15)	–2 (–21)	–10 (–8)
Total tax revenue, billion ¥							
2014	41	297	98	240	54	11	740
2015	44	345	120	262	58	11	840
2016	44	338	132	260	57	11	842
Change (%)	3 (7)	41 (14)	34 (35)	21 (9)	3 (5)	0 (2)	101 (14)

¥: yuan.

Notes: One cigarette pack contains 20 sticks. Total tax revenues include excise and other indirect taxes on consumption, but exclude enterprise income tax. The conversion rate in 2016 was 1 US$ to ¥ 6.64.

Data source: State Tobacco Monopoly Administration.[24,25]

Fig. 1. **Annual cigarette production, China 2002–2016**



Notes: Class I and II represent cigarette packs in the producer price range of > 7 yuan (¥)/pack, class III represents cigarette packs in the producer price range of 3–7 ¥/pack, and class IV and V represent cigarette packs in the producer price range of < 3 ¥/pack. The State Tobacco Monopoly Administration adjusted the price classification of cigarettes in 2007, leading to the unusual change in the proportion of classes.

Data source: State Tobacco Monopoly Administration.[24]

Tax incidence and revenue

Table 4 shows the tax incidence, that is, the burden of tax faced by consumers. Tax incidence is measured as the proportion of tax in the retail price of each class. The tax increase did not change the fundamental characteristics of tax incidence on cigarettes, with mid-price class III brands still recording the lowest tax incidence, due to being the highest-priced class included under the lower *ad valorem* tax rate of 36% at the producer level. Overall, the average total tax incidence rose from 51.7% to 55.7%.

Tax revenue from cigarettes reported by the monopoly amounted to ¥ 842 billion (US$ 127 billion) in 2016, representing almost 6.5% of fiscal revenue in China. Excise revenue from cigarettes amounted to about ¥ 520 billion, or around 62% of total cigarette tax revenue. Total tax revenues from cigarettes increased by 14%, from ¥ 740 to ¥ 842 billion between 2014 and 2016, reflecting an extra 101 billion yuan (US$ 15 billion) in tax revenues for the government. After accounting for inflation of around 3.5% over this period, cigarette tax revenues increased by 10% in real terms between 2014 and 2016.

Smoking prevalence

The Global Adult Tobacco Survey found that 27.7% of China's adult population were smokers in 2015, representing about 318 million smokers.[10] Assuming a price prevalence elasticity of –0.1 to–0.3 and using our estimated 7% of inflation-adjusted increase in cigarette prices, we predict that the reduction in the proportion of smokers could be between 0.2% and 0.6%. While this decrease may seem relatively modest, it would correspond to between 2.2 and 6.5 million fewer smokers. Thus, this tax increase would potentially make a measurable contribution to tobacco control efforts to reduce the number of smokers both in China and globally.

However, it is important to recognize that the single tax increase may not have such a significant or lasting impact on smoking prevalence in China. First, public expectations that cigarette prices will continue to increase may encourage more people to quit smoking, especially in countries where governments regularly increase tobacco taxes.[32] However, taxes and prices in China have not changed for at least six-years before 2015, and therefore it seems unlikely that the single increase will have altered Chinese smokers' expectations about future tax increases. Second, cigarettes in China remain very affordable, and will become more so over time due to continued growth in people's incomes. Thus, the Chinese government may need to continue raising taxes and prices on cigarettes regularly to fully secure the estimated impact on smoking prevalence.

Next steps

To confirm our estimated reduction in smoking prevalence due to the 2015 tax increase, field research is needed in China.

The Chinese government should raise tobacco taxes more significantly over the coming decade to pursue the country's development objectives. In

Table 4. **Changes in excise and total tax incidence per cigarette pack between 2014 and 2016, China**

Tax	Tax incidence, %, by cigarette class[a]						Weighted average, %
	I(A)	I(B)	II	III	IV	V	
Excise							
2014	31.4	35.4	37.2	25.1	26.4	29.8	30.8
2015	34.7	37.6	39.9	29.5	30.4	32.4	34.4
2016	34.7	37.6	39.9	29.5	30.4	32.4	34.5
Change	3.4	2.3	2.8	4.5	4.1	2.6	3.7
Total							
2014	51.7	56.4	58.7	45.5	48.0	54.0	51.7
2015	55.4	58.8	61.7	50.4	52.2	56.0	55.6
2016	55.4	58.9	61.8	50.4	52.4	56.2	55.7
Change	3.8	2.5	3.0	4.9	4.4	2.2	4.0

¥: yuan.

[a] Classification according to the State Tobacco Monopoly Administration. Class I has a wide retail price span, so we divided class I in to (A) and (B), where I(A) spans retail prices above 43 ¥ per pack. However, given that (A) has a very small market share, we don't address this category in detail in this paper.

Notes: One cigarette pack contains 20 sticks. Total tax includes excise and other indirect taxes on consumption, but excludes enterprise income tax. The conversion rate in 2016 was 1 United States dollar to ¥ 6.64.

October 2016, President Xi Jinping announced the national strategy Healthy China 2030. The strategy sets several ambitious targets including to reduce smoking prevalence to 20% by 2030.[33] To successfully achieve this target, policymakers will need to implement a range of tobacco control policies. Evidence shows that taxation is the single most effective tobacco control measure and thus, higher tobacco taxes will be required to help achieve the Healthy China 2030 strategy.[33] This link to broader development objectives in the SDGs and Healthy China 2030 can be facilitated through multisectoral research and dialogue, to develop consistent cross-sectoral objectives for tobacco tax policy.

In many countries, tobacco taxation is underutilized as a tobacco control measure.[29] This is often due to industry interference in the policy-making process. In China, greater emphasis on health sector objectives in tobacco tax policy design could help against interference. Several other countries, such as the Philippines and Thailand, have also taken specific measures under Article 5.3 of the FCTC to protect policy-making from industry interference. The earmarking of some tobacco tax revenues to public health programmes could be another way to maximize benefits to the health sector, while also strengthening public support for further tax increases.[8,34]

Finally, China's 2015 tax increase has highlighted the monopoly's ability to under-shift taxes and to maintain a wide price gap among brands to support its long-term optimization strategy of promoting key mid- and high-price brands, while maintaining cheap offerings in the market. In particular, the availability of very cheap brands continues to pose a major challenge to public health, as it encourages smoking among young and poor people. The government may therefore need to develop tax policies tailored at raising the price of these cheap brands. Such policies could include significantly raising the specific rate, removing the *ad valorem* tiers at the producer level and/or implementing high minimum prices.

Conclusion

Achieving the SDGs will require integrated, multisectoral approaches. Tobacco taxation is an example of such an approach, with progress needing to be underpinned by greater policy coherence between the government's health and finance sectors. Indeed, it is well-documented that tobacco taxation policies contribute to improved health outcomes and better public finances, via reduced tobacco use yet increased tax revenue.[29] China's 2015 tobacco tax reform provides yet another practical demonstration of these dual benefits. ■

Competing interests: None declared.

ملخص

تقييم أولي لزيادة الضريبة المفروضة على التبغ عام 2015 في الصين

في عام 2015، قامت الحكومة الصينية برفع الضريبة غير المباشرة على التبغ للمرة الأولى منذ عام 2009. وتحولاً عن الممارسة السابقة فقد قامت إدارة حصر التبغ الوطنية برفع أسعار السجائر في نفس الوقت. وقد قمنا بتقييم التأثير المبكر للزيادة الضريبية لعام 2015 على أسعار السجائر وحجم المبيعات وإدرار إيرادات الضرائب والتأثير المحتمل لانتشار التدخين في الصين. وقد ارتفع سعر البيع بالتجزئة للسجائر بمتوسط ٪11 ما بين عامي 2014 و2016، مع ارتفاع أسعار أرخص الأصناف من ماركات السجائر بنسبة ٪20. وارتفع متوسط نسبة الضريبة في سعر السجائر من ٪51.7 إلى ٪55.7. وانخفضت مبيعات السجائر السنوية بنسبة ٪7.8 وذلك من 127 إلى 117 مليار علبة سجائر. ويمكن أن يرتبط الارتفاع في أسعار السجائر بالانخفاض بنسبة ٪0.2 إلى ٪0.6 في نسبة تدخين البالغين، مما يمثل انخفاض بمعدل ما بين 2.2 و6.5 مليون في أعداد المدخنين. وقد ارتفعت إيرادات الضرائب من السجائر بنسبة ٪14 وذلك من 740 مليار يوان صيني إلى 842 مليار يوان صيني ما بين عامي 2014 و2016، وهو ما يعادل 101 مليار يوان صيني إضافي في إيرادات الضرائب الحكومية. وتوضح زيادة الضريبة في عام 2015 الدليل على أنه من شأن فرض الضرائب على التبغ أن يقدم فوائد ملموسة لكل من الصحة العامة والتمويل في الصين. وتسلط التجربة كذلك الضوء على إمكانية إسهام الضرائب المفروضة على التبغ في تحقيق أهداف التنمية الأوسع نطاقاً في الصين، بما يشمل أهداف التنمية المستدامة وهدف الحصول على صين بصحة جيدة عام 2030. وبالتطلع للمستقبل سنجد أنه من الممكن تيسير هذه الصلة بالتنمية من خلال البحوث متعددة القطاعات والحوار لتطوير أهداف متناسقة ومشتركة بين عدة قطاعات لتصميم سياسة ضريبة التبغ وتنفيذها

摘要

关于中国 2015 年上调烟草税的早期评估

2015 年，中国政府自 2009 年以来首次上调烟草消费税。与 2009 年卷烟消费税调整不同的是，国家烟草专卖局此次同时提高了卷烟价格。我们评估了 2015 年税收上调对卷烟价格、销量、税收收入的早期影响以及对中国吸烟流行率的潜在影响。2014 年至 2016 年，卷烟零售价格平均上涨了 11%，最便宜的卷烟品类的价格上涨了 20%；税收占零售价格的比重平均从 51.7% 增加至 55.7%；年度卷烟销量从 1270 亿包下降至 1170 亿包，降幅为 7.8%；卷烟价格上涨预计使得成人吸烟率下降 0.2% 至 0.6%，这意味着吸烟者人数减少 220 万至 650 万。2014 至 2016 年，烟草税收收入从 7400 亿人民币增加至 8420 亿人民币，涨幅为 14%。对政府而言，这相当于增加约 1010 亿人民币的额外税收收入。中国 2015 年上调烟草税的举措证明提高烟草税是对公众健康和政府收入均有益处的“双赢”策略。这次税改同时也证明烟草税 具备促进中国实现更广阔的发展目标的潜力，包括可持续发展目标和“健康中国 2030”规划纲要的目标。展望未来，可通过加强跨学科研究和围绕跨部门共同目标的对话来完善中国烟草税的制度设计，以促进可持续发展目标的实现。

Résumé

Première évaluation de la hausse de la fiscalité sur le tabac opérée en Chine en 2015

En 2015, le gouvernement chinois a augmenté la fiscalité sur le tabac pour la première fois depuis 2009. Contrairement aux pratiques passées, l'Administration du monopole d'État sur le tabac a décidé d'augmenter en même temps les prix des cigarettes. Nous avons évalué les premiers impacts de la hausse de 2015 des taxes sur le tabac, les volumes vendus, les recettes fiscales qui en ont découlé et l'effet potentiel de cette mesure sur la prévalence du tabagisme en Chine. Entre 2014 et 2016, le prix de vente au détail des cigarettes a augmenté de 11% en moyenne, avec une augmentation de 20% pour les marques les moins chères. La proportion moyenne des taxes sur le prix des cigarettes est passée de 51,7% à 55,7%. Les ventes annuelles de cigarettes ont baissé de 7,8%, passant de 127 à 117 milliards de paquets. L'augmentation des prix des cigarettes pourrait être associée à une réduction comprise entre 0,2% et 0,6% de la proportion de fumeurs dans la population adulte, ce qui représente entre 2,2 et 6,5 millions de fumeurs en moins. Les recettes fiscales obtenues sur la vente de cigarettes ont augmenté de 14% (740 milliards de yuans en 2014 contre 842 milliards en 2016), apportant ainsi au gouvernement 101 milliards de yuans de recettes fiscales supplémentaires. La hausse de la fiscalité opérée en 2015 en Chine montre que la taxation du tabac peut avoir des bénéfices appréciables à la fois sur la santé publique et sur les finances publiques. Cette expérience révèle aussi le potentiel de la taxation du tabac dans la poursuite des objectifs plus larges de développement de la Chine, notamment des objectifs de développement durable et des objectifs du programme «Healthy China 2030» (une Chine saine en 2030). À l'avenir, ce lien avec les objectifs de développement pourrait être optimisé par des recherches et un dialogue multisectoriels visant à définir des objectifs intersectoriels cohérents pour l'élaboration et l'application des politiques fiscales sur le tabac.

Резюме

Оценка первых последствий повышения налога на табак в Китае в 2015 году

В 2015 году, впервые с 2009 года, правительство Китая повысило акцизный налог на табак. В отличие от ранее принятой практики, Государственное табачное монопольное управление одновременно повысило и цены на сигареты. Авторы оценили первые последствия повышения налога на стоимость сигарет в 2015 году, объемы продаж, объемы налоговой выручки и потенциальное воздействие этого фактора на частоту курения в Китае. В период между 2014 и 2016 годами розничные цены на сигареты выросли в среднем на 11%, при этом наиболее дешевые марки подорожали на 20%. Средняя доля налогов в стоимости сигарет выросла с 51,7 до 55,7%. Годовой объем продаж сигарет снизился на 7,8% — с 127 до 117 миллиардов пачек. Рост цен на сигареты может ассоциироваться с падением доли взрослых курильщиков на 0,2–0,6%. Это означает, что таких курильщиков стало меньше на 2,2–6,5 миллиона человек. Налоговая выручка от продажи сигарет выросла в период между 2014 и 2016 годами на 14% — с 740 до 842 миллиардов юаней. Это означает, что правительство получило около 101 миллиарда юаней прибыли в виде налогов. Повышение налога на табак в 2015 году в Китае демонстрирует, что налогообложение табака может приносить заметную пользу как финансовому сектору, так и здравоохранению. Этот опыт также указывает на то, что налогообложение табака может быть полезным и для достижения более широких целей развития, которые перед собой ставит Китай, включая устойчивое развитие и «здоровый Китай к 2030 году». Если смотреть в будущее, то достичь этой связи с развитием можно через разнонаправленные исследования и диалог между различными секторами, чтобы выработать устойчивые кросс-секторальные цели для последующей разработки политики налогообложения табака и ее реализации.

Resumen

Evaluación temprana de la subida del impuesto sobre el tabaco en China en 2015

En 2015, el gobierno chino subió el impuesto especial sobre el tabaco por primera vez desde 2009. De manera distinta a la práctica anterior, la Administración Estatal de Monopolio de Tabaco subió los precios de los cigarrillos al mismo tiempo. Se evalúa el impacto inicial de la subida de impuestos de 2015 sobre los precios de los cigarrillos, los volúmenes de venta, la generación de ingresos tributarios y el posible efecto sobre la prevalencia del tabaco en China. Entre 2014 y 2016, el precio minorista de los cigarrillos subió de media un 11 % y la categoría más barata de marcas de cigarrillos subió en un 20 %. La proporción media de impuestos en el precio de los cigarrillos subió del 51,7 % al 55,7 %.

Las ventas anuales de cigarrillos cayeron un 7,8 %, de 127 000 a 117 000 millones de paquetes. La subida de los precios de los cigarrillos podría estar asociada con una reducción del 0,2 % al 0,6 % en la proporción de fumadores adultos, lo que representa entre 2,2 y 6,5 millones de fumadores menos. Los ingresos fiscales procedentes de los cigarrillos aumentaron un 14%, de 740 000 a 842 000 millones de yuanes chinos entre 2014 y 2016, lo que se refleja un aumento de 101 000 millones de yuanes chinos en ingresos fiscales para el gobierno. La subida tributaria de 2015 muestra que el impuesto sobre el tabaco puede brindar unos beneficios considerables tanto para la salud pública como para las finanzas en China. Los ingresos tributarios de los cigarrillos subieron un 14 %, de 740 000 a 842 000 millones de yuanes chinos entre 2014 y 2016, lo que equivale a 15 000 millones adicionales de dólares estadounidenses en ingresos fiscales para el gobierno. La subida de los impuestos sobre el tabaco en China en 2015 supone una demostración de que los impuestos sobre el tabaco podrían generar beneficios cuantificables tanto para la salud pública como para las finanzas. La experiencia también destaca el potencial de los impuestos sobre el tabaco de contribuir a los objetivos de desarrollo más amplios de China, incluidos los objetivos de desarrollo sostenible y salud de China para 2030. De cara al futuro, este vínculo con el desarrollo puede facilitarse a través de la investigación y el diálogo multisectoriales para desarrollar objetivos intersectoriales coherentes para el diseño y la implementación de la política tributaria del tabaco.

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FDA Playing Catch-Up as JUUL and Imitators Give Nicotine Jolt to E-Cig Business

fairwarning.org/2018/06/fda-juul-nicotine-e-cigarette

By Angus Chen on June 7, 2018 June 7, 2018

An ad promoting the JUUL device. Note the warning in tiny type at the bottom: "This product contains nicotine. Nicotine is an addictive chemical."

Teenagers from local high schools flock to Brooklyn Vape in downtown Brooklyn. The store is small – a single room with vape paraphernalia stacked to the ceiling in glass cabinets. Many of the teens walk awkwardly through the shop and ask the clerk, a man who goes by Ali and wouldn't give his last name, if they can buy an e-cigarette. Ali says most of them ask for a JUUL, a vaporizer fashioned into a sleek, rectangular prism that can vanish into a closed fist, but occasionally they're looking for something a little different.

"Sometimes they ask for the Phix," Ali said. "About once a week they ask for the Suorin Drop or Suorin Air." Then, Ali says, when it comes time to buy, they say they left their IDs at home.

The federal government classifies e-cigarettes as tobacco products and, as such, youths under 18 (or under 21 in New York City) are barred from buying them. Of course, rules never stop all teenagers, and a teen vaping trend has gained serious steam over the last year. Most of the attention revolves around the JUUL device, whose starter kit normally sells for about $50, but new offerings with similar features have rapidly entered the market.

"We've already begun to see a whole new generation of e-cigarettes, all of which are designed to deliver far higher levels of nicotine in far more sleek containers than have existed in the past," said Matthew Myers, the president of the Campaign for Tobacco-Free Kids. "Whether intentionally or by mistake," he later added, "the original creators of JUUL produced the perfect next-fad product for our nation's kids."

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For public health authorities, the popularity of JUUL and its rivals highlights the conundrum of e-cigarettes. They provide a safer way for smokers to get their nicotine fix by delivering far less of the toxic and cancer-causing baggage of conventional cigarettes. But will e-cigarettes ultimately lead to less tobacco smoking or more? Critics fear, and some studies suggest, that many kids who would never experiment with regular cigarettes will try e-cigarettes, become addicted, and graduate to tobacco as a more satisfying way to get nicotine. “If you could get every smoker to switch to vaping, that would be a huge public health victory,” said Meghan Morean, a psychologist at Oberlin College who studies substance abuse among teens. “But sometimes great ideas have really negative unintended consequences.”

The concerns are being heightened by the massive numbers of adolescents taking up vaping – at a point in their lives when heavy nicotine consumption can affect brain development. The University of Michigan’s most recent national survey of drug use by adolescents found that, in 2017, 19 percent of high school seniors reported nicotine vaping in the previous 12 months. The Centers for Disease Control and Prevention today released data showing that 11.7 percent of high school students last year reporting using e-cigarettes in the previous 30 days, up from 1.5 percent in 2011.

A lack of regulation has eased the way for the boom in e-cigarette sales. Last summer, the U.S. Food and Drug Administration came under fierce attack from public health advocates for granting e-cigarette makers a long delay in seeking approval for new products. Under the moratorium announced by the agency, the companies will have until 2022 to submit information on their manufacturing and marketing practices. But now, amid growing alarm about teens taking up the vaping habit, the FDA has started to take some action.

In April, the FDA announced an undercover operation cracking down on retailers that sell JUUL products to minors. The agency also demanded that JUUL Labs, the San Francisco-based company that markets the JUUL device, turn over documents related to its marketing practices and research, including information on the health effects of its products.

E-cigarette products on display at a Brooklyn, N.Y. shop. (Photo by Angus Chen)

“We don’t yet fully understand why these products are so popular among youth. But it’s imperative that we figure it out, and fast. These documents may help us get there,” FDA Commissioner Scott Gottlieb said in a written statement. In May, the FDA demanded similar records from other e-cigarette manufacturers, including J Well, YGT Investment, 7 Daze, Liquid Filling Solutions and SVR.

JUUL officials declined to answer a question from FairWarning about whether they felt any qualms about their device’s powerful appeal to youth. But they pointed to a company statement that their “mission is to eliminate cigarettes and help the more than one billion smokers worldwide switch to a better alternative… At the same time, we are committed to deterring young people, as well as adults who do not currently smoke, from using our products. We cannot be more emphatic on this point: No young person or non-nicotine user should ever try JUUL.”

JUUL Labs has set up a $30 million fund to investigate and prevent underage nicotine use, and reached out to Iowa Attorney General Tom Miller to set up an advisory group that would influence JUUL’s future policies and designs. That group would have no real power over JUUL, though, and what the company does won’t affect the policies of the vape industry as a whole.

JUUL fired up the e-cigarette business. The original e-cigarettes came in two basic styles. One was a long, slim cylinder with a LED light that lit up on draws – making it look like a tobacco cigarette – and the other was a large, handheld battery with an atomizer screwed on top that hissed and turned users into fog machines.

Adam Bowen and James Monsees, JUUL's designers and the founders of the business that became JUUL Labs, intended their e-cigarette to be different. They wanted it to be the cigarette-killer, JUUL spokeswoman Victoria Davis said via e-mail. For that, it had to be sexier than cigarettes. The design featured a gem-shaped cartridge window separating the JUUL's gunmetal gray battery from a black mouthpiece. There are no buttons – sucking on the mouthpiece activates the device. And JUUL comes with disposable pods, which each last about 200 puffs and are filled with 50 milligrams of nicotine – about the same as a pack of cigarettes. The whole thing is shorter than the palm of your hand and resembles a long, slim USB memory drive.

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It was important that the JUUL didn't look like older e-cigarettes or tobacco cigarettes. "We know adult smokers who want to switch [to e-cigarettes] do not want to be reminded of combustible cigarettes," Davis said. Likewise, teenagers often are turned off by traditional cigarettes. "They don't want to be considered smokers," said Oberlin College's Morean.

The new approach clicked. Upon its introduction three years ago, JUUL was greeted with a review in Wired magazine headlined, "This Might Just Be the First Great E-Cig." Meanwhile, with JUUL the dominant company, the e-cigarette industry's revenues have boomed. According to a recent Wells Fargo analysis, overall sales for the vape industry in the U.S. this year will grow about 25 percent to reach $5.5 billion.

A JUUL nicotine delivery device (JUUL Labs photo)

Milan, a Brooklyn high school student whose last name is being withheld to protect her privacy, offers an explanation for JUUL's popularity. "It's about style," she said. "Because the design is so cool, it lures people in." Plus, Milan added, "Because it's small, you can get away with" using it in school.

Other manufacturers have followed JUUL's lead in coming out with their own thin, sleek devices with interchangeable, prefilled pods. Ramakanth Kavuluru, a data scientist at the University of Kentucky who has tracked e-cigarette use on social media, likens the trend to what happened in the smartphone business. JUUL, he says, was the iPhone of e-cigarettes. The others are like Androids – emulating the industry leader but offering a wider range of flavors and nicotine concentrations.

A new vape, the Suorin Drop, seems to be emerging as a top rival to JUUL among youths. Video reviews have come out on YouTube with titles like “Suorin Drop (THE JUUL KILLER)” and “Suorin Drop, Better than the JUUL?” In one video, a young man holds up a JUUL and says, “I’ve had this JUUL for many months but it hasn’t been getting me that buzz lately, you know?” Then he holds up a Suorin Drop. It’s a flat device that, like the JUUL, can fit in the palm of a hand, but is shorter, wider and molded into the shape of a teardrop.

Perhaps the biggest selling point is the fact that Suorin pods are refillable. Vapers can buy liquids that have even higher concentrations of nicotine, and more flavors, than the JUUL. It’s cheaper, too. A four-pack of JUUL pods costs about $17, while a bottle of vape juice that would refill a Suorin several times can go for $15 or less.

Because the Suorin is shorter than the JUUL, surreptitious vaping is easier. Matt, a 15-year-old Suorin user from San Jose, California, says teachers at his school are catching onto the JUUL and other vapes that look like it. But, he said, “They don’t know what the Suorin looks like,” making it easier to sneak at schools.

The Suorin Drop so far doesn’t seem to have caught the FDA’s attention, either. The company that makes it, Shenzhen Bluemark Technology Co, wasn’t among the e-cigarette firms ordered this spring to provide information to the agency about its youth business.

In response to a question from FairWarning about whether the company was concerned about selling a product widely used by underage consumers and exposing them to the risk of nicotine addiction, Shenzhen Bluemark replied, “Our product is intended for use by adult smokers of legal age who want to get rid of cigarette[s].” The company said it has taken measures to ensure its product isn’t sold to minors.

Meanwhile, adolescents who are heavy users of e-cigarettes risk becoming addicted to the nicotine. “I don’t feel like I need it like some of my friends who are at the point like, ‘Oh my God, I’m so addicted. I need it,’” Matt said.

“I’m just like whatever,” he said. “ I just use it a couple times.” A couple times a day? After a moment, Matt replied, “A couple times every hour maybe. But my friends use it every five minutes.”

MONITORING *the* FUTURE

NATIONAL SURVEY RESULTS
ON DRUG USE
1975–2017

2017 Overview

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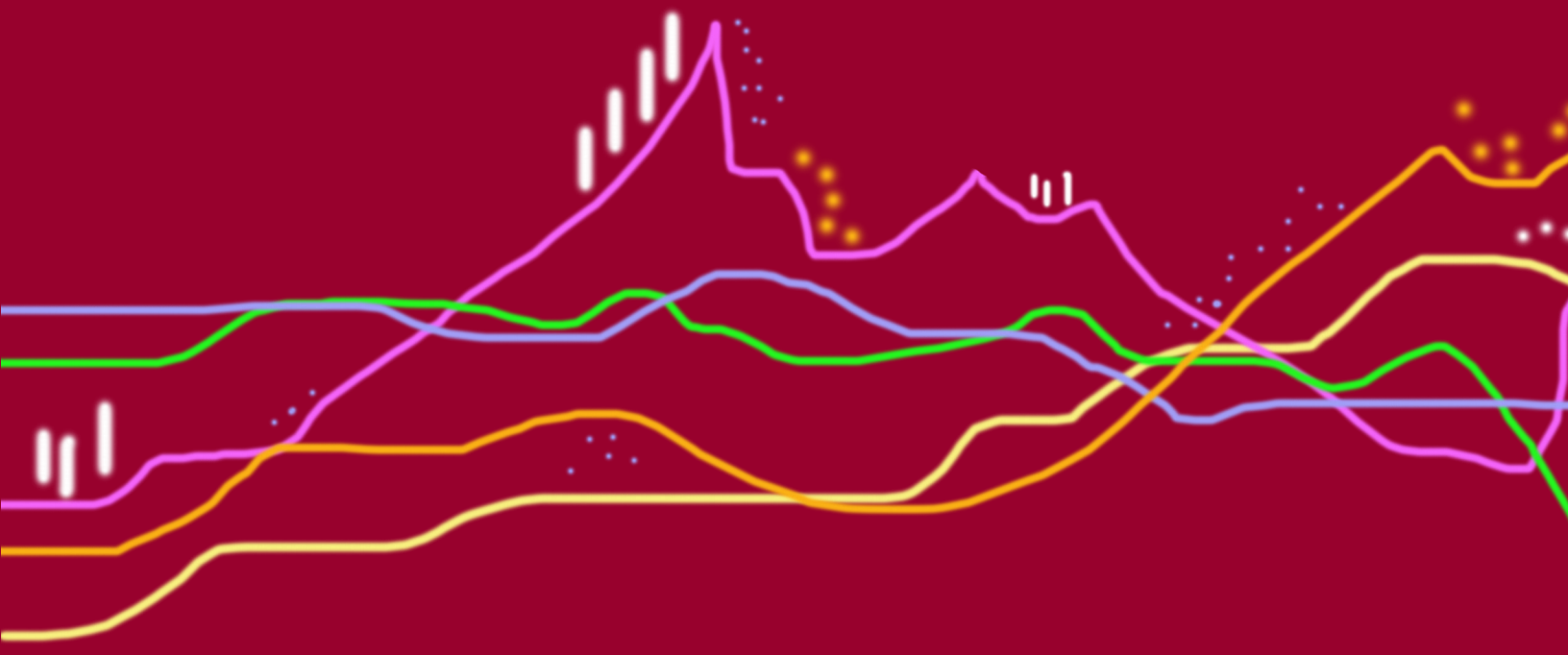

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NATIONAL SURVEY RESULTS ON DRUG USE

2017 Overview Key Findings on Adolescent Drug Use

by

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Summary of Key Findings

Monitoring the Future (MTF) is a long-term study of substance use and related factors among U.S. adolescents, college students, and adult high school graduates through age 55. It is conducted annually and supported by the National Institute on Drug Abuse. MTF findings identify emerging susbstance use problems, track substance use trends, and inform national policy and intervention strategies.

MTF is designed to detect age, period, and cohort effects in substance use and related attitudes. Age effects are similar changes at similar ages seen across multiple class cohorts; they are common during adolescence. Period effects are changes that are parallel over a number of years across multiple age groups (in this case, all three grades under study—8, 10, and 12). Cohort effects are similar changes among those of a similar age or grade in school, that are then maintained as the cohorts age. The key findings for 8th, 10th, and 12th graders surveyed across the coterminous U.S. in 2017 are summarized below.

The analyses and associated tables that follow present substance use trends for all three grades separately, as well as trends in key attitudes, beliefs, and perceived availability. In a number of cases we provide insight into the age and cohort effects and secular trends that underlie trends in use and in key attitudes and beliefs.

An additional set of tables provides an overview of drug use trends for the three grades combined (Tables 1–4). This information gives a summary of the general nature of secular trends over the last several years, though it obscures any age or cohort effects that may be occurring. Also, for simultaneous trends that are in the same direction and magnitude across all three grades, these combined analyses provide greater statistical power to detect whether secular trends are statistically significant.

Illicit Drugs Showing an Increase in Use in 2017

Annual ***marijuana*** prevalence rose by a significant 1.3 percentage points to 23.9% in 2017 based on data from the three grades combined.[1] (While increases were seen in all three grades separately, they did not reach statistical significance.) Annual prevalence stands at 10%, 26%, and 37% in grades 8, 10, and 12. Importantly, ***daily marijuana*** changed little this year, with rates at 1%, 3%, and 6% respectively.

The index of use of ***any illicit drug***, which tends to be driven by marijuana—by far the most prevalent of the illicit drugs, also rose some in each of the three grades, although not enough to reach statistical significance. Data for the three grades combined also did not reach significance.

However, the annual prevalence of the index of ***any illicit drug including inhalants*** rose significantly for the three grades combined (up 2.0 percentage points to 28.3%, ss), with sizeable increases in all three grades (up 2.3 percentage points in grade 8, ss).[2]

Eighth graders, who consistently have the highest prevalence for ***inhalants***, accounted for all of the increase in inhalant use in 2017 (their annual prevalence was up by 0.9 percentage points to 4.7%, s) and all of the increase in the index including inhalants. Until 2017 inhalant use had been in a steady decline in all grades for roughly a decade or more, so this year's possible reversal of that trend bears watching.

Illicit Drugs Showing Declines in Use in 2017

Relatively few drugs exhibited a significant decline in use in 2017, although the use of most drugs is well below the peak levels reached in recent years.

Synthetic marijuana use declined for the three grades combined—down 0.4 percentage points to 2.8% (s). Its use declined only in grades 8 and 10 this year, significantly so in 8th. Annual prevalence has declined by more than half at each grade level since it was first measured around 2013.

Annual prevalence for ***salvia*** had declined appreciably in all three grades prior to 2017, and it declined further in 2017, but only among 8th graders (down 0.6 percentage points to 0.4%, s). This drug is now below 1.6% annual prevalence in all three grades.

Bath salts (synthetic stimulants) continued their long term decline in 2017 in all three grades, though only the decline for all three grades combined reached statistical significance (down 0.3 percentage points to 0.5%, s). Annual prevalence is now below 0.7% in all three grades.

[1] Prevalence refers to the percent of the study sample that report using a drug once or more during a given period—i.e.in their lifetime, past 12 months [annual prevalence], past 30 days, or daily in the past 30 days.

[2] Significance notations: s for p<.05, ss for p<.01, sss for p<.001, and ns for non-significant

Use of ***Vicodin***, a narcotic analgesic, fell in all three grades, though significantly so only in 12th grade, where annual prevalence dropped by 1.0 percentage points to 2.0% (s). There has been a sharp drop in its use in all grades since around 2010.

The other major class of narcotic analgesics that we track, ***OxyContin***, has also shown an appreciable drop in use over the same interval, though it started from a lower level than Vicodin. Annual prevalence continued down in 12th grade, but that decline did not quite reach statistical significance (down 0.7 percentage points to 2.7%, ns).

Ritalin, a prescription controlled stimulant, also has been gradually decreasing in use since it was first measured in 2001. It continued to decline in the lower two grades in 2017, significantly so in 8th grade (annual prevalence down 0.4 percentage points to 0.4%, s).

Most Illicit Drugs Held Steady in Use in 2017

There are many classes of drugs tracked in the MTF study, and the majority of them held relatively steady in 2017. These include an ***index of any illicit drug other than marijuana, LSD, hallucinogens other than LSD, MDMA*** (ecstasy, Molly), ***cocaine, crack, heroin*** (overall, and when used with or without a needle), ***amphetamines*** (taken as a class), ***sedatives, tranquilizers, methamphetamine, crystal methamphetamine,*** and ***steroids***.

While not strictly speaking illicit drugs, over the counter ***cough and cold medications*** used to get high (most of which contain dextromethorphan) also remained level in 2017, with an annual prevalence of 3.0% for the three grades combined.

Psychotherapeutic Drugs

Use of ***psychotherapeutic drugs*** outside of medical supervision warrants special attention, given that they came to make up a substantially larger part of the overall U.S. drug problem in the 2000s. This is in part because of increases in nonmedical use of many prescription drugs over that period, and in part because use of a number of street drugs has declined substantially since the mid- to late-1990s.

It seems likely that young people are less concerned about the dangers of using these prescription drugs outside of medical regimen because they are widely used for legitimate purposes. (Indeed, the low levels of perceived risk for sedatives and amphetamines observed among 12th graders illustrate this point.) Also, prescription psychotherapeutic drugs are now being advertised directly to the consumer, which implies that they are both widely used and safe.

Fortunately, the use of most of these drugs began to decline by the start of this decade. The proportion of 12th graders misusing any of these prescription drugs (i.e., amphetamines, sedatives, tranquilizers, or narcotics other than heroin) in the prior year continued its gradual decline in 2017 (-1.0%, not significant) to 11%, down from a high of 17% in 2005, when this index was first calculated. Use of ***narcotics*** other than heroin without a doctor's orders (reported only for 12th grade) continued a gradual decline begun after 2009, when annual prevalence was 9.2%; it was 4.2% after a non-significant decline of 0.5 percentage points in 2017.

Given the epidemic of narcotics use in older populations along with concurrent rise in medical emergencies and deaths, it is particularly good news that young people are moving away from the use of these drugs. This is true not only because adolescents will be less vulnerable to tragedies resulting from the use of these drugs, but because they may well take their more cautious behaviors with them into their twenties, thirties, and beyond—ages in which overdose deaths are currently most prevalent. In other words, a cohort effect may emerge. Indeed, it is quite possible that the increases in overdose deaths in older age groups themselves reflect the result of a cohort effect in which earlier classes of 12th graders carried their increased narcotic use during adolescence with them into adulthood.

Most Forms of Tobacco Use Continue to Decline

Cigarette smoking continued its long decline in 2017 and is now at or very close to the lowest levels in the history of the survey. For the three grades combined, thirty-day prevalence of cigarette use, which reached a peak in the mid 1990s, has fallen by 81%. Daily prevalence has fallen by 86%, and current half-pack-a-day prevalence by 91% since their peaks in the 1990s. Current prevalence of half-pack-a-day smoking stands at just 0.2% for 8th graders, 0.7% for 10th graders, and 1.7% for 12th graders. Because of the strong cohort effect that we have consistently observed for cigarette smoking, we have predicted use at 12th grade to continue to show declines, as the lighter-using cohorts of 8th and 10th graders become 12th graders.

Initiation of ***cigarette*** use also continues its long-term and extremely important decline. Lifetime prevalence declined between 2016 and 2017 in all three grades: to 9% in 8th grade (down 0.4 percentage points, ns), to 16% in 10th grade (down 1.6 percentage points, ns), and to 27% in 12th grade (down 1.7 percentage points, ns). The fact that fewer young people now initiate cigarette smoking is an important reason for the large declines in their current use. The proportion of students who have ever tried cigarettes has fallen from peak levels reached in 1996 or

1997 by roughly four fifths, three quarters, and three fifths in the three grades, respectively.

Overall increases in perceived risk and disapproval appear to have contributed to the downturn in cigarette use. Perceived risk of smoking one or more packs of cigarettes per day increased substantially and steadily in all grades from 1995 through 2004, with 62%, 68%, and 74% of 8th, 10th, and 12th graders seeing great risk in 2004. Since then, changes have been small and uneven, and the corresponding figures in 2017 are only slightly changed, at 62%, 70%, and 75%. Disapproval of smoking one or more packs of cigarettes per day has increased somewhat steadily in all three grades since 1996 and has reached very high levels. In 2017 disapproval stood at 89%, 88%, and 87% in grades 8, 10, and 12, respectively.

It seems likely that some of the attitudinal change surrounding cigarettes is attributable to the considerable adverse publicity aimed at the tobacco industry in the 1990s, as well as a reduction in cigarette advertising and an increase in antismoking campaigns reaching youth.

Various other attitudes toward smoking became more unfavorable during that interval as well, though most have since leveled off. For example, among 8th graders, the proportions saying that they "prefer to date people who don't smoke" rose from 71% in 1996 to 81% by 2004, where it remained through 2017. Similar changes occurred in 10th and 12th grades. Thus, at the present time, smoking is likely to make an adolescent less attractive to the great majority of potential romantic age-mates. Likewise, most of the other negative connotations of smoking and smokers have leveled off in the past few years after rising previously.

In addition to changes in attitudes and beliefs about smoking, price almost surely also played an important role in the decline in use. Cigarette prices rose appreciably in the late 1990s and early 2000s as cigarette companies tried to cover the costs of the 1998 Master Settlement Agreement, and as many states increased excise taxes on cigarettes. A significant increase in the federal tobacco tax passed in 2009 may have contributed to the continuation of the decline in use since then.

Cigarillos. One consequence of the rise in cigarette prices is that it may have shifted some adolescents to less expensive alternatives, like cigarillos (little or small cigars), which are taxed at a lower rate than cigarettes. Taking into account this form of smoking of tobacco raises the 30-day prevalence of students smoking tobacco—by about three-fourths among 8th and 10th graders and by more than half among 12th graders—over what it would be if just cigarette smoking were counted. It does appear, however, that the prevalence of using small cigars is also in decline, with 13% of 12th graders in 2017 reporting any past-year use, down substantially from 23% in 2010. Of note is the fact that the majority of users of small cigars in each grade smoke flavored ones.

Annual prevalence of smoking tobacco using a ***Hookah*** (water pipe) had been increasing steadily until 2014 among 12th graders (8th and 10th graders are not asked about this practice), reaching 23% in 2014; but use declined non-significantly by three percentage points to 20% in 2015 and declined significantly in both 2016 and 2017to reach 10% by 2017.

Smokeless tobacco. From the mid-1990s to the early 2000s, smokeless tobacco use declined substantially, but a rebound in use developed from the mid-2000s through 2010. Since 2010, prevalence levels have declined modestly in all three grades. Perceived risk and disapproval appear to have played important roles in the earlier decline in smokeless tobacco use. In all three grades, perceived risk and disapproval rose fairly steadily from 1995 through 2004, accompanying the declines in use. However, there was not much change in use between 2004 and 2010, suggesting that other factors may have led to the increases in smokeless tobacco use during that time interval; perhaps including increased promotion of these products, a proliferation of types of smokeless tobacco products available, and increased restrictions on places where cigarette smoking is permitted. The decline in smokeless tobacco use since 2010 (including significant declines among among 8th and 12th graders in 2017) may be attributable, at least in part, to the 2009 increase in federal taxes on tobacco. Perceived risk has not changed appreciably since 2010 at any grade level.

Snus, a form of smokeless tobacco, showed a significant decline in use this year for the three grades combined (annual prevalence fell from 3.6% to 2.6%).

Vaping

Vaping involves the inhalation of vapors (sometimes including nicotine) using battery-powered devices such as e-cigarettes, "mods," Juuls, and e-pens. Prior to 2017 the questions on vaping asked about vaping in general, and then asked which of several substances were vaped on last use. Based on that question, thirty-day prevalence of vaping fell significantly in each grade in 2016 to levels of 6%, 11%, and 13% in the respective grades.

This marked the first reversal of vaping prevalence, which grew rapidly from near zero prevalence in 2011 to one of the most common forms of adolescent substance use by 2015.

In 2017 the question was changed to ask separately about vaping marijuana, vaping nicototine, and vaping "just

flavoring." Annual prevalence of ***marijuana vaping*** was considerable: 3%, 8%, and 10% in grades 8, 10, and 12. So were levels of ***nicotine vaping***: 8%, 16%, and 19%, respectively. ***Vaping "just flavoring"*** showed an annual prevalence of 12%, 19%, and 21% in the three grades. Trends are not yet available on these new questions.

Despite the decline in 2016 the prevalence of vaping remains substantially higher than the use of any other tobacco product, including cigarettes. Whether teen vaping has peaked is an issue that MTF will be able to determine in the coming years.

The percentage of students who associated vaping with "great risk" increased slightly as vaping prevalence declined. ***E-cigarettes*** are the most commonly used vaping device, and e-cigarettes have some of the lowest levels of perceived risk of any substance.

Alcohol Use Levels After a Long Decline

Alcohol remains the substance most widely used by today's teenagers. Despite recent declines by the end of high school six out of every ten students (62%) have consumd alcohol (more than just a few sips), and about a quarter (23%) have done so by 8th grade. In fact, nearly half (45%) of 12th graders and one in eleven (9%) 8th graders in 2017 reported having been drunk at least once in their life.

Alcohol use began a substantial decline in the 1980s. To some degree, alcohol trends have tended to parallel the trends in illicit drug use. These include a modest increase in binge drinking (defined as having five or more drinks in a row at least once in the past two weeks) in the early to mid-1990s, though it was a proportionally smaller increase than was seen for cigarettes and most of the illicit drugs. Fortunately, binge drinking rates leveled off in the early 2000s, just about when the illicit drug rates began to turn around, and in 2002, a drop in ***drinking*** and ***drunkenness*** resumed in all grades. Gradual declines in all three grades continued into 2016, which marked the lowest levels for alcohol use and drunkenness ever recorded by the survey in the three grades combined.

In 2017, however, lifetime prevalence, annual prevalence, 30-day prevalence, and daily prevalence all showed little or no change, with no significant changes for any grade or for the three grades combined. This is the first time in some years that this has happened, and may herald the end of the long-term decline in adolescent alcohol use.

Still, prior to this year lifetime prevalence and annual prevalence for the three grades combined both declined by roughly four-tenths from the peak levels of use reached in the mid-1990s; 30-day prevalence was down by about one-half since then; and daily prevalence by two-thirds. These are dramatic declines for such a culturally ingrained behavior and good news to many parents. However, there was no further decline in 2017.

Introduction

Monitoring the Future (MTF) is a long-term study of substance use and related factors among U.S. adolescents, college students, and adult high school graduates through age 55. It has been conducted annually by the University of Michigan's Institute for Social Research since its inception in 1975 and is supported under a series of investigator-initiated, competitive research grants from the National Institute on Drug Abuse.

The need for a study such as MTF is clear. Substance use by young people in the U.S. has proven to be a rapidly changing phenomenon, requiring frequent assessments and reassessments. Since the mid-1960s, when it burgeoned in the general youth population, illicit drug use has remained a major concern for the nation. Smoking, drinking, and illicit drug use are leading causes of morbidity and mortality during adolescence as well as later in life. How vigorously the nation responds to teenage substance use, how accurately it identifies the emerging substance abuse problems, and how well it comes to understand the effectiveness of policy and intervention efforts largely depend on the ongoing collection of valid and reliable data. MTF is uniquely designed to generate such data in order to provide an accurate picture of what is happening in this domain and why, and the study has served that function well for the past 43 years. Policy discussions in the scientific literature and media, in government, education, public health institutions, and elsewhere have been informed by the ready availability of extensive and consistently accurate information from the study relating to a large and ever-growing number of substances. Similarly, MTF findings help to inform organizations and agencies that provide prevention and treatment services.

The 2017 MTF survey involved about 43,700 students in 8th-, 10th-, and 12th grades enrolled in 360 secondary schools nationwide. The first published results based on the 2017 survey are presented in this report. Recent trends in the use of licit and illicit drugs are emphasized, as well as trends in the levels of perceived risk and personal disapproval associated with each drug. This project has shown these beliefs and attitudes to be particularly important in explaining current trends in use, and even in predicting future ones. In addition, trends in the perceived availability of each drug are presented, which at times have proven important to explaining changes in usage levels for certain drugs.

MTF is designed to detect age effects, period effects (also referred to as secular trends), and cohort effects in substance use and related attitudes and beliefs. Age effects (similar changes at similar ages seen across multiple class cohorts) are common during adolescence, and we typically find that use, as well as positive attitudes and beliefs about use, increase across 8th, 10th, and 12th grades. When changes over time in substance use (and perhaps related attitudes and beliefs) are parallel over some time interval across all three grades, they reflect period effects, which are also common.

Cohort effects pertain to differences in substance use and related attitudes and behaviors among those born at different times that are maintained as the birth cohorts age (or in this case, as class-in-school cohorts, which are strongly correlated with age). Such cohort effects sometimes drive changes in substance use prevalence at the population level. For example, much of the decline in the prevalence of U.S. cigarette smoking has its roots in youth cohorts that did not take up smoking and then continued to abstain from smoking as they aged into adulthood. As subsequent youth cohorts continued to avoid smoking and then grew older, these cohorts contributed to a further decline in the overall population prevalence of smoking. Cohort effects can also act in the opposite direction, with newer cohorts increasingly taking up a substance and continuing to have greater use of it than previous cohorts as they get older. One important contribution of the MTF study has been the specification of cohort effects that emerged starting in the early 1990s, when an increase in youth substance use occurred for many drugs.

MTF allows detection of cohort effects at an early age through comparison of substance use prevalence of 8th, 10th, and 12th graders relative to each other. Often 8th grade substance use is a bellwether, and year-to-year changes that are unique to 8th grade can signify an emerging increase or decrease in substance use at later grade levels with some time lag.

The analyses and associated tables that follow present substance use trends for all three grades separately, as well as trends in key attitudes, beliefs, and perceived availability. In a number of cases we provide insight into the age and cohort effects and secular trends that underlie trends in use and in key attitudes and beliefs.

An additional set of tables provides an overview of drug use trends for the three grades combined (Tables 1–4). This information gives a summary of the general nature of secular trends over the last several years, though it obscures any age or cohort effects that may be occurring. Also, for simultaneous trends that are in the same direction and magnitude across all three grades, these combined analyses provide greater statistical power to detect whether secular trends are statistically significant.

A synopsis of the design and methods used in the study follows this introductory section. We then provide a separate section for each individual drug class, including figures that show trends in the overall proportions of students at each grade level (a) using the drug, (b) seeing a "great risk" associated with its use (perceived risk), (c) disapproving of its use (disapproval), and (d) saying that it would be "fairly easy" or "very easy" to get if they wanted to (perceived availability). For 12th graders, annual data are available since 1975 and for 8th and 10th graders since 1991, the first year they were included in the study.

The tables at the end of this report provide the statistics underlying the figures; in addition, they present data on lifetime, annual, 30-day, and (for selected drugs) daily prevalence.[3] For the sake of brevity, we present these prevalence statistics here in tabular form only for the 1991–2017 interval, but statistics on 12th graders going back to 1975 are available in other MTF publications. For each prevalence period, the tables indicate which one-year changes from 2016 to 2017 are statistically significant. (In the text below, 's' indicates $p \leq .05$, 'ss' indicates $p \leq .01$, 'sss' indicates $p \leq .001$, and 'ns' indicates not statistically significant). The graphic depictions of multiyear trends often reveal gradual change that may not reach significance in a given one-year interval but nevertheless may be shown to be real over a longer time frame.

An extensive analysis of the study's findings on secondary school students may be found in *Volume I*, the second publication in this series, published at the end of May each year.[4] *Volume I* contains a more detailed description of the study's methodology, as well as chapters on grade of initiation, attitudes toward drugs, the social milieu, and a summary of other publications from the study that year (mostly journal articles). *Volume I* also contains an appendix explaining how to test the significance of differences between groups and of trends over time. The most recent such volume, as well as earlier editions, are always available on the MTF website, www.monitoringthefuture.org, listed under Publications.

MTF's findings on American college students and adults through age 55 are not covered in this early *Overview* report because the follow-up data from those populations become available later in the year. Those findings will be covered in *Volume II*, the third monograph in this annual series, published at the end of July each year.[5]

Two annual MTF Occasional Papers are published each year in conjunction with *Volumes I* and *II*, providing trends in use for various demographic subgroups.[6]

A fourth monograph, *HIV/AIDS: Risk and Protective Behaviors Among Young Adults*, dealing with national trends in HIV/AIDS-related risk and protective behaviors among young adults 21 to 40 years old, was added to the series beginning in 2010.[7] It is published in October of each year. From 2005 to 2009, these findings were reported as part of *Volume II*.

For the publication years prior to 2010, the volumes in these annual series are available from the NIDA Drug Publications Research Dissemination Center (877-NIDA-NIH, drugpubs.drugabuse.gov) and can also be found on the MTF website. Beginning with the 2010 publication date, the volumes are available at the MTF website immediately upon publication. Further information on the study, including its latest press releases, a listing of all publications, and freely accessible reports may also be found at www.monitoringthefuture.org.

[3] Prevalence refers to the proportion or percentage of the sample reporting use of the given substance on one or more occasions in a given time interval—e.g., lifetime, past 12 months, or past 30 days. For most drugs, the prevalence of daily use refers to reported use on 20 or more occasions in the past 30 days, except for cigarettes and smokeless tobacco, for which actual daily use is measured, and for binge drinking, defined as having 5+ drinks on at least one occasion in the prior two weeks.

[4] The most recent publication of *Volume I* is Miech, R. A., Johnston, L. D., O'Malley, P. M., Bachman, J. G., Schulenberg, , J. E, & Patrick, M. E. (2017). *Monitoring the Future national survey results on drug use, 1975–2016: Volume I, Secondary school students.* Ann Arbor, MI: Institute for Social Research, University of Michigan, 636 pp.

[5] The most recent publication of *Volume II* is Schulenberg, J. E., Johnston, L. D., O'Malley, P. M., Bachman, J. G., Miech, R. A., & Patrick, M. E. (2017). *Monitoring the Future national survey results on drug use, 1975–2016: Volume II, College students & adults ages 19–55*. Ann Arbor, MI: Institute for Social Research, University of Michigan, 445 pp.

[6] Johnston, L. D., O'Malley, P. M., Bachman, J. G., Schulenberg, J. E., & Miech, R. A. (2017). *Demographic subgroup trends among adolescents in the use of various licit and illicit drugs 1975-2016* (Monitoring the Future Occasional Paper No. 88). Ann Arbor, MI: Institute for Social Research, University of Michigan, 694 pp; Johnston, L. D., O'Malley, P. M., Bachman, J. G., Schulenberg, J. E., Miech, R. A., & Patrick, M. E. (2017). *Demographic subgroup trends among young adults in the use of various licit and illicit drugs 1989-2016* (Monitoring the Future Occasional Paper No. 89). Ann Arbor, MI: Institute for Social Research, University of Michigan, 109 pp.

[7] The most recent publication in the *HIV/AIDS monograph series* is Johnston, L. D., O'Malley, P. M., Bachman, J. G., Schulenberg, J. E., Patrick, M. E., & Miech, R. A. (2017). *HIV/AIDS: Risk and protective behaviors among adults ages 21-40 in the U.S., 2004–2016*. Ann Arbor, MI: Institute for Social Research, University of Michigan, 130 pp.

Study Design and Methods

Monitoring the Future's main data collection involves a series of large, annual surveys of nationally representative samples of public and private secondary school students throughout the coterminous United States. Every year since 1975, such samples of 12th graders have been surveyed. In 1991, the study was expanded to include comparable, independent national samples of 8th and 10th graders. The year 2017 marked the 43rd survey of 12th graders and the 27th survey of 8th and 10th graders.

Sample Sizes

In 2017 about 43,700 students in 360 secondary schools participated in the study, with sample sizes in 8th, 10th, and 12th grades of about 16,000, 14,200, and 13,500, respectively. The number of cases upon which a particular statistic is based may be less than the total sample size. Multiple questionnaire forms are distributed randomly at each grade level to increase coverage of attitudinal and behavioral domains relevant to substance use. To reduce burden on the respondents, not all questions are contained in all forms. The tables here contain notes on the number of forms used for each statistic if less than the total sample is used.

Field Procedures

University of Michigan staff members administer the questionnaires to students, usually in the student classroom during a regular class period. Participation is voluntary. Parents are notified well in advance of the survey administration and are provided the opportunity to decline their child's participation. Questionnaires are self-completed and are formatted for optical scanning. Procedures are kept consistent over time.

In 8th and 10th grades the questionnaires are completely anonymous, and in 12th grade they are confidential (name and address information is gathered separately from the 12th grade questionnaire to permit the longitudinal follow-up surveys of random subsamples of participants after high school). Extensive procedures are followed to protect the confidentiality of the participants and their data. All procedures are reviewed and approved on an annual basis by the University of Michigan's Institutional Review Board (IRB) for compliance with federal guidelines for the treatment of human subjects.

Measures

A standard set of three questions is used to determine usage levels for most of the drugs. For example, we ask, "On how many occasions (if any) have you used marijuana… (a)…in your lifetime? (b)…during the last 12 months? (c)…during the last 30 days?" Each of the three questions is answered on the same answer scale: 0, 1–2, 3–5, 6–9, 10–19, 20–39, and 40 or more occasions.

For the psychotherapeutic drugs (amphetamines, sedatives [barbiturates], tranquilizers, and narcotics other than heroin), respondents are instructed to include only use "…on your own—that is, without a doctor telling you to take them." A similar qualification is used in the question on use of anabolic steroids, OxyContin, Vicodin, and several other drugs.

For cigarettes, respondents are asked two questions about use. First, they are asked, "Have you ever smoked cigarettes?" The answer categories are "never," "once or twice," "occasionally but not regularly," "regularly in the past," and "regularly now." The second question asks, "How frequently have you smoked cigarettes during the past 30 days?" The answer categories are "not at all," "less than one cigarette per day," "one to five cigarettes per day," and about one-half, one, one and one half, and two packs or more per day.

Smokeless tobacco questions parallel those for cigarettes. There are also questions recently added about vaping, e-cigarettes, small cigars, and a number of other tobacco products. In general, their use is asked on a prevalence/frequency scale for either the last 12 months or the last 30 days. Beginning in 2017 respondents are asked separate questions about vaping nicotine, vaping marijuana, and vaping "just flavoring."

Alcohol use is measured using the three questions illustrated above for marijuana. A parallel set of three questions asks about the frequency of being drunk. Binge drinking is assessed with the question, "How many times (if any) have you had five or more drinks in a row" over the past two weeks? Extreme binge drinking, also called high-intensity drinking, among 12th graders is assessed with similar questions about consuming 10 or more and 15 or more drinks in a row. Among 8th and 10th graders, it is assessed using only the question about 10 or more drinks.

In general, we try to keep measures consistent across time. When a change is warranted, we usually splice the older and newer measures for at least one year to permit an assessment of whether the change has any effect on reported prevalence levels.

Perceived risk is measured by the question, "How much do you think people risk harming themselves (physically or in other ways), if they…" try or use a drug—for example, "…try marijuana once or twice." The answer

categories are "no risk," "slight risk," "moderate risk," "great risk," and "can't say, drug unfamiliar." Parallel questions refer to using the same drug "occasionally" and "regularly."

Disapproval is measured by the question "Do YOU disapprove of people doing each of the following?" followed by "trying marijuana once or twice," for example. Answer categories are "don't disapprove," "disapprove," and "strongly disapprove." In the 8th and 10th grade questionnaires, a fourth category—"can't say, drug unfamiliar"—is provided and included in the calculation of percentages.

Perceived availability is measured by the question "How difficult do you think it would be for you to get each of the following types of drugs, if you wanted some?" Answer categories are "probably impossible," "very difficult," "fairly difficult," "fairly easy," and "very easy." For 8th and 10th graders, an additional answer category—"can't say, drug unfamiliar"—is provided and included in the calculation of percentages.

Any Illicit Drug

MTF routinely reports three different indexes of illicit drug use—any illicit drug,[8] any illicit drug other than marijuana, and any illicit drug including inhalants. In this section we discuss only the first two; the statistics for all three may be found in Tables 5–7.

In order to make direct comparisons over time, we have generally kept the definitions and measurement of these indexes constant. The levels of prevalence of each of the indexes could be somewhat affected by the inclusion of newer substances. Typically, the effects would be minimal, primarily because most individuals using newer ones are also using the more prevalent drugs included in the indexes. The major exception has been inhalants, the use of which is quite prevalent in the lower grades, so in 1991 a special index that includes inhalants was added.

Trends in Use

In the late 20th century, U.S. adolescents reached extraordinarily high levels of illicit drug use by U.S. as well as international standards. The trends in *lifetime* use of ***any illicit drug*** are shown in the first (upper left) panel on the facing page.[9] In 1975, when MTF began, the majority of young people (55%) had used an illicit drug by the time they left high school. This figure rose to two thirds (66%) in 1981 before a long and gradual decline to 41% by 1992—the low point. After 1992—in what we have called the "relapse phase" in the drug epidemic—the proportion rose considerably to a recent high point of 55% in 1999; it then declined gradually to 47% in 2009, and has remained between 48% and 50% since 2011.

Trends for *annual*, as opposed to lifetime, prevalence are shown in the second (upper right) panel. They are quite parallel to those for lifetime prevalence, but at a lower level. Among 8th graders, a gradual and continuing falloff occurred after 1996. Peak rates since 1991 were reached in 1997 in the two upper grades and declined little for several years. Between 2001 and 2007 all three grades showed declines, but the annual use rates in all three grades then rose some through 2012. Following that there was some decline in all three grades after 2013, but in 2017 these declines halted.

Because marijuana is much more prevalent than any other illicit drug, trends in its use tend to drive the index of any illicit drug use. Thus we also report an index that excludes marijuana and shows the proportions of students who use any of the other illicit drugs. The proportions who have used ***any illicit drug other than marijuana*** in their *lifetime* are shown in the third facing panel (lower left). In 1975 over one third (36%) of 12th graders had tried some illicit drug other than marijuana. This figure rose to 43% by 1981, then declined for over a decade to a low of 25% in 1992. An increase followed in the 1990s as the use of a number of drugs rose steadily, and it reached 30% by 1997. (In 2001 it was 31%, but this apparent upward shift in the estimate was an artifact due to a change in the question wording for "other hallucinogens" and tranquilizers.[10]) Lifetime prevalence among 12th graders then fell slightly to 24% by 2009, before dropping to 20% by 2017. The fourth (lower right) panel presents the *annual* prevalence data for any illicit drug other than marijuana, which shows a pattern of change over the past few years similar to the index of any illicit drug use, but with much less pronounced change since 1991.

The annual prevalence of any illicit drug other than marijuana dropped fairly steadily and gradually in all three grades in recent years, reaching 13% among 12th graders by 2017. In fact, prevalence declined in all three grades in 2016—significantly so in 8th grade. There was no appreciable change in 2017, however.

Overall, these data reveal that while use of individual drugs (other than marijuana) may fluctuate widely, the proportion using *any* of them is much more stable. In other words, the proportion of students prone to using such drugs and willing to cross the normative barriers to such use changes more gradually. The usage rate for each individual drug, on the other hand, reflects many more rapidly changing determinants specific to that drug, such as how widely its psychoactive potential is recognized, how favorable the reports of its supposed benefits are, how risky its use is seen to be, how acceptable it is in the peer group, how accessible it is, and so on.

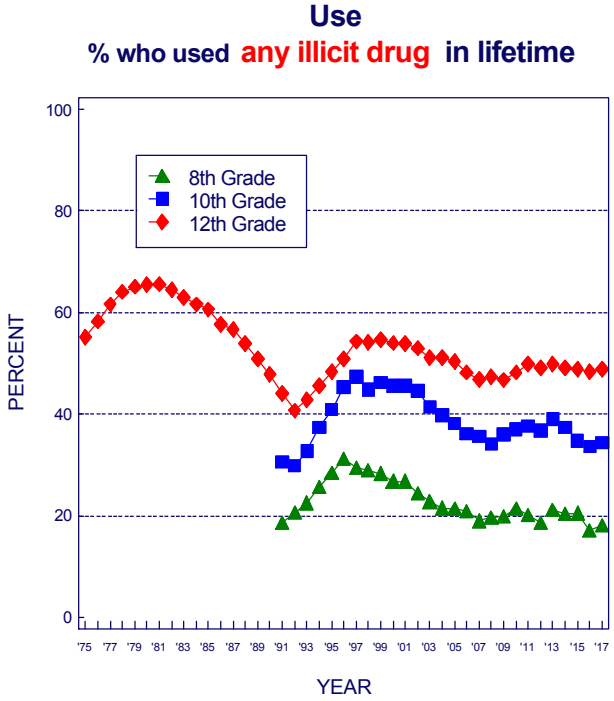
[8] Footnote 'a' to Tables 5 through 8 provides the exact definition of any illicit drug.

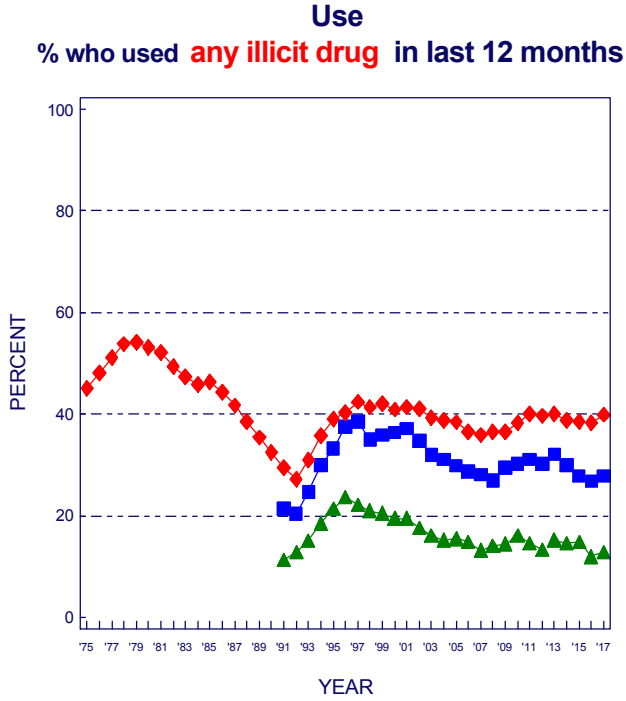
[9] This is the only set of figures in this *Overview* presenting lifetime use statistics. Lifetime statistics for all drugs may be found in Table 5.

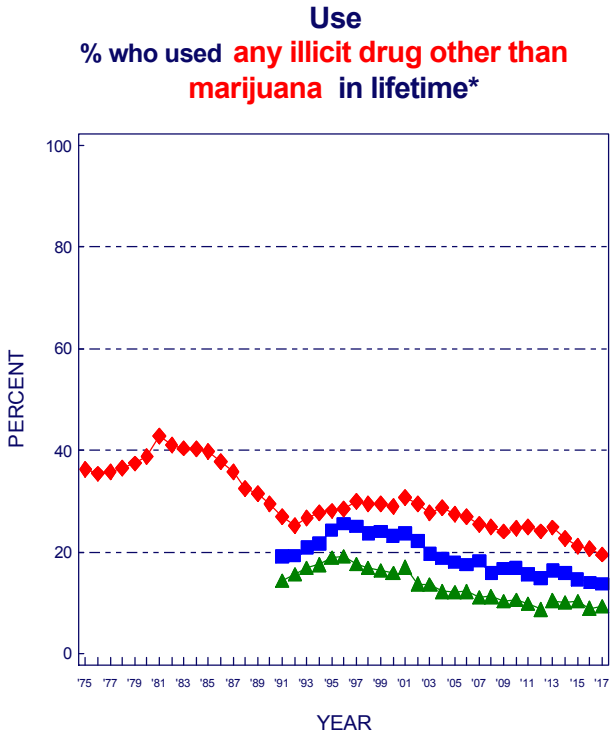
[10] The term psychedelics was replaced with hallucinogens, and "shrooms" was added to the list of examples, resulting in somewhat more respondents indicating use of this class of drugs. For tranquilizers, Xanax was added to the list of examples given, slightly raising the reported prevalence of use.

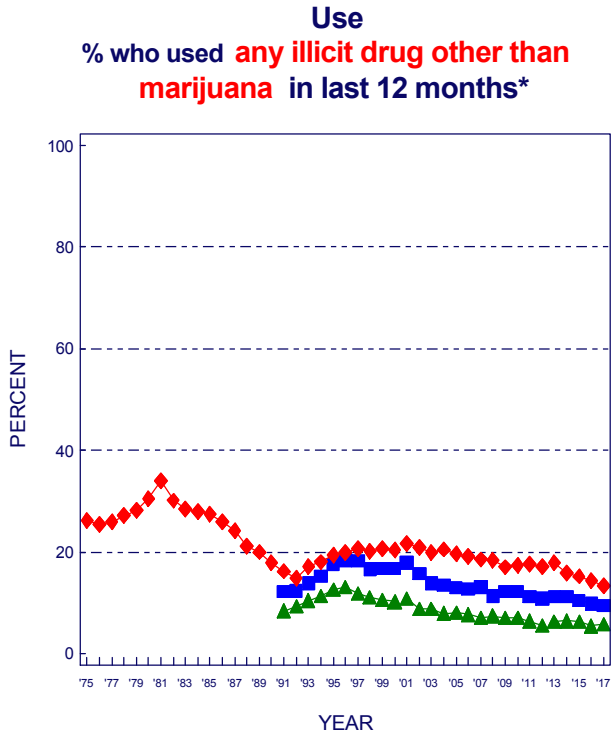
Any Illicit Drug and Any Illicit Drug Other than Marijuana : Trends in Lifetime and Annual Use

Grades 8, 10, 12









Source. The Monitoring the Future study, the University of Michigan.

*In 2001, a revised set of questions on other hallucinogen use and tranquilizer use were introduced. In 2013, a revised set of questions on amphetamine use was introduced. Data for any illicit drug other than marijuana were affected by these changes.

Marijuana

Marijuana has been the most widely used illicit drug throughout MTF's 43-year .. It can be taken orally, mixed with food or drink, vaped, and smoked, including in a concentrated form as hashish.The great majority of recreational use in the U.S. involves smoking it in rolled cigarettes ("joints"), in pipes or water pipes ("bongs"), or in hollowed-out cigars ("blunts"). More recently, methods include smoking, vaping, or eating different forms of resin extracts like hash oil, honey oil, or shatter—a solid form.

Trends in Use

Annual marijuana prevalence peaked among 12th graders in 1979 at 51%, following a rise that began during the 1960s. Then use declined fairly steadily to 22% in 1992—a decline of more than half. Use resurged in the 1990s, peaking in 1996 at 8th grade and in 1997 at 10th and 12th grades. Use then declined among all three grades through 2007 or 2008, followed again by an upturn .in use in all three grades. Annual marijuana prevalence among 8th graders increased in use from 2007 to 2010, decreased slightly from 2010 to 2012, declined significantly in 2016, and leveled in 2017. Among 10th graders, use increased somewhat from 2008 to 2013 and then declined, before rising slightly in 2017. Among 12th graders, use increased from 2006 to 2011, fell some through 2015, and then increased through 2017 As shown in Table 8, *daily* use increased in all three grades after 2007, reaching peaks in 2011 (at 1.3% in 8th), 2013 (at 4.0% in 10th), and 2011 (at 6.6% in 12th), before declining slightly since. Daily prevalence rates in 2017 were 0.8%, 2.9%, and 5.9%, respectively, with one in seventeen 12th graders currently smoking daily.

For the first time in 2017 we included questions about vaping marijuana in the past 30 days, in the past 12 months, and in the student's lifetime. These are the first ever national estimates of marijuana vaping of this kind. One in ten 12th grade students reported vaping in the past 12 months, and the prevalence was 8% and 3% for 10th and 8th grade students, respectively. In each grade, more than one quarter of students who had used marijuana had experience vaping it. These levels are quite high, considering that vaping was virtually unknown among adolescents just five years ago.

Perceived Risk

The proportion of students seeing great risk from smoking marijuana regularly fell during the rise in use in the 1970s and again during the subsequent rise in use in the 1990s. Indeed, for 10th and 12th grades, perceived risk declined a year before use rose in the upturn of the 1990s, making perceived risk a leading indicator of change in use. (The same may have happened for 8th grade but our data do not start early enough to show it.) The decline in perceived risk halted in 1996 in 8th and 10th grades; the increases in use in 10th and 12th grades ended a year or two later, again making perceived risk a leading indicator of trends in use. From 1996 to 2000, perceived risk held fairly steady, and the decline in use in the upper grades stalled. After some decline prior to 2002, perceived risk increased a bit in all grades through 2004 accompanied by decreases in use. Since 2004 in 8th grade, 2005 in 12th grade, and 2008 in 10th grade, perceived risk has fallen substantially, presaging some resurgence in marijuana use lasting three to five years; however, no increase in perceived risk preceded the recent leveling of use. Rather, perceived risk has continued a steep decline since the mid-2000s without a concomitant further rise in overall use. We have shown that recent sharp declines in the use of "gateway drugs"—in particular cigarette smoking, with which marijuana use has been highly correlated— played a major role in this disconnect.[11]

Disapproval

Personal disapproval of trying marijuana has declined some since 2007 or 2008 in all three grades, but disapproval of regular use still remains quite high with 81%, 70%, and 65% in 8th, 10th, and 12th grades, respectively. During the early to mid 1990s, as use increased and perceived risk decreased, disapproval fell considerably—by 17, 21, and 19 percentage points for the three grades. As is often the case, perceived risk fell before disapproval. Since 2007 there has been some decline in disapproval, with declines for experimental use in 2017 being significant for all three grades.

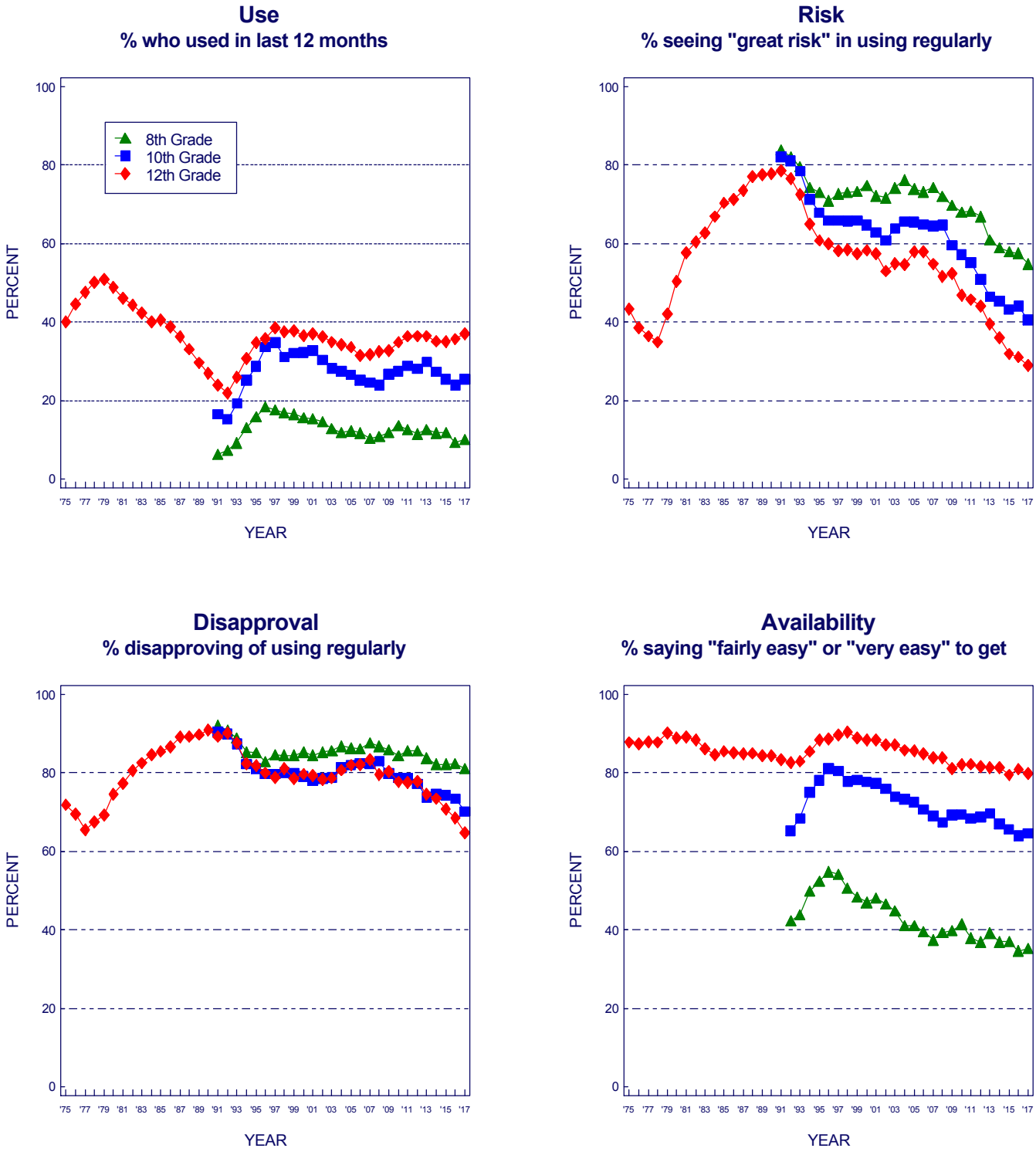
Availability

Since 1975, between 80% and 90% of 12th graders each year have said that marijuana would be fairly or very easy to get if they wanted some, with that figure standing at 80% in 2017. Marijuana has been somewhat less readily available to 10th graders and considerably less available to 8th graders, with 65% and 35%, respectively, reporting it to be fairly or very easy to get in 2017. Though availability has declined appreciably, especially among the younger adolescents, marijuana remains readily available to most 12th graders.

[11] Miech, R. A., Johnston, L. D., & O'Malley, P. M. (2017). Prevalence and attitudes regarding marijuana use among adolescents over the past decade. *Pediatrics, 140*(6).

Marijuana : Trends in Annual Use, Risk, Disapproval, and Availability

Grades 8, 10, 12



Source. The Monitoring the Future study, the University of Michigan.

Synthetic Marijuana

Synthetic marijuana has generally been sold over the counter under such labels as Spice and K-2. It usually contains some herbal materials that have been sprayed with one or more of the designer chemicals that fall into the cannabinoid family. Until March 2011, these drugs were not scheduled by the Drug Enforcement Administration (DEA), so they were readily and legally available on the Internet and in convenience stores, head shops, gas stations, etc. However, the DEA scheduled some of the most widely used chemicals beginning March 1, 2011, making their possession and sale no longer legal; subsequent laws have expanded the list of banned chemicals, but producers keep tweaking the chemical formula to avoid legal control. These drugs can be dangerous both because the active ingredients keep changing and because those ingredients have never undergone testing to determine their effects on humans.

Trends in Use

MTF first addressed the use of synthetic marijuana in its 2011 survey by asking 12th graders about their use in the prior 12 months (which would have covered a considerable period of time prior to the drugs being scheduled). Annual prevalence was found to be 11.4%, making synthetic marijuana the second most widely used class of illicit drug after marijuana itself among 12th graders at that time. Despite the DEA's intervention, use among 12th graders remained unchanged in 2012 at 11.3%, which suggests either that compliance with the new scheduling had been limited or that producers of these products succeeded in continuing to change their chemical formulas to avoid using the ingredients that had been scheduled. In 2012, for the first time, 8th and 10th graders were asked about their use of synthetic marijuana; their annual prevalence rates also were high at 4.4% and 8.8%, respectively. Use in all 3 grades dropped in 2013, with a sharp and significant decline among 12th graders, and significant declines for both 10th and 12th graders in 2014. These sharp declines continued through 2017 among both 8th and 10thgraders, but halted among 12th graders. Annual prevalence in 2017 was down to 2.0%, 2.7%, and 3.7% for the three grades, reflecting a dramatic drop in use since 2012.

Perceived Risk

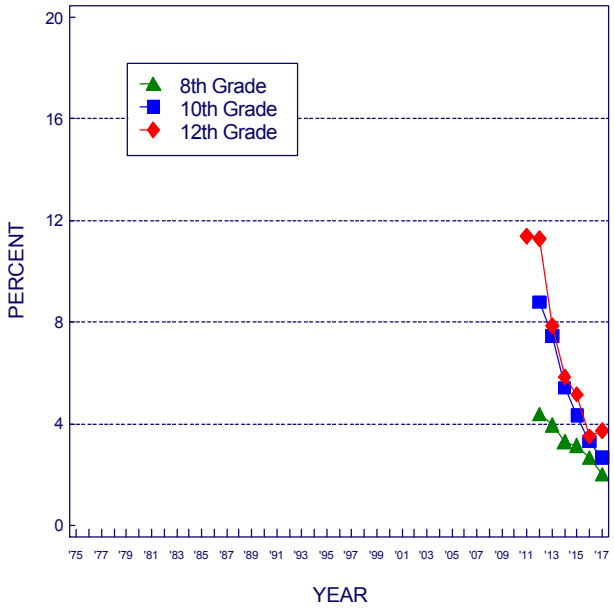
All three grades were asked whether they associated great risk with trying synthetic marijuana once or twice. As can be seen on the facing page, the level of perceived risk for experimental use was quite low in 2012 (between 24% and 25%) but has risen some, particularly among 12th graders, to 36% in 2016. (The pecent would be higher if those answering "Can't say, Drug unfamiliar" were excluded.) In 2017 there was a slight decline in perceived risk in all three grades, including a significant one in 8th grade. The availability of these drugs over the counter probably had the effect of communicating to teens that they must be safe, though in fact they are not.

Disapproval and Availability have not been measured for this class of drugs.

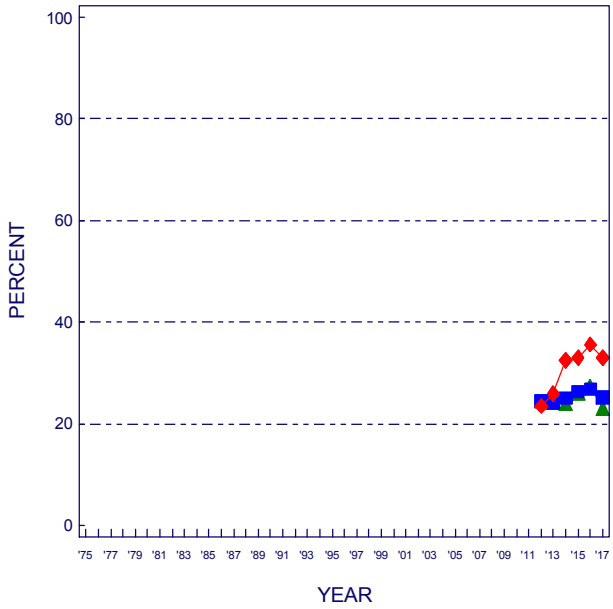
Synthetic Marijuana : Trends in Annual Use and Risk

Grades 8, 10, 12

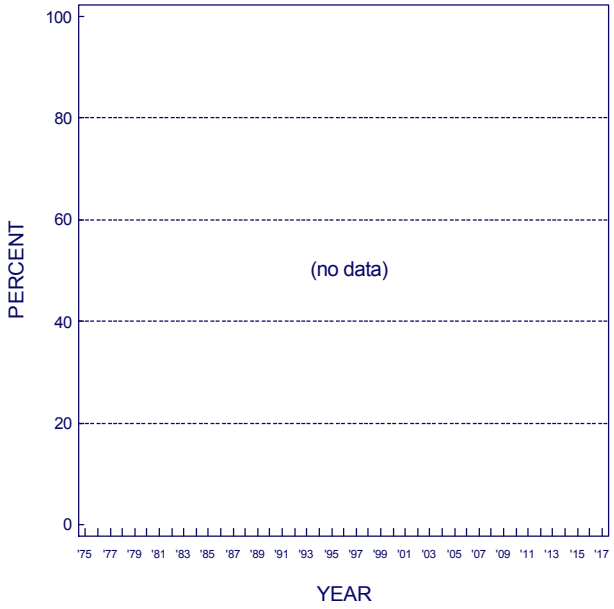
Use
% who used in last 12 months



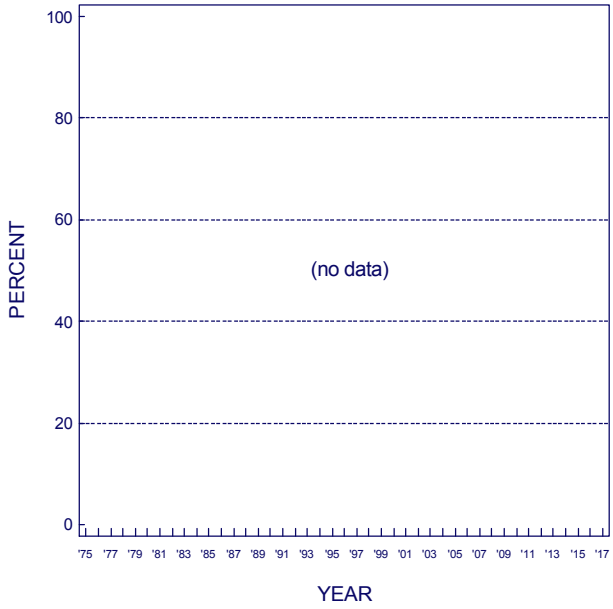
Risk
% seeing "great risk" in using once or twice



Disapproval
% disapproving of using once or twice



Availability
% saying "fairly easy" or "very easy" to get



Source. The Monitoring the Future study, the University of Michigan.

Inhalants

Inhalants are any non-combusted and non-heated gases or fumes that can be inhaled to get high. These include many household products—the sale and possession of which is legal—including glue, nail polish remover, gasoline, solvents, butane, and propellants used in certain commercial products such as whipped cream dispensers . Unlike nearly all other classes of drugs, their use is most common among younger adolescents and tends to decline as youth grow older. The use of inhalants at an early age may reflect the fact that many inhalants are cheap, readily available (often in the home), and legal to buy and possess. The decline in use with age likely reflects their coming to be seen as "kids' drugs," in addition to the fact that a number of other drugs become available to older adolescents, who are also more able to afford them.

Trends in Use

Inhalant use (excluding the use of nitrite inhalants) by 12th graders rose gradually from 1976 to 1987, which was somewhat unusual because most other forms of illicit drug use were in decline during the 1980s. Use of inhalants rose among 8th and 10th graders from 1991, when those grades were first included in the study, through 1995; it rose among 12th graders from 1992 to 1995. All grades then exhibited a fairly steady and substantial decline in use through 2001 or 2002. After 2001 the grades diverged somewhat in their trends: 8th graders showed a significant increase in use for two years, followed by a decline from 2004 to 2013, and a leveling in 2014, before resuming the decline in 2015 and 2016; 10th graders showed an increase after 2003 but a considerable decline since 2007; and 12th graders showed a brief increase from 2003 to 2005 but also a considerable decline since then. For the three grades combined, annual use declined significantly in both 2012 and 2013, held steady in 2014 and then declined further in 2015 and 2016. In 2017, 8th graders showed a significant increase, while 10th and 12th graders showed a continued decline.

Perceived Risk

Only 8th and 10th graders have been asked questions about the degree of risk they associated with inhalant use. Relatively low proportions think that there is a "great risk" in using an inhalant once or twice. However, significant increases in this belief were observed between 1995 and 1996 in both 8th and 10th grades, probably due to an anti-inhalant advertising initiative launched by The Partnership for a Drug-Free America. That increase in perceived risk marked the beginning of a long and important decline in inhalant use, when no other drugs showed a turnaround in use. However, the degree of risk associated with inhalant use declined steadily between 2001 and 2008 among both 8th and 10th graders, perhaps explaining the increase in use in 2003 among 8th graders and in 2004 in the upper grades. The hazards of inhalant use were communicated during the mid-1990s, but generational forgetting of those hazards has likely taken place as replacement class cohorts who were too young to get that earlier message now comprise the nation's adolescents. The decline in perceived risk is worrisome, and it resumed after 2015. In this case, the decline in perceived risk between 2001 and 2008 did not translate into a large surge in use, but it may leave future class cohorts at risk for a resurgence of inhalant use.

Disapproval

Until 2016, over 80% of 8th and 10th grade students said that they would disapprove of even trying an inhalant. (The question was not asked of 12th graders.) There was a very gradual upward drift in disapproval from 1995 through about 2001, with a gradual falloff since then in both grades. For 8th graders there has been some decline in disapproval of trying inhalants since 2012. Since 2014 it has dropped among 10th graders as well, including significant declines in 2015 and 2017.

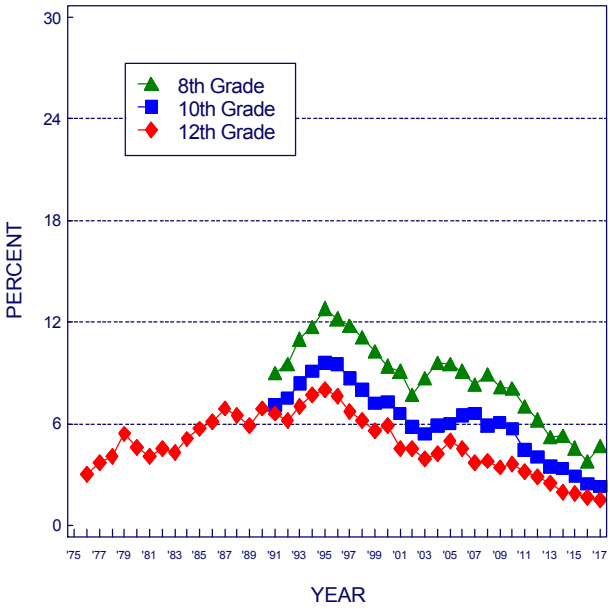
Availability

Respondents have not been asked about the availability of inhalants, because we assume that these products are universally available to young people in these age ranges.

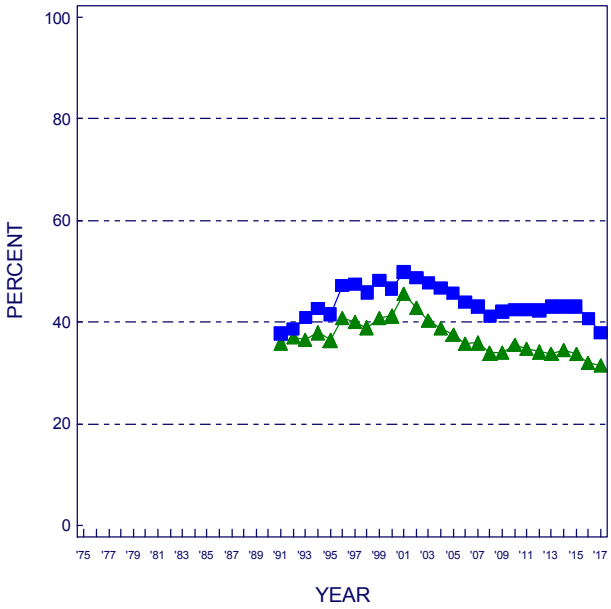
Inhalants : Trends in Annual Use, Risk, and Disapproval

Grades 8, 10, 12

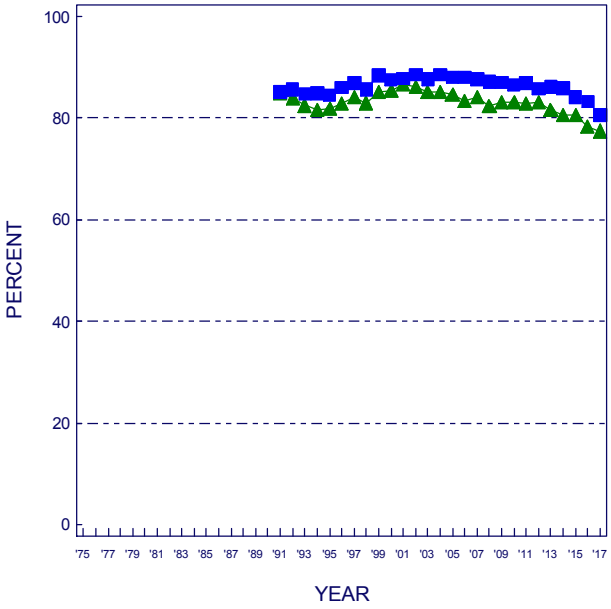
Use
% who used in last 12 months



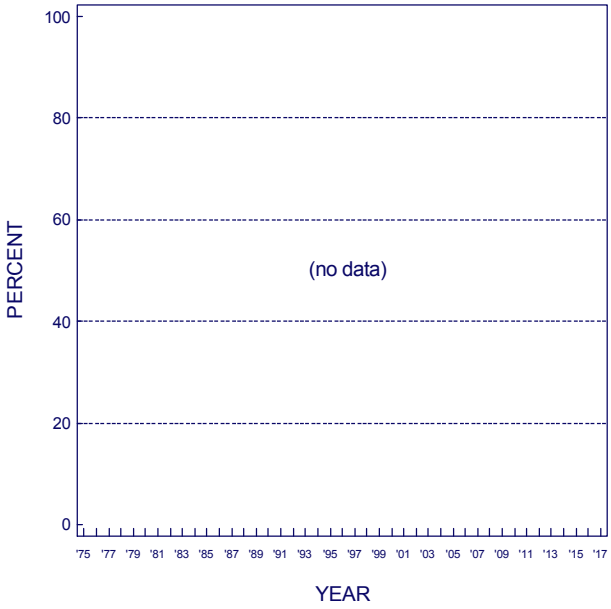
Risk
% seeing "great risk" in using once or twice



Disapproval
% disapproving of using once or twice



Availability
% saying "fairly easy" or "very easy" to get



Source. The Monitoring the Future study, the University of Michigan.

LSD

For some years, LSD was the most widely used drug within the larger class of hallucinogens. This was no longer true for some subsequent years, due to sharp decreases in its use combined with an increasing use of psilocybin. (Statistics on overall hallucinogen use and on use of hallucinogens other than LSD are shown in the tables at the end of this report.) Now overall hallucinogen use and use of hallucinogens other than LSD are about equivalent due to a drop in the use of the other hallucinogens.

Trends in Use

Annual prevalence of LSD use among 12th graders has been below 10% since MTF began. Use declined some for the first 10 years among 12th graders, likely continuing a decline that had begun before 1975. Use was fairly level in the latter half of the 1980s but, as was true for a number of other drugs, rose in all three grades between 1991 and 1996. Between 1996 and 2006 or so, use declined in all three grades, with particularly sharp declines between 2001 and 2003. Since then use has remained at very low levels although there has been a slight increase in the upper grades since 2013.

Perceived Risk

We think it likely that perceived risk for LSD use increased during the early 1970s, before MTF began, as concerns grew about possible neurological and genetic effects (most of which were never scientifically confirmed) as well as "bad trips" and "flashbacks." However, there was some decline in perceived risk in the late 1970s, after which it remained fairly level among 12th graders through most of the 1980s. A substantial decline occurred in all grades in the early 1990s as use rose. Since about 2000, perceived risk declined steadily and substantially among 8th graders until 2007, when it leveled; it declined considerably among 10th graders before leveling around 2002, dropping through 2007, and then leveling after that. Since 2014 and 2015 risk has declined once again in both 10th and 12th graders. Among 12th graders, the recent decline in perceived risk marks the end of a levelling that had been in place since 2002. The decline in the lower grades initially suggests that younger teens may be less knowledgeable about this drug's effects than their predecessors—through what we have called "generational forgetting"—making them vulnerable to a resurgence in use. (The percentages who respond "can't say, drug unfamiliar" to questions about LSD have risen in recent years, consistent with the notion of "generational forgetting.")

The decline of LSD use until recent years, despite a fall in perceived risk, suggests that some factors other than a change in underlying attitudes and beliefs contributed to the downturn—prior to 2001 some displacement by ecstasy may have been a factorwhile more recently a decline in availability (discussed below) likely is a factor.

Disapproval

Disapproval of LSD use was quite high among 12th graders through most of the 1980s but began to decline after 1991 along with perceived risk. All three grades exhibited a decline in disapproval through 1996, with disapproval of experimentation dropping 11 percentage points between 1991 and 1996 among 12th graders. After 1996 a slight increase in disapproval emerged among 12th graders, accompanied by a leveling among 10th graders and some further decline among 8th graders. From 2001 to 2008, disapproval of LSD use diverged among the three grades, declining considerably among 8th graders, declining less among 10th graders, and increasing significantly among 12th graders. Note, however, that the percentages of 8th and 10th graders who respond with "can't say, drug unfamiliar" increased through 2008; thus the base for disapproval has shrunk, suggesting that the real decline of disapproval among the younger students is less than it appears here. Since 2010 the divergence has reversed, with levels of disapproval declining for 12th grade students, staying level for 10th grade students, and increasing for 8th grade students.

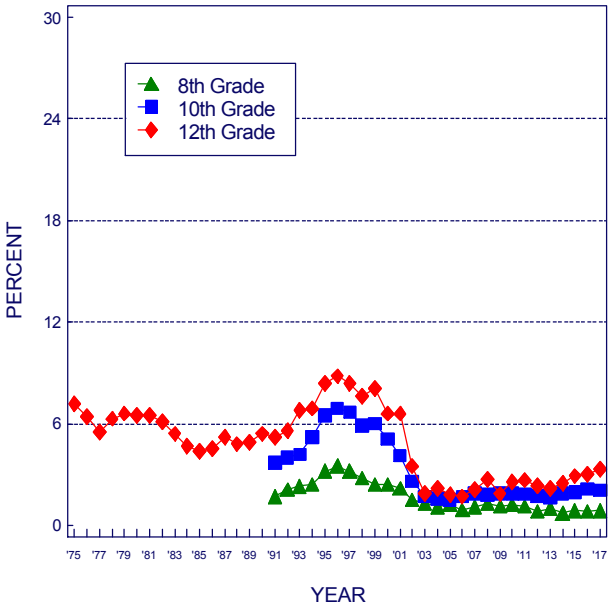
Availability

Reported availability of LSD by 12th graders fell considerably from 1975 to 1979, declined a bit further until 1986, and then began a substantial rise, reaching a peak in 1995. LSD availability also rose somewhat among 8th and 10th graders in the early 1990s, reaching a peak in 1995 or 1996. Since those peak years, there has been considerable falloff in reported availability in all three grades, quite possibly in part because fewer students have LSD-using friends from whom they could gain access. There was also very likely a decrease in supply due to the closing of a major LSD-producing lab by the Drug Enforcement Administration in 2000. It is clear that attitudinal changes cannot explain the substantial declines in use.

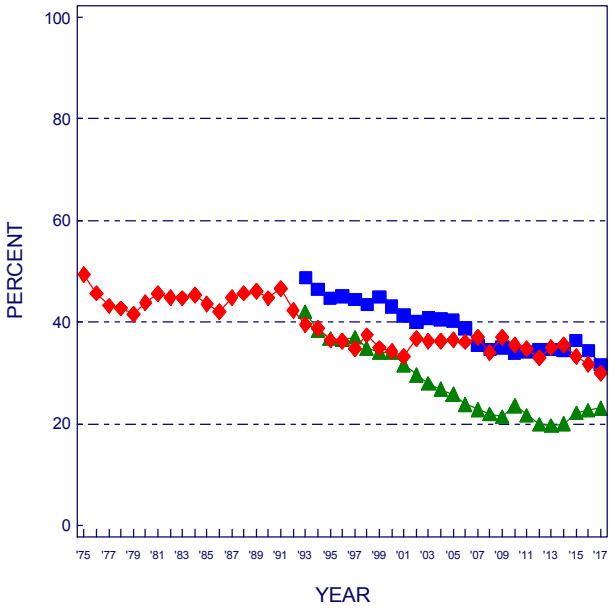
LSD: Trends in Annual Use, Risk, Disapproval, and Availability

Grades 8, 10, 12

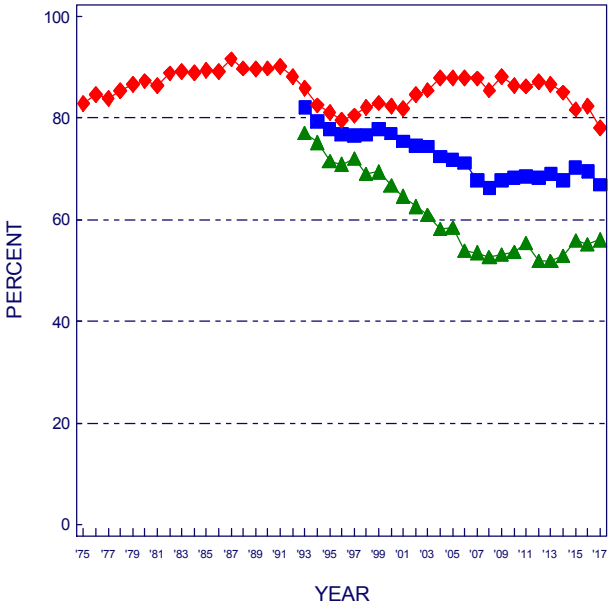
Use
% who used in last 12 months



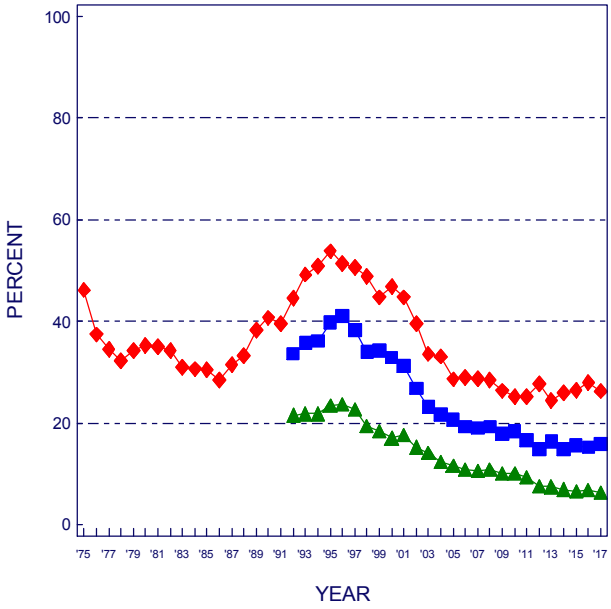
Risk
% seeing "great risk" in using once or twice



Disapproval
% disapproving of using once or twice



Availability
% saying "fairly easy" or "very easy" to get



Source. The Monitoring the Future study, the University of Michigan.

Cocaine

Cocaine was used almost exclusively in powder form for some years, though "freebasing" emerged for a while. The early 1980s brought the advent of crack cocaine. Our original questions did not distinguish among different forms of cocaine or modes of administration. Since 1987, though, we have asked separate questions about the use of crack and "cocaine other than crack," which has consisted almost entirely of powder cocaine use. Data on cocaine use in general (i. e., all forms of cocaine) are presented in the figures in this section, and results for crack alone are presented in the next section.

Trends in Use

There have been some important changes in the levels of overall cocaine use over the life of MTF. Use among 12th graders originally burgeoned in the late 1970s and remained fairly stable through the first half of the 1980s before starting a precipitous decline after 1986. Annual prevalence among 12th graders dropped by about three quarters between 1986 and 1992. Between 1992 and 1999, use reversed course again during the relapse phase of the overall drug epidemic and doubled before declining by 2000. Use also rose among 8th and 10th graders after 1992 before reaching peak levels in 1998 and 1999. Over the last seventeen years, use has declined in all three grades, except for a rise in 12th grade use in 2017 (ns); annual 12th grade use stands at just 2.7% in 2016, with use by 8th and 10th graders still lower, at 0.8% and 1.4%.

Perceived Risk

Questions about the dangers of cocaine in general (without specifying any particular form of cocaine) have been asked only of 12th graders. The results tell a fascinating story. They show that perceived risk for experimental use fell in the latter half of the 1970s (when use was rising), stayed level in the first half of the 1980s (when use was level), and then jumped very sharply in a single year (by 14 percentage points between 1986 and 1987), just when the substantial decline in use began. The year 1986 was marked by a media frenzy over crack cocaine and the widely publicized role of cocaine in the death of Len Bias, a National Basketball Association first-round draft pick. Bias' death was originally reported as resulting from his first experience with cocaine. Though that was later proven to be incorrect, the message had already "taken." We believe that this event helped to persuade many young people that use of cocaine at any level is dangerous, no matter how healthy the individual.[12] Perceived risk continued to rise through 1991 as the fall in use continued. Perceived risk declined modestly from 1991 to 2000, and use rose from 1992 to 2000. Perceived risk has leveled in recent years at far higher levels than existed prior to 1987, and there was a gradual upward drift for about six years in grades 8 and 10, before leveling. In 2017, 10th graders showed a significant decline. For the 12th graders, perceived risk also increased for about six years before leveling after 2013. There is as yet little evidence of generational forgetting of cocaine's risks. For 12th graders, survey questions on both risk and disapproval referred to cocaine in general, until 1986. After that they referred to cocaine powder and crack separately, as did the questions asked of 8th and 10th graders. The question change seemed to matter rather little in the results.

Disapproval

Disapproval of cocaine use by 12th graders followed a cross-time pattern similar to that for perceived risk, although its seven percentage-point jump in 1987 was not quite as pronounced. Some decline from 1991 to 1997 was followed by a period of stability. Subsequent years showed a gradual increase in disapproval in all three grades. This upward drift ended in recent years, but disapproval of even trying cocaine remains very high and is above 85% in all grades in 2017.

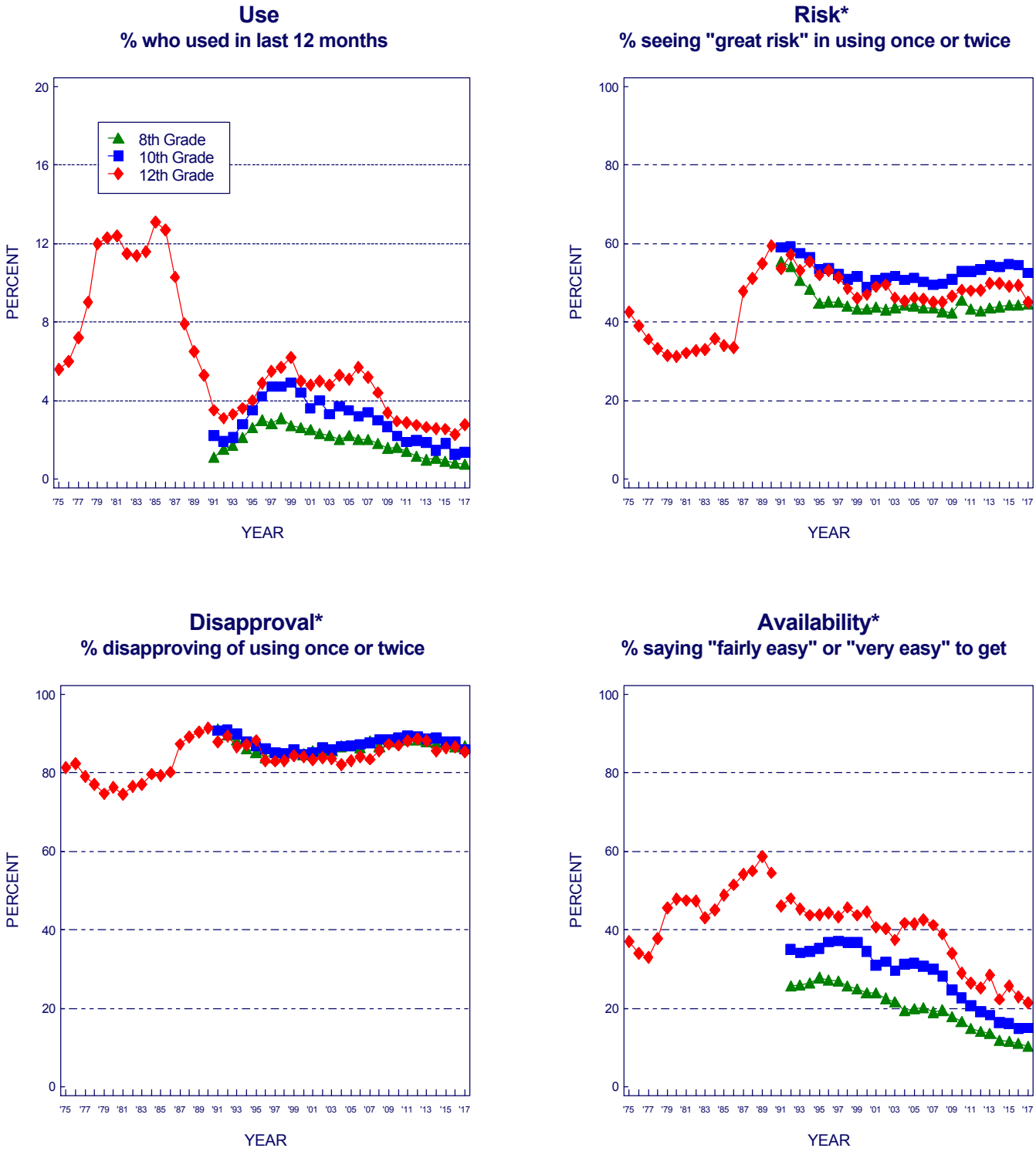
Availability

The proportion of 12th graders saying that cocaine would be "fairly easy" or "very easy" for them to get if they wanted some was 33% in 1977, rose to 48% by 1980 as use rose, and held fairly level through 1982; it increased steadily to 59% by 1989 (in a period of rapidly declining use). Perceived availability then fell back to about 47% by 1994. Since around 1997, perceived availability of cocaine has fallen considerably in all three grades. Among 12th graders it stood at 27% in 2017—less than half of its peak level in 1989. Note that the pattern of change does not map well onto the pattern of actual use, suggesting that changes in overall availability have not been a major determinant of use—particularly during the sharp decline in use in the late 1980s.

[12] Among 12th graders trends in perceived risk in Table 8 show a particularly sharp rise from 34% in 1986 to 48% in 1987 for trying cocaine once or twice.

Cocaine (including Crack) : Trends in Annual Use, Risk, Disapproval, and Availability

Grades 8, 10, 12



Source. The Monitoring the Future study, the University of Michigan.
*Prior to 1991, data reported here is based on questions on use of cocaine in general. Starting in 1991, data based on questions on use of cocaine powder specifically.

Crack

Several indirect indicators suggest that crack use grew rapidly in the period 1983–1986, before we had direct measures of its use. In 1986 a single usage question was included in one of the five 12th grade questionnaire forms, asking those who indicated any cocaine use in the prior 12 months if they had used crack. The results from that question represent the first data point in the first panel on the facing page. After that, three questions about crack use covering the usual three prevalence periods were introduced into several questionnaire forms; the data generated by them may be seen in the tables at the end of this volume.

Trends in Use

Clearly crack use rose rapidly in the early 1980s, judging by the 4% annual prevalence reached in 1986; but after 1986 there was a precipitous drop in crack use among 12th graders; the drop continued through 1991. After 1991 for 8th and 10th graders (when data were first available) and after 1993 for 12th graders, all three grades showed a slow, steady increase in use through 1998 during what we have called the relapse phase of the overall drug epidemic. Since 1999, annual prevalence has dropped by about three quarters in 8th and 10th grades and nearly two thirds in 12th grade. By 2016 crack use was at historic lows in all three grades, but in 2017 all three grades showed nonsignificant increases in use. As with many drugs, the decline at 12th grade lagged behind those in the lower grades due to a cohort effect.

Perceived Risk

By the time we added questions about the perceived risk of using crack in 1987, crack was already seen by 12th graders as one of the most dangerous illicit drugs: 57% saw a great risk in even trying it. This compared to 54% for heroin, for example. Perceived risk for crack rose still higher through 1990, reaching 64% of 12th graders who said they thought there was a great risk in taking crack once or twice. (Use was dropping during that interval.) After 1990 some falloff in perceived risk began, well before crack use began to increase in 1994, making perceived risk again a leading indicator. Between 1991 and 1998 there was a considerable falloff in this belief in grades 8 and 10, as use rose steadily. Perceived risk leveled in 2000 in grades 8 and 12 and a year later in grade 10. We think that the declines in perceived risk for crack and cocaine during the 1990s may well reflect an example of generational forgetting wherein the class cohorts that were in adolescence when the adverse consequences were most obvious (i.e., in the mid-1980s) were replaced by cohorts who were less knowledgeable about these dangers. By 2017 perceived risk for crack remained at about the same or even declined a bit in all three grades.

Disapproval

Disapproval of crack use was not assessed until 1990, when it was at a very high level, with 92% of 12th graders saying that they disapproved of even trying it. Disapproval of crack use declined slightly but steadily in all three grades from 1991 through about 1997 as perceived risk decreased and use increased. After 1997, disapproval in all three grades rose back to high levels by 2012 before beginning a gradual and small decline.

Availability

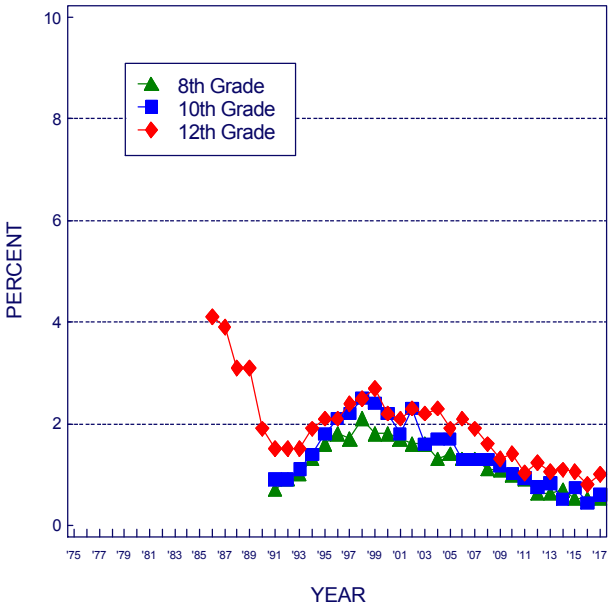
Crack availability did not change dramatically in the early years for which data are available. It began a sustained decline after 1995 among 8th graders, after 1999 among 10th graders, and after 2000 among 12th graders. Since 2000, availability has declined considerably, reaching historic lows in 2017 in all three grades.

NOTE: The distinction between crack cocaine and other forms of cocaine (mostly powder) was made several years after the study's inception. The figures on the facing page begin their trend lines when these distinctions were introduced. Figures are not presented here for the "other forms of cocaine" measures, simply because the trend curves look extremely similar to those for crack. (All statistics are contained in the tables.) Although the trends are very similar, the absolute levels of use, risk, etc., are somewhat different. Usage levels tend to be higher for cocaine powder compared to crack, and the levels of perceived risk a bit lower, while disapproval has been close for the two different forms of cocaine and relative availability has varied (Tables 9 through 14).

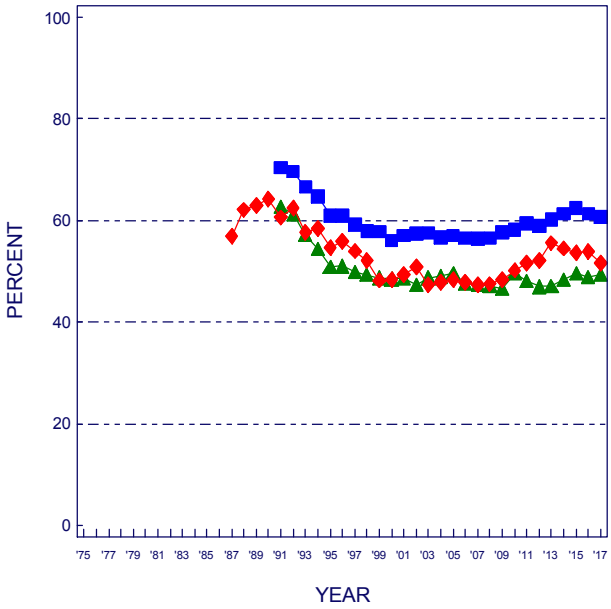
Crack: Trends in Annual Use, Risk, Disapproval, and Availability

Grades 8, 10, 12

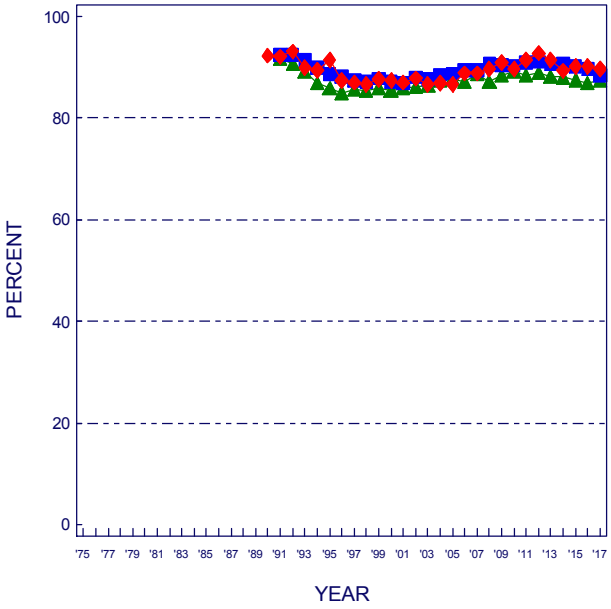
Use
% who used in last 12 months



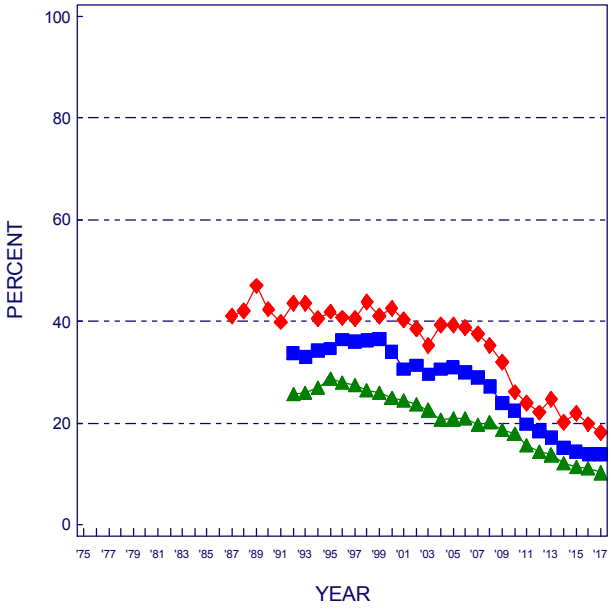
Risk
% seeing "great risk" in using once or twice



Disapproval
% disapproving of using once or twice



Availability
% saying "fairly easy" or "very easy" to get



Source. The Monitoring the Future study, the University of Michigan.

Amphetamines and Other Stimulant Drugs

Amphetamines, a class of psychotherapeutic stimulants, had a relatively high prevalence of use in the youth population for many years. Amphetamines are controlled substances—they are not legally bought or sold without a doctor's prescription—but some are diverted from legitimate channels, and some are manufactured and/or imported illegally. . .Another controlled stimulant .included here is Ritalin which is used to treat ADHD, as is Adderall, the most prevalent of the amphetamines.

Trends in Use

The use of these stimulants rose in the last half of the 1970s, reaching a peak in annual prevalence of 26% in 1981 (likely exaggerated due to commonly used "look-alikes")—two years after marijuana use peaked. From 1981 to 1992, 12th graders showed a steady and very substantial decline in stimulant use, reaching 6%.

As with many other illicit drugs, these stimulants made a comeback in the 1990s. Use peaked in the lower two grades by 1996 and for many years declined steadily in 8th grade and sporadically in 10th grade. Only in 2003 it began to decline in 12th grade—likely reflecting a cohort effect. The decline paused in 2008 for 8th graders and 2008/2009 for 12th graders, and then resumed. The 12th grade decline reversed from 2009 to 2013. In 2013 the amphetamines/stimulants prevalence question text was changed in half of the questionnaire forms. The 2013 report used data from the changed forms only, to be comparable to the 2014 measure. In 2014 the remaining forms were changed; the 2014 and subsequent data presented here are for all the forms. From 2009 to 2013 use rose in the upper grades, likely due to use intended to assist with academic performance. Since 2013 there has been a downward drift in annual prevalence but a steeper decline in 30-day prevalence(significant in the upper grades).

See Table 6 for the trends in annual use of two specific amphetamines—Ritalin and Adderall. Since it was first measured in 2001, Ritalin use has declined by 75% to 85% in all three grades. Adderall use declined in the lower grades since it was first measured in 2009; but annual prevalence increased significantly in 12th grade between 2009 (to 5.4%) and 2013 (to 7.4%) where it remained in 2015 before falling to 5.5% in 2017.

Perceived Risk

Only 12th graders are asked about the amount of risk they associate with amphetamine/stimulant use. For a few years, changes in perceived risk were not correlated with changes in usage levels (at the aggregate level). Specifically, in the interval 1981–1986, risk was quite stable even though use fell considerably, likely as a result of some displacement by increasing cocaine use. There was, however, a decrease in risk during the period 1975–1981 (when use was rising), some increase in perceived risk in 1986–1991 (when use was falling), and some decline in perceived risk from 1991 to 1995 (in advance of use rising again). Perceived risk generally rose until 2010 , very likely contributing to the decline in use that occurred among 12th graders after 2002. In 2011 the examples of specific amphetamines provided in the text of the questions on perceived risk, disapproval, and availability were updated with the inclusion of Adderall and Ritalin. This led to some discontinuities in the trend lines in 2011. (Levels of perceived risk and disapproval lowered as a result.) Based on the revised question, some decline has occurred since 2013.

Disapproval

Disapproval of amphetamine/stimulant use also is asked in 12th grade only. Relatively high proportions of 12th graders have disapproved of even trying amphetamines/stimulants throughout the life of the study. Disapproval did not change in the late 1970s despite an increase in use. From 1981 to 1992, disapproval rose gradually and substantially from 71% to 87% as perceived risk rose and use declined. In the mid-1990s disapproval declined along with perceived risk, but it increased fairly steadily from 1996 through 2009 before leveling. There has been a very slight falloff since 2013.

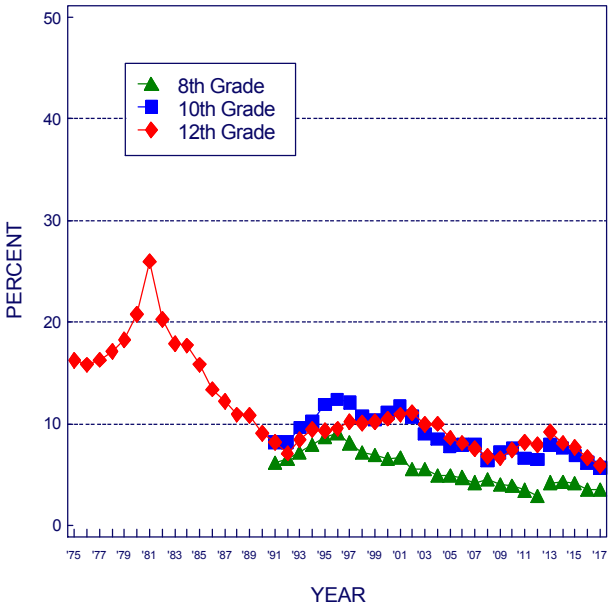
Availability

In 1975, amphetamines/stimulants had a high level of reported availability. The level fell by about 10 percentage points by 1977, drifted up a bit through 1980, jumped sharply in 1981, and then began a long, gradual decline through 1991. There was a modest increase in availability at all three grade levels in the early 1990s as use rose, followed by a very large long-term decline which continued through 2017.

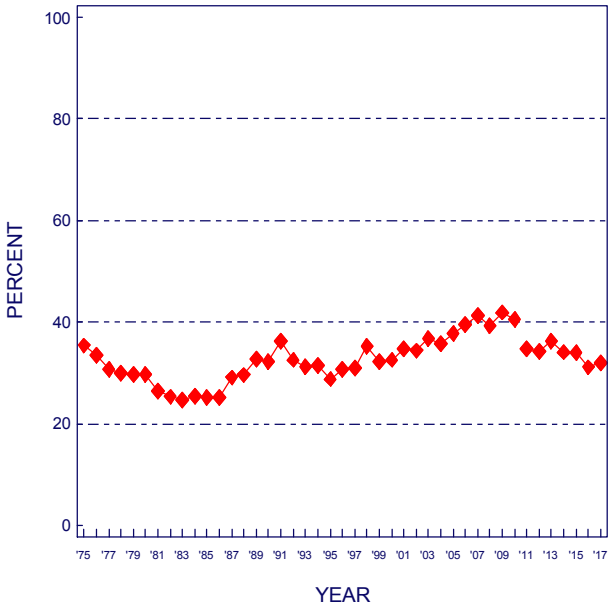
Amphetamines : Trends in Annual Use, Risk, Disapproval, and Availability

Grades 8, 10, 12

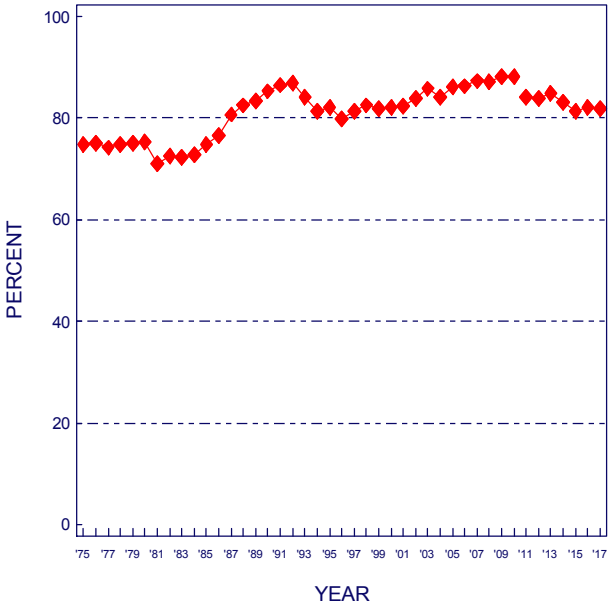
Use*
% who used in last 12 months



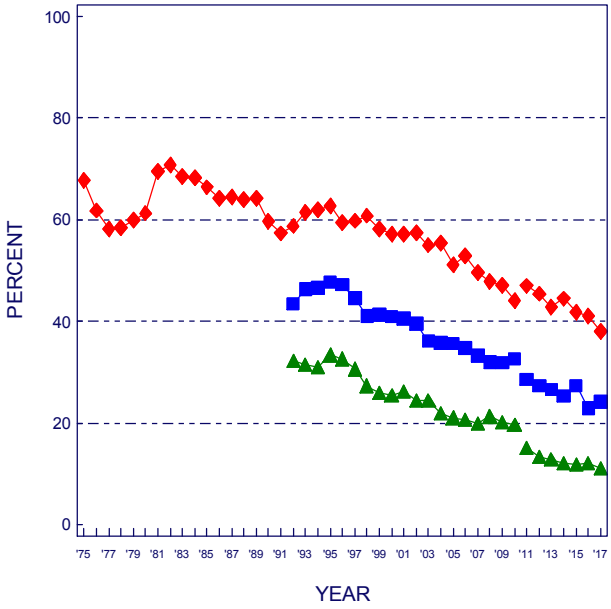
Risk**
% seeing "great risk" in using once or twice



Disapproval**
% disapproving of using once or twice



Availability**
% saying "fairly easy" or "very easy" to get



Source. The Monitoring the Future study, the University of Michigan.

*In 2013 the question text was changed on two of the questionnaire forms for 8th and 10th graders and four of the questionnaire forms for 12th graders, and changed on the remaining forms in 2014. Beginning in 2013, data presented here include only the changed forms.

**In 2011 the list of examples was changed from uppers, pep pills, bennies, speed to uppers, speed, Adderall, Ritalin, etc. These changes likely explain the discontinuity in the 2011 results.

Methamphetamine and Crystal Methamphetamine (Ice)

One subclass of amphetamines is called methamphetamine ("speed"). This subclass has been around for a long time and gave rise to the phrase "speed kills" in the 1960s. Probably because of the reputation it got at that time as a particularly dangerous drug, it was not popular for some years, so we did not include a full set of questions about its use in MTF's early questionnaires. One form of methamphetamine, crystal methamphetamine or "ice," grew in popularity in the 1980s. It comes in crystallized form, as the name implies, and the chunks can be heated and the fumes inhaled, much like crack cocaine.

Trends in Use

For most of the life of the study, the only question about ***methamphetamine*** use has been contained in one of the six 12th-grade questionnaire forms. Respondents who indicate using any type of amphetamine in the prior 12 months are asked in a sequel question to indicate on a pre-specified list the types they have used during that period. Methamphetamine is one type on the list, and data exist on its use since 1976. (The rates are not graphed here until 1990.) In 1976, annual prevalence using this measure was 1.9%; it then roughly doubled to 3.7% by 1981 (the peak year), before declining for over a decade all the way down to 0.4% by 1992. Use then rose again in the mid-1990s, as did use of a number of drugs, reaching 1.3% by 1998. In other words, it has followed a cross-time trajectory fairly similar to that for amphetamines as a whole. No questions have yet been added to the study on perceived risk, disapproval, or availability with regard to overall methamphetamine use.

In 1990, in the 12th-grade questionnaires only, we introduced our usual set of three questions for ***crystal methamphetamine***, measuring lifetime, annual, and 30-day use. Among 12th graders in 1990, 1.3% indicated any use in the prior year; use climbed to 3.0% by 1998, and has generally been declining since then, reaching an all-time low of 0.5% in 2015 and then 0.8% in both 2016 and 2017. This variable is charted on the first panel of the facing page.

Responding to the growing concern about methamphetamine use in general—not just crystal methamphetamine use—we added a full set of three questions about the use of any methamphetamine to the 1999 questionnaires for all three grade levels. These questions yield a somewhat higher annual prevalence for 12th graders: 4.3% in 2000, compared to the sum of the methamphetamine and crystal methamphetamine answers in the other, branching question format, which totaled 2.8%. It would appear, then, that the long-term method we had been using for tracking methamphetamine use probably yielded an underestimate of the absolute prevalence level, perhaps because some proportion of methamphetamine users did not correctly categorize themselves initially as amphetamine users (even though methamphetamine was given in the question as one of the examples of amphetamines). We think it likely that the shape of the trend curve was not distorted, however.

The newer questions for ***methamphetamine*** (not graphed here) show annual prevalence rates in 2017 of 0.5% for 8th graders, 0.4% for 10th graders, and 0.6% for 12th graders. These levels are the lowest ever recorded for 10th and 12th graders and very near the lowest for 8th graders. The 2017 levels for all three grades are down considerably from the first measurement taken in 1999, when they were 3.2%, 4.6%, and 4.7% (see Table 6). So, despite growing public concern about the methamphetamine problem in the United States, use actually showed a fairly steady and substantial decline since 1999, at least among secondary school students. (A similar decline in methamphetamine use did not begin to appear among college students and young adults generally until after 2004, likely reflecting a cohort effect. See *Volume II* in this series for data on adults through age 55.)

Other Measures

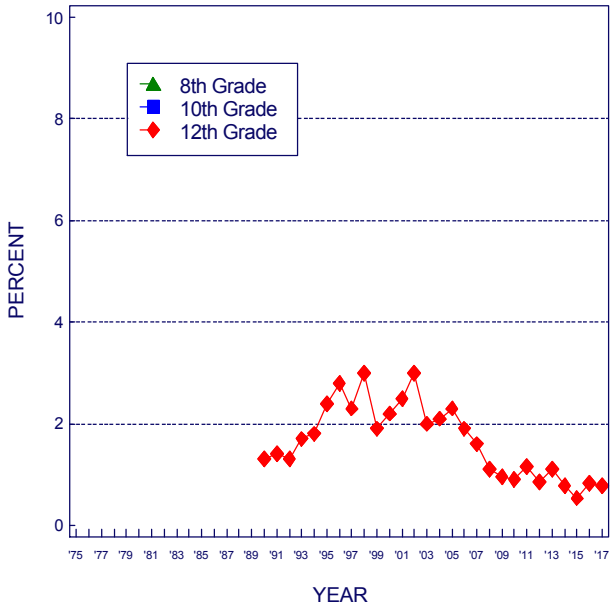
Data on perceived risk and availability for crystal methamphetamine, specifically, may be found on the facing page.

Clearly, the perceived risk of using crystal methamphetamine has risen considerably since 2003, very likely explaining much of the decline in use since then. Perceived risk then leveled after 2013. Perceived availability generally has been falling in all three grades since 2006, perhaps in part because there are many fewer crystal methamphetamine users from whom to get the drug.

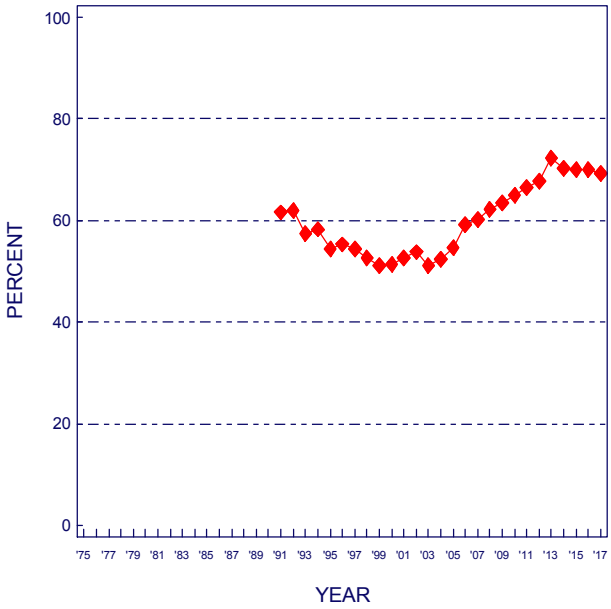
Crystal Methamphetamine (Ice) : Trends in Annual Use, Risk, and Availability

Grades 8, 10, 12

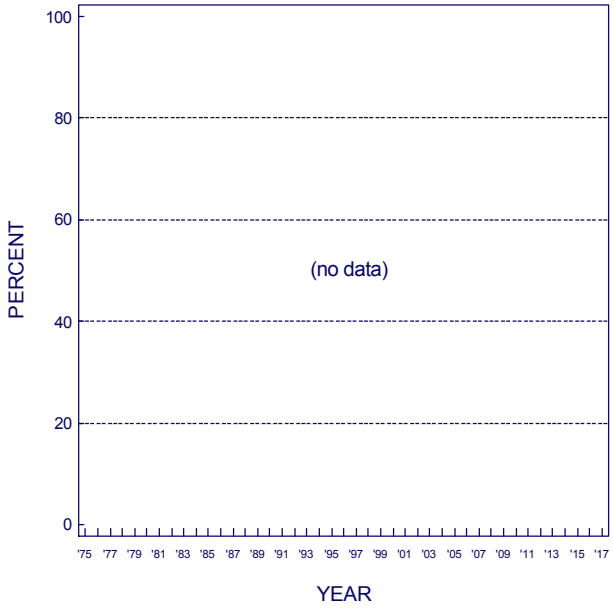
Use
% who used in last 12 months



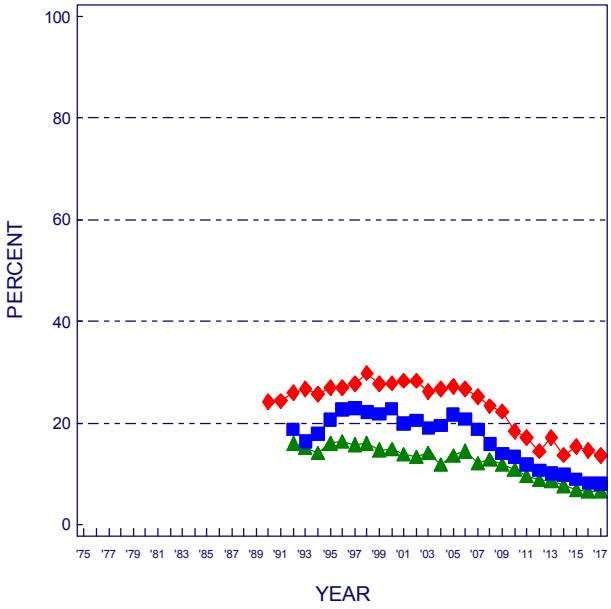
Risk
% seeing "great risk" in using once or twice



Disapproval
% disapproving of using once or twice



Availability
% saying "fairly easy" or "very easy" to get



Source. The Monitoring the Future study, the University of Michigan.

Heroin

For many decades, heroin—a derivative of opium—was administered primarily by injection into a vein. However, in the 1990s the purity of available heroin reached very high levels, making other modes of administration (e.g., snorting, smoking) practical alternatives. Thus, in 1995 we introduced questions that asked separately about using heroin with and without a needle to determine whether non-injection use explained the upsurge in heroin use we observed. The usage statistics presented on the facing page are based on heroin use by any method, but data on the two specific types of administration are provided in the tables at the end of this report.

Trends in Use

The annual prevalence of heroin use among 12th graders fell by half between 1975 and 1979, from 1.0% to 0.5%. The rate then held amazingly steady until 1994. Use rose in the mid- and late-1990s, along with the use of most drugs; it reached peak levels in 1996 among 8th graders (1.6%), in 1997 among 10th graders (1.4%), and in 2000 among 12th graders (1.5%), suggesting a cohort effect. Following those peak levels, use declined, with annual prevalence in all three grades fluctuating between 0.7% and 0.9% from 2005 through 2010. Since then, annual prevalence for the three grades combined declined, from 0.8% in 2010 to 0.3% in 2017. In 2016 use reached its lowest levels in all three grades (0.3% in each) with little change in 2017.

Because the questions about use with and without a needle were not introduced until the 1995 survey, they did not encompass much of the period of increasing heroin use. The new questions showed that, by then, about equal proportions of all 8th grade users were taking heroin by each method of ingestion and some—nearly a third of users—were using both means. At 10th grade, a somewhat higher proportion of all users took heroin without a needle, and at 12th grade, the proportion was higher still. Thus, much of the increase in overall heroin use after 1995 occurred in the proportions using it without injecting, which we strongly suspect was true in the immediately preceding period of increase as well. Likewise, much of the decrease since the recent peak levels has been due to decreasing use of heroin without a needle. In 2012, there were significant decreases in use of heroin without a needle for 8th and 12th graders, and very slight declines since then in 8th and 10th grades.

Use with a needle has fallen considerably in all three grades since the mid-1990s; annual prevalence in 2017 of all three grades combined stood at 0.2%, including significant declines in 8th and 10th grades from the 2014 to 2015 prevalence levels. The proportional declines were greatest in the lower grades. While a heroin epidemic continues among adults, our data—as well as those from the National Survey on Drug Use and Health—suggest that use has grown primarily among young adults and not among adolescents.

Perceived Risk

Students have long seen heroin to be one of the most dangerous drugs, which helps to account for both the consistently high level of personal disapproval of use (see below) and the quite low prevalence of use. Nevertheless, perceived risk levels have changed some over the years. Between 1975 and 1986, perceived risk gradually declined, even though use dropped and then stabilized in that interval. Then there was a big spike in 1987 (when perceived risk for cocaine also jumped dramatically), where it held for four years. In 1992, perceived risk dropped to a lower level again, presaging an increase in use a year or two later. Perceived risk rose in the latter half of the 1990s, and use leveled off and then declined. Risk at 12th grade is still rising, but has been level for some time at 8th and 10th grades. Perceived risk of use without a needle rose in 8th and 10th grades between 1995 and 1997, foretelling an end to the increase in that form of use. Note that perceived risk has served as a leading indicator of use for this drug as well as a number of others. During the 2000s, perceived risk was relatively stable at a high level.

Disapproval

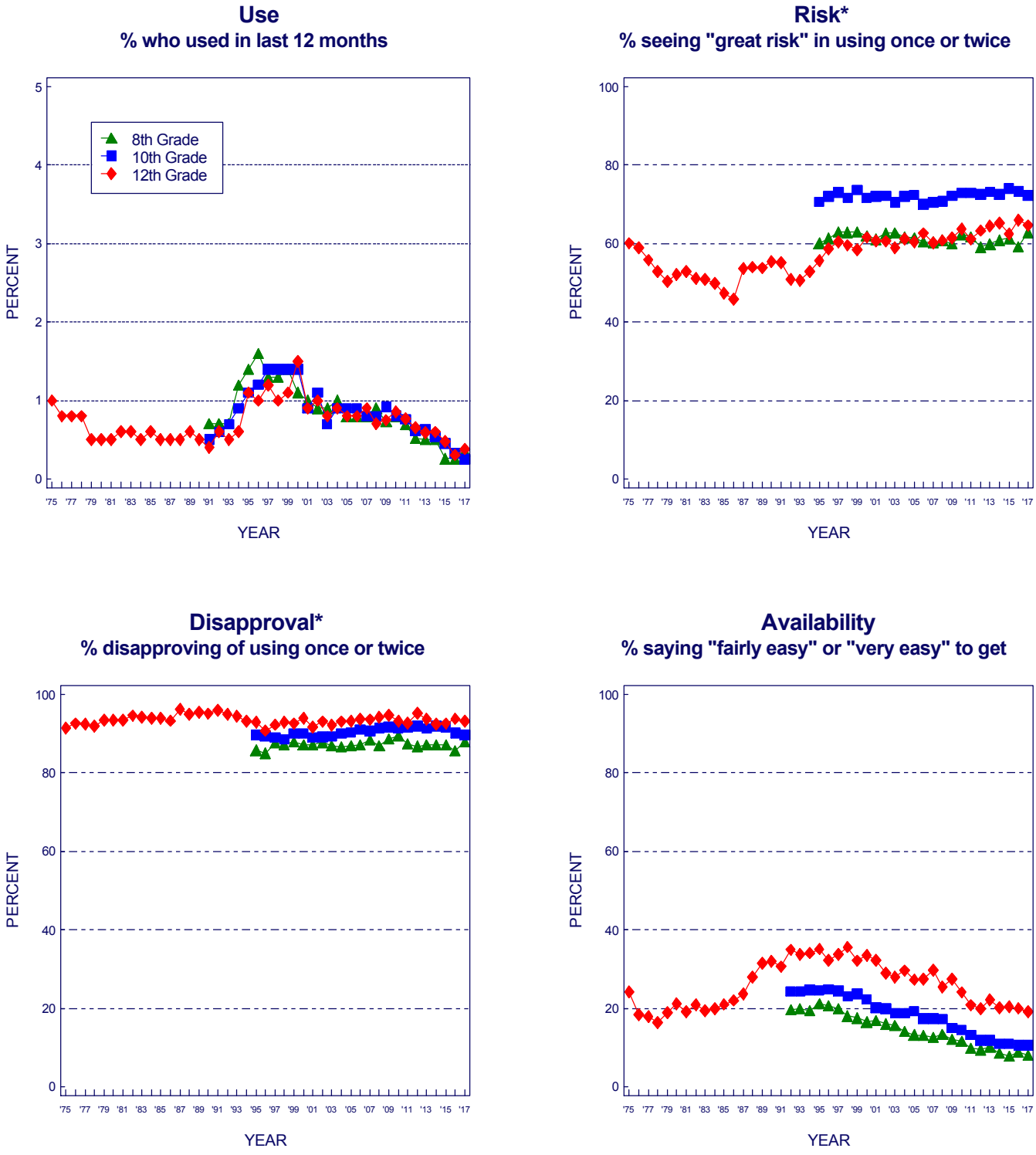
There has been little fluctuation in the very high levels of disapproval of heroin use over the years, though it did rise gradually between 2000 and 2010. The small changes that have occurred have been generally consistent with changes in perceived risk and use.

Availability

The proportion of 12th grade students saying they could get heroin fairly or very easily if they wanted some remained around 20% through the mid-1980s. It then increased considerably from 1986 to 1992 before stabilizing at about 35% from 1992 through 1998. From the mid- to late-1990s through 2014, perceived availability of heroin declined gradually but substantially in all three grades before leveling in 2014 or 2015.

Heroin: Trends in Annual Use, Risk, Disapproval, and Availability

Grades 8, 10, 12



Source. The Monitoring the Future study, the University of Michigan.

*Prior to 1995, the questions asked about heroin use in general. Since 1995, the questions have asked about heroin use without a needle.

Other Narcotic Drugs, Including OxyContin and Vicodin

There are a number of narcotic drugs other than heroin—all controlled substances. Many are analgesics that can be prescribed by physicians and dentists for pain. Like heroin, many are derived from opium, but there are also a number of synthetic analogues in use today, with OxyContin and Vicodin being two of the major ones.

Throughout the life of the MTF study, we have asked about the use of any narcotic drug other than heroin without specifying which one. Examples of drugs in the class are provided in the question stem. In one of the six 12th grade questionnaire forms, however, respondents indicating that they had used any narcotic in the past 12 months were then asked to check which of a fairly long list of such drugs they used. Table E-4 in Appendix E of *Volume I* of this annual monograph series provides trends in their annual prevalence data. In the late 1970s, opium and codeine were among the narcotics most widely used. In recent years Vicodin, codeine, Percocet, OxyContin, and hydrocodone have been the most prevalent.

Trends in Use

Use is reported for 12th graders only, because we considered the data from 8th and 10th graders to be of questionable validity. As shown in the first panel of the facing page, 12th graders' use of narcotics other than heroin generally trended down from about 1977 through 1992, dropping considerably. After 1992 use rose rather steeply as all forms of substance use were increasing, with annual prevalence nearly tripling from 3.3% in 1992 to 9.5% in 2004, before leveling through about 2009. Since then, use has been declining, particularly since 2009.

In 2002, the question was revised to add Vicodin, OxyContin, and Percocet to the examples given, which clearly had the effect of increasing reported prevalence, as may be seen in the first panel on the facing page. So the extent of the increase over the full time span likely is exaggerated, although probably not by much, because these drugs came onto the scene later, during the rise. They simply were not being fully reported until the late 1990s. Narcotics had become one of the most widely used classes of illicit drugs by 2004, when annual prevalence reached 9.5%.

In a departure from the usual arrangement on the facing page, use rates for two narcotics of recent interest—OxyContin and Vicodin—are presented in the second and third panels instead of risk and disapproval. There are no data on disapproval for other narcotics, and only limited 12th grade data on perceived risk (since 2010), showing high but gradually declining risk levels (see Table 11).

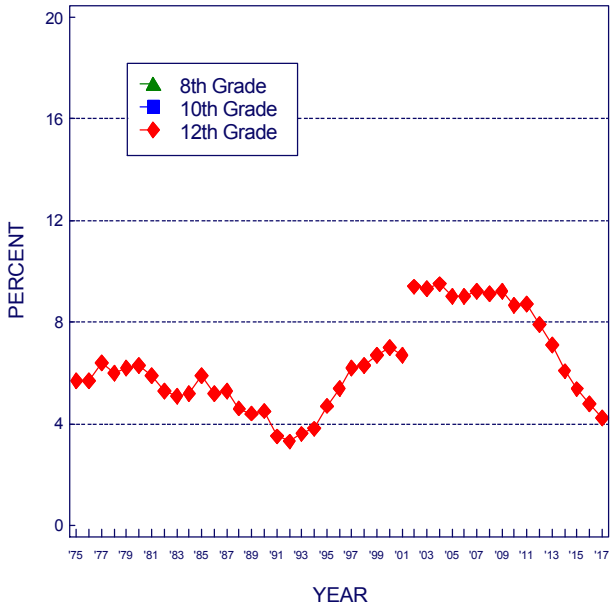
OxyContin use increased some in all grades from 2002 (when it was first measured) through roughly 2009, though the trend lines have been irregular. Since 2009 or 2010, the prevalence rate has dropped in all grades. Annual prevalence in 2017 was down to 0.8%, 2.2%, and 2.7% in grades 8, 10, and 12, respectively. Use of ***Vicodin***, on the other hand, remained fairly steady at somewhat higher levels from 2002—the first year it was measured—until 2009, after which it declined substantially in all grades. In 2017, annual prevalence rates continued to decline and were 0.7%, 1.5%, and 2.0% for 8th, 10th, and 12th graders respectively.

Availability

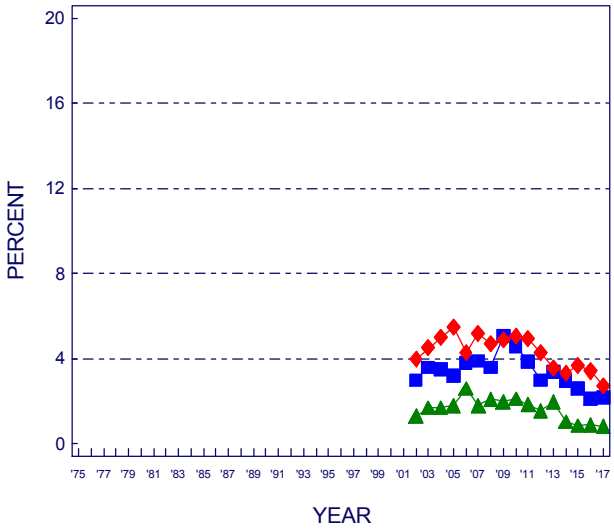
Questions were asked about the availability of narcotics other than heroin, taken as a class. (See facing fourth panel.) Perceived availability increased gradually among 12th graders for more than a decade (from 1978 through 1989), even as reported use was dropping. Perceived availability then rose further for another decade (from 1991 through 2001) as use rose quite sharply before leveling by about 2000 and then declining after 2006. In contrast, perceived availability had declined among 8th and 10th graders since the late 1990s. (In all three grades, a change in question wording in 2010 to include OxyContin and Vicodin as examples presumably accounts for the jump in reported availability that year.) Availability has declined further in all three grades since 2010.

Narcotics other than Heroin and OxyContin and Vicodin Specifically :
Trends in Annual Use and Availability
Grades 8, 10, 12

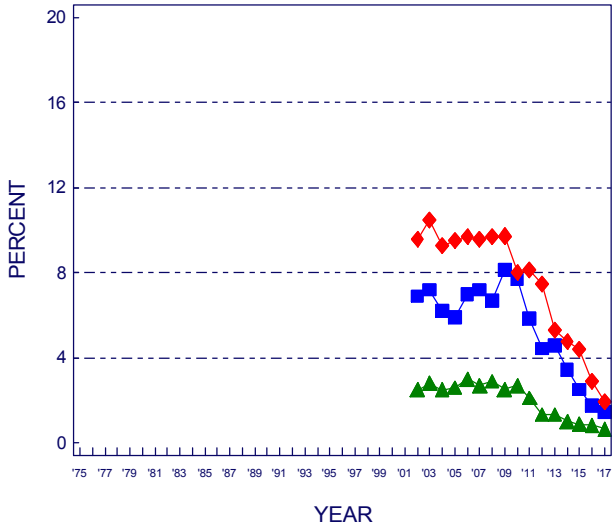
Use of Narcotics other than Heroin
% who used any narcotics other than heroin in last 12 months*



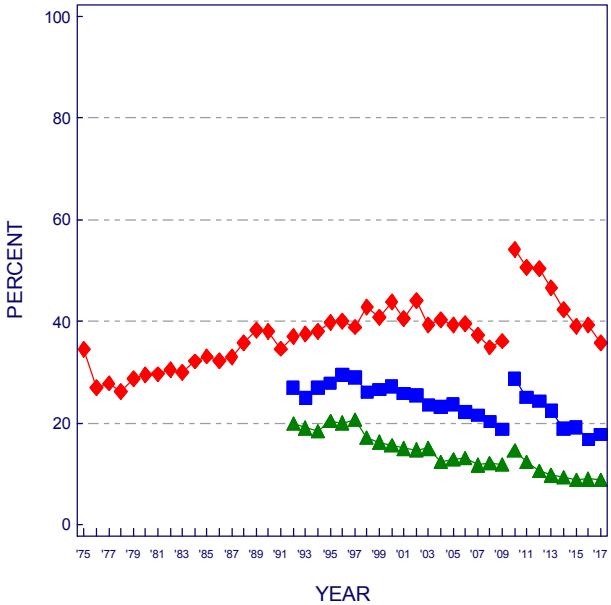
OxyContin Use
% who used OxyContin in last 12 months



Vicodin Use
% who used Vicodin in last 12 months



Availability of Narcotics other than Heroin**
% saying "fairly easy" or "very easy" to get



Source. The Monitoring the Future study, the University of Michigan.
*Beginning in 2002, a revised set of questions on other narcotics use was introduced in which Talwin, laudanum, and paregoric were replaced as examples given with Vicodin, OxyContin, and Percocet.
**In 2010 the list of examples was changed from methadone, opium to Vicodin, OxyContin, Percocet, etc.

Tranquilizers

Tranquilizers are psychotherapeutic drugs that are legally sold only by prescription. They are central nervous depressants and, for the most part, comprise benzodiazepines (minor tranquilizers), although some non-benzodiazepines have been introduced. Respondents are instructed to exclude any medically prescribed use from their answers. At present, ***Xanax*** is the tranquilizer most commonly used by 12th graders (only 12th graders are asked to indicate which specific tranquilizers they used). (See Table E-3 in appendix E of *Volume I* in this series for details.) Valium, Klonopin, and Ativan are other tranquilizers, used at somewhat lower levels. In 2001, the examples given in the tranquilizer question were modified to reflect changes in the drugs in common use—Miltown was dropped and Xanax was added. As the first panel on the facing page shows, this caused a modest increase in the reported level of tranquilizer use in the upper grades, so we have broken the trend line to reflect the point of redefinition.

Trends in Use

During the late 1970s and all of the 1980s, tranquilizers fell steadily and substantially from popularity, with 12th graders' use declining by three fourths over the 15-year interval between 1977 and 1992. Their use then increased, as happened with many other drugs during the 1990s. Annual prevalence more than doubled among 12th graders, rising steadily through 2002, before leveling. Use also rose steadily among 10th graders, but began to decline some in 2002. Use peaked much earlier among 8th graders in 1996 and then declined slightly for two years. Tranquilizer use remained relatively stable among 8th graders through 2010 at considerably lower levels than the upper two grades. Use in 8th grade showed a brief decline in 2011 before stabilizing again. From 2002 to 2005, there was some decline among 10th graders, followed by a leveling, then a resumption of the decline through 2014 before drifting up again. Among 12th graders, there was a very gradual decline from 2002 through 2007, before leveling and then decreasing in 2010 and again in 2013. This staggered pattern of change across the grades suggests that a cohort effect has been at work. There has been little further change since 2013. In 2017, the prevalence of use of these prescription-type drugs was somewhat lower than their recent peak levels, with annual prevalence rates of 2.0%, 4.1%, and 4.7% in grades 8, 10, and 12, respectively.

Perceived Risk and Disapproval

Data have not been collected on perceived risk and disapproval for tranquilizers, primarily due to questionnaire space limitations.

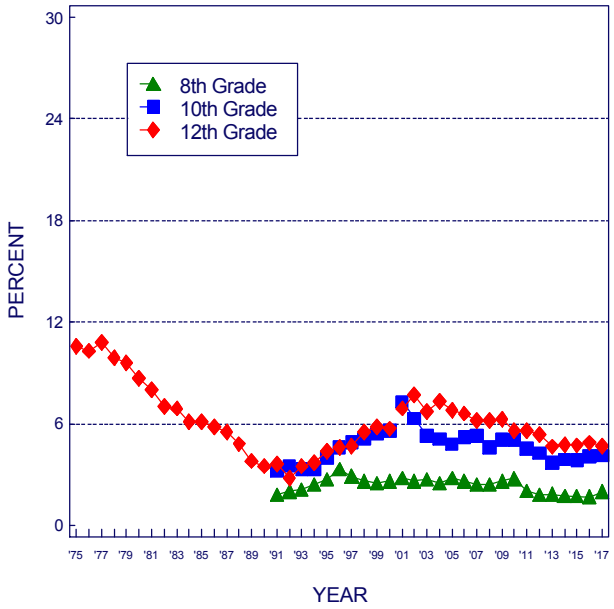
Availability

As the number of 12th graders reporting nonmedically prescribed tranquilizer use fell dramatically during the 1970s and 1980s, so did the proportion saying that tranquilizers would be fairly or very easy to get. Whether declining use caused the decline in availability or vice versa is unclear. However, 12th graders' perceived availability has continued to fall since then, even as use rebounded in the 1990s; it is now down by eight tenths over the life of the study—from 72% in 1975 to 15% by 2017 saying that tranquilizers would be fairly or very easy to get if they wanted some. Availability fell fairly continuously after 1991 in the lower grades, as well, though not as sharply. Since 2014, availability has either leveled or increased in all three grades.

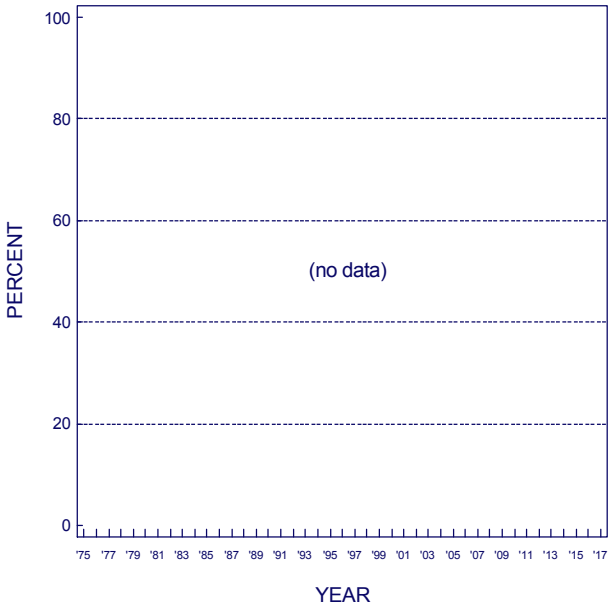
Tranquilizers : Trends in Annual Use and Availability

Grades 8, 10, 12

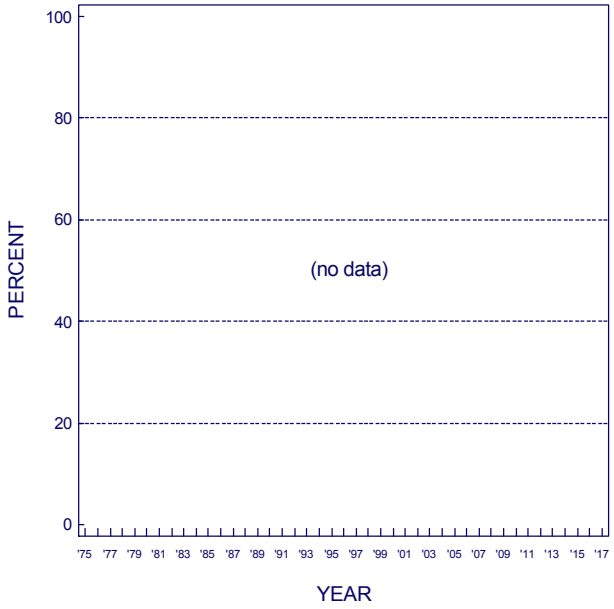
Use*
% who used in last 12 months



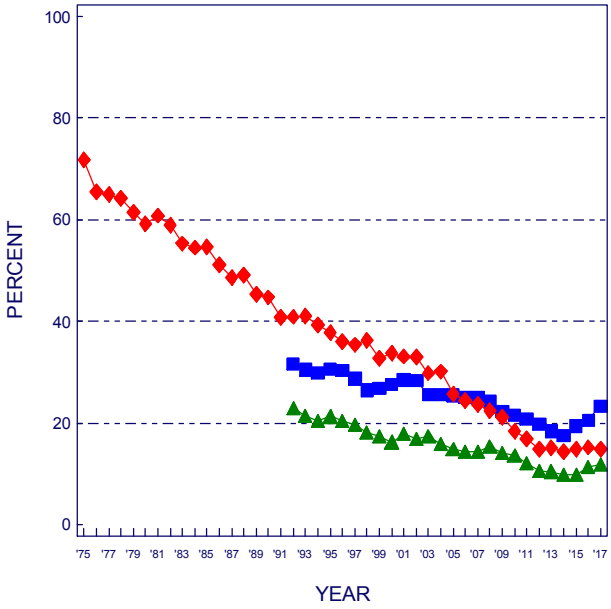
Risk
% seeing "great risk" in using once or twice



Disapproval
% disapproving of using once or twice



Availability
% saying "fairly easy" or "very easy" to get



Source. The Monitoring the Future study, the University of Michigan.
*Beginning in 2001, a revised set of questions on tranquilizer use was introduced in which Xanax replaced Miltown in the list of examples.

Sedatives (Barbiturates)

Like tranquilizers, sedatives are prescription-controlled psychotherapeutic drugs that act as central nervous system depressants. They are used to assist sleep and relieve anxiety.

Though for many years respondents have been asked specifically about their use of barbiturate sedatives, they likely have been including other classes of sedatives in their answers. In 2004, the question on use was revised to say "sedatives/barbiturates"—a change that appeared to have no impact on reported levels of use. Respondents are told for what purposes sedatives are prescribed and are instructed to exclude from their answers any use under medical supervision. Usage data are reported only for 12th graders because we believe that 8th and 10th grade students tend to over report use, perhaps including in their answers their use of nonprescription sleep aids or other over-the-counter drugs.

Trends in Use

As with tranquilizers, the use of sedatives (barbiturates) fell steadily among 12th graders from the mid-1970s through the early 1990s. From 1975 to 1992, annual prevalence fell by three fourths, from 10.7% to 2.8%. As with many other drugs, a gradual, long-term resurgence in sedative use occurred after 1992, but unlike the case with most illegal drugs, sedative (barbiturate) use continued to rise steadily through 2005, well beyond the point at which the use of most illegal drugs began falling. (Recall that tranquilizer use also continued to rise into the early 2000s.) Use has declined some since 2005, and by 2017 the annual prevalence rate was down by about six tenths from its recent peak, falling to 2.9%. The sedative methaqualone (known as Quaaludes) was included in the MTF study from the very beginning, and was never as popular among 12th graders as barbiturates; use rates have generally been declining since 1975, reaching an annual prevalence of just 0.5% in 2007, about where it remained through 2012, after which the question was dropped.

Perceived Risk

Trying sedatives (barbiturates) was never seen by most students as very dangerous; and it is clear from the upper right panel on the facing page that changes in perceived risk cannot explain the trends in use that occurred from 1975 through 1986, when perceived risk was actually declining along with use. But then perceived risk shifted up some through 1991 while use was still falling. It dropped back some through 1995, as use was increasing, and then remained relatively stable for a few years. Perceived risk has generally been at quite low levels, which may help to explain why the use of this class of psychotherapeutic drugs (and likely others) continued to grow in the first half of the decade of the 2000s. However, perceived risk began to rise a bit after 2000, foretelling the decline in use that began after 2005. When the term "sedatives" was changed to "sedatives/barbiturates" in 2004, the trend line shifted down slightly, but perceived risk continued to climb gradually through 2013, before turning down. Prior to that point use declined as perceived risk rose.

Disapproval

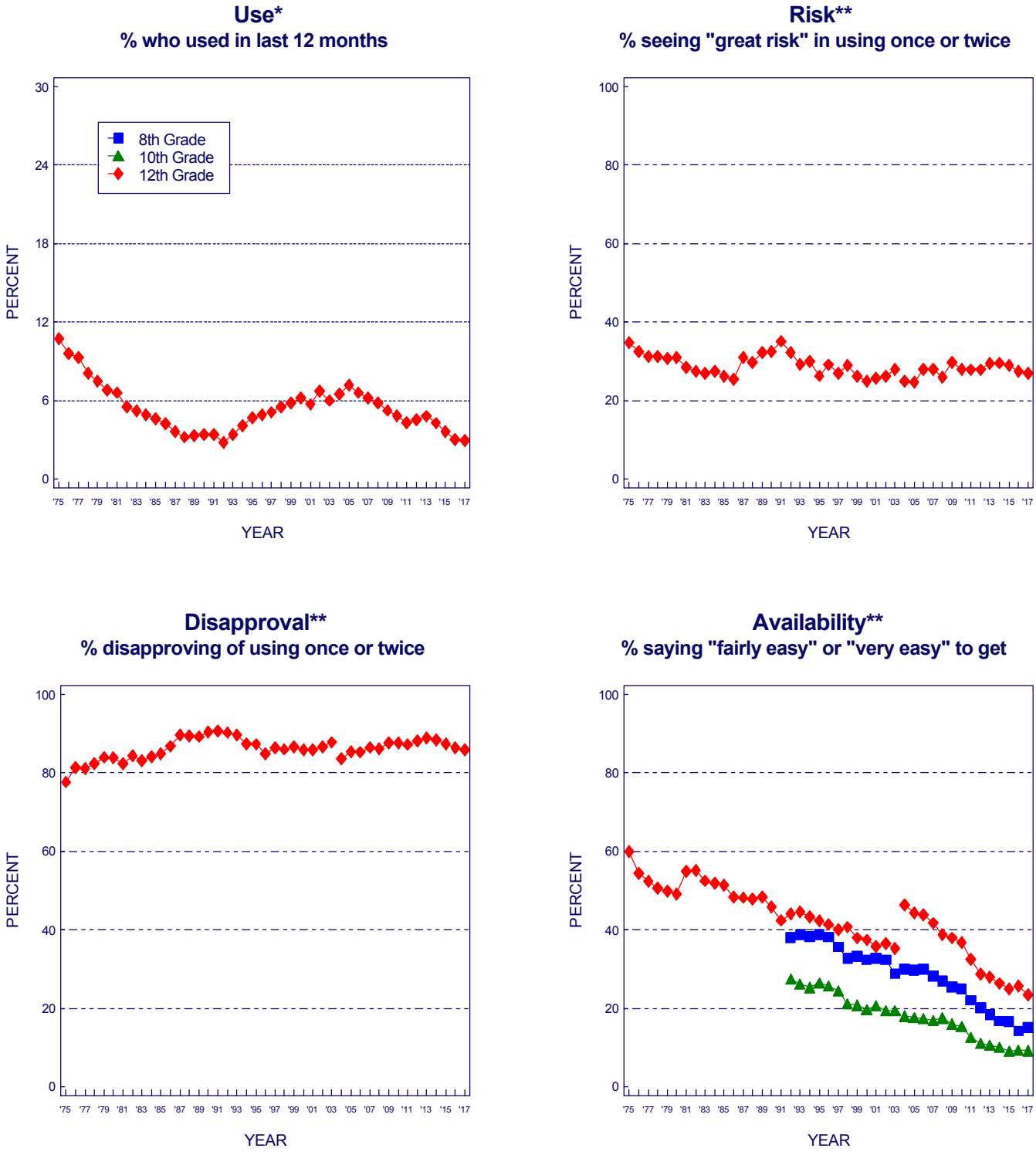
Like many illicit drugs other than marijuana, sedative (barbiturate) use has received the disapproval of most high school seniors since 1975, with some variation in disapproval rates that have moved consistently with usage patterns. The change in question wording in 2004 appeared to lessen disapproval slightly. There has been a modest increase in disapproval since 2000, although that appears to have stopped in 2014 and has been followed by a slight decrease since then.

Availability

As the fourth panel on the facing page shows, the perceived availability of sedatives (barbiturates) has generally been declining during most of the life of the study, except for one upward shift that occurred in 1981—a year in which look-alike drugs became more widespread. (The change in question text in 2004 appears to have had the effect of increasing reported availability among 12th graders but not among students in the lower grades.) Perceived availability for sedatives (barbiturates) has continued to decline overall through 2017.

Sedatives (Barbiturates) : Trends in Annual Use, Risk, Disapproval, and Availability

Grades 8, 10, 12



Source. The Monitoring the Future study, the University of Michigan.

*In 2004 the question text was changed. Barbiturates was changed to Sedatives, including barbiturates and "have you taken barbiturates..." was changed to "have you taken sedatives..." In the list of examples downs, downers, goofballs, yellows, reds, blues, rainbows were changed to downs, or downers, and include Phenobarbital, Tuinal, and Seconal.

**In 2004 the question text was changed from barbiturates to sedatives/barbiturates and the list of examples was changed from downers, goofballs, reds, yellows, etc. to just downers. These changes likely explain the discontinuity in the 2004 results.

MDMA (Ecstasy, Molly) and Other "Club Drugs"

"Club drugs," so called because they have been popular at nightclubs and raves, include LSD, MDMA (known as ecstasy, and more recently, Molly), methamphetamine, GHB (gammahydroxybutyrate), ketamine (special K), and Rohypnol. (For discussion of LSD and meth-amphetamine, see prior pages.) We focus here initially on MDMA (ecstasy, Molly) and treat the other drugs in the last section below.

Trends in MDMA (Ecstasy, Molly) Use

Ecstasy (3, 4-methylenedioxymethamphetamine or MDMA) is used more for its mildly hallucinogenic properties than for its stimulant properties. Questions on ecstasy use were added to the surveys in 1996.

In 1996, annual prevalence of ecstasy use was 4.6% in 10th and 12th grades—considerably higher than among college students (2.8%) and young adults (1.7%)—but use declined over the next two years. Use then rose sharply, bringing annual prevalence up to 3.5%, 6.2%, and 9.2% for 8th, 10th, and 12th graders by 2001. From 2001 to 2005, use declined substantially to 1.7%, 2.6%, and 3.0%, respectively. Following some irregular changes in recent years, in 2014 use was down slightly in 8th grade (to 0.9%) and 10th grade (to 2.3%) and up slightly in 12th grade (to 3.6%). "Molly," reputedly a purer form of MDMA, received much attention in 2013. Because that term was not used in the 2013 questionnaires, it is not clear whether students included it in their answers about ecstasy use that year. The inclusion of Molly as an example in some of the 2014 questionnaires seemed to make a modest difference in reported prevalence. (The 2014 data reported here show one point based on the unmodified questionnaires and another based on the modified ones for each grade.) After 2014, the change was downward and significantly so by 2016 in all three grades, despite the inclusion of Molly. Use leveled in 2017, however.

Perceived Risk

In 2001, 12th graders' perceived risk of ecstasy use jumped by 8 percentage points and in 2002, by another seven. Significant increases occurred in 2003 for all grades. This sharp rise in perceived risk likely caused the drop in use, as we had predicted. From 2004 to 2011, we saw a troubling drop in perceived risk (first among 8th and 10th, and then among 12th graders), corresponding to the increase in use in the upper two grades and then in all three grades. This suggests a generational forgetting of the dangers of ecstasy use. In 2012, only 8th graders showed much further decline. The rebound in use after 2004 might be explained by the sizable drop in perceived risk. The addition of Molly as an example caused a considerable jump in perceived risk after 2013 in grades 8 and 10, suggesting that they see it as more dangerous than ecstasy.

Disapproval

Disapproval of ecstasy use declined some after 1998 but increased significantly in all three grades in 2002, perhaps due to the rise in perceived risk. The rise in disapproval continued through 2003 for 8th, 2004 for 10th, and 2006 for 12th graders, suggesting some cohort effect in this attitude. After those peaks, disapproval dropped sharply among 8th graders and less among 10th graders before leveling, and it did not drop among 12th graders until 2010—again suggesting a cohort effect. Since 2015 there has been a further decline in disapproval in the lower two grades. The erosion in perceived risk and disapproval—which was sharpest among 8th graders—left these groups more vulnerable to a possible rebound in use; some rebound appears to have occurred during the past decade.

Availability

The figure shows a dramatic rise in 12th graders' perceived availability of ecstasy after 1991, particularly between 1999 and 2001, consistent with informal reports about growing importation of the drug. Perceived availability then declined considerably in all grades, including significant declines in 2016 at 10th and 12th grades. Decreased availability may help to account for the declines in use in the past few years.

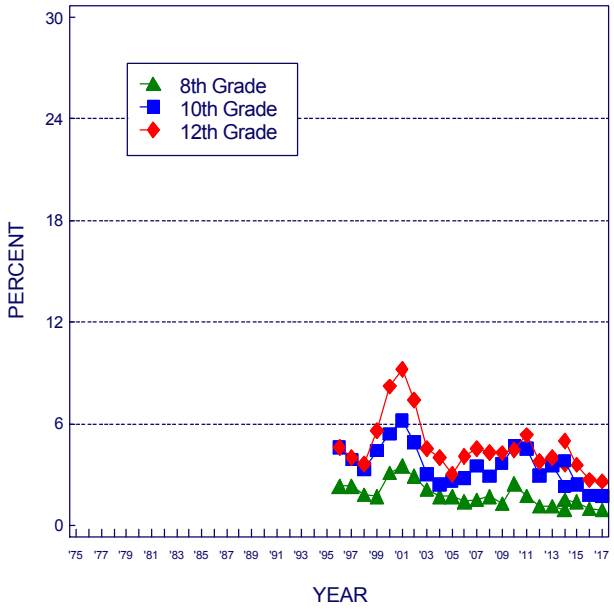
Rohypnol, GHB, and Ketamine

Rohypnol, GHB, and ***ketamine*** are called "date rape drugs" because they can have amnesiac effects and can be added to food or drink without a victim's knowledge. By 2017 annual prevalence of all these drugs in 12th grade had declined by at least half since reaching their peak prevalence in the mid-1990s and early 2000s. In 2017, 0.8% of 12th grade students had used Rohypnol in the last year, compared to a high of 1.6% in 2002 (when the question was last updated). The 0.4% annual prevalence of GHB in 2017 compares with a level of 1.9% in 2000. And the 1.2% prevalence of ketamine in 2017 compares with a level of 2.5% in 2000. In 8th and 10th grades the levels of Rohypnol were 0.4% or less in 2017. (Questions about GHB and ketamine were discontinued in these grades in 2012 due to low prevalence and to make room for questions on other drugs).

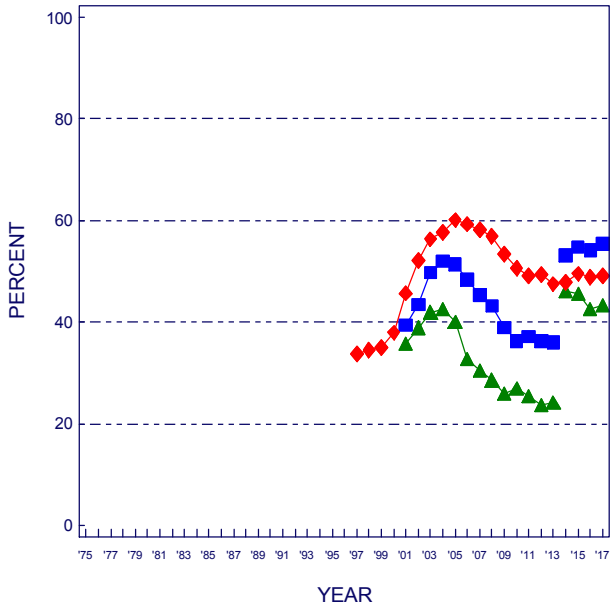
Ecstasy (MDMA) : Trends in Annual Use, Risk, Disapproval, and Availability

Grades 8, 10, 12

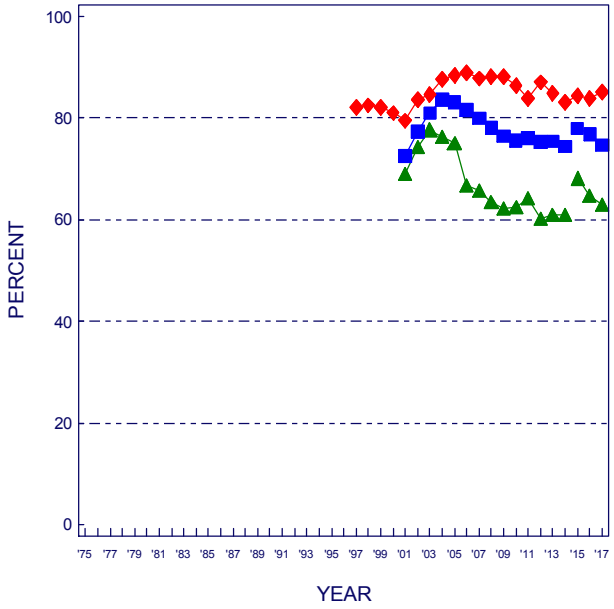
Use*
% who used in last 12 months



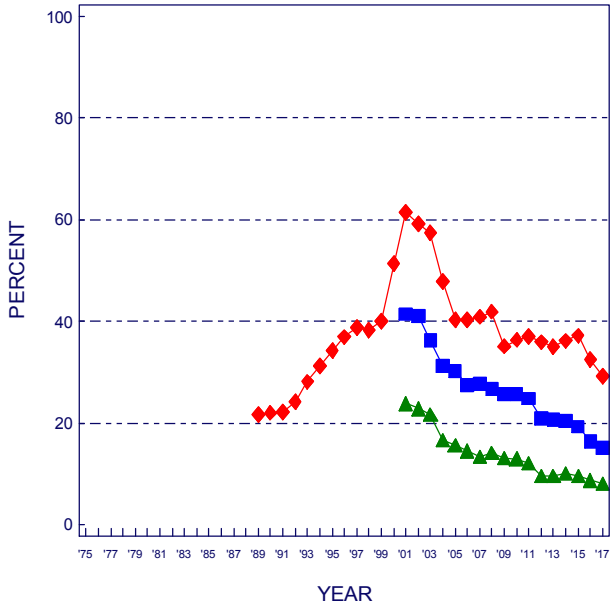
Risk*
% seeing "great risk" in using once or twice



Disapproval*
% disapproving of using once or twice



Availability
% saying "fairly easy" or "very easy" to get



Source. The Monitoring the Future study, the University of Michigan.
*In 2014/2015, revised sets of questions on ecstasy were introduced in which molly was added to the description. This likely explains the discontinuity in the results for those years.

Alcohol

Alcohol has been widely used by young people in the U.S. for a very long time. In 2017, the proportions of 8th, 10th, and 12th graders who reported drinking an alcoholic beverage in the 30-day period prior to the survey were 8%, 20%, and 33%, respectively. Various measures of alcohol use are presented in the tables at the end of this report. Here we focus on episodic heavy or "binge" drinking (defined as having five or more drinks in a row on one or more occasions in the prior two weeks) because heavy alcohol consumption is of substantial concern from a public health perspective.

Trends in Use

Among 12th graders, binge drinking peaked in 1979 along with overall illicit drug use. The prevalence of binge drinking then declined substantially from 41% in 1983 to 28% in 1992, a drop of almost one third (also the low point of any illicit drug use). Although illicit drug use rose sharply in the 1990s, binge drinking rose by only a small fraction, and that rise was followed by some decline at all three grades. By 2017, proportional declines since the recent peaks reached in the 1990s were 72%, 59%, and 47% for grades 8, 10, and 12, respectively (Table 8). The observed prevalence of binge drinking continued to decline in 2016 but halted in all grades in 2017, as did most of the other measures of alcohol use, thus raising the possibility that the long-term decline in alcohol use may be over. The binge drinking rates in 2017 were 4%, 10%, and 17% for grades 8, 10, and 12, respectively— all up slightly from 2016.

In 2005 two measures of extreme binge drinking (also called high intensity drinking) were introduced at 12th grade—one based on having 10 or more drinks on one or more occasions in the past two weeks, and the other based on having 15 or more drinks (see Table 9).

It should be noted that there is little evidence of any displacement effect in the aggregate between alcohol and marijuana—a hypothesis frequently heard. The two drugs have moved mostly in parallel over the decades rather than in opposite directions.

Perceived Risk

Across the past four decades, since the MTF study began, the majority of 12th graders have not viewed binge drinking on weekends as carrying a great risk. However, an increase from 36% to 49% occurred between 1982 and 1992 as use declined substantially. By 1997 a decline in risk occurred (to 43%) as use rose, before risk stabilized. After 2003, perceived risk rose in all grades, at least through 2011 or 2012, after which it either leveled or declined some in all grades. These changes are consistent with changes in actual binge drinking. We believe that the public service advertising campaigns in the 1980s against drunk driving, as well as those that urged use of designated drivers when drinking, contributed to the increase in perceived risk of binge drinking generally. Drunk driving by 12th graders declined during that period by an even larger proportion than binge drinking. Also, we showed that increases in the minimum drinking age during the 1980s were followed by reductions in drinking and increases in perceived risk associated with drinking, policy-driven effects that may still be deterring alcohol use among adolescents.[13]

Disapproval

Disapproval of weekend binge drinking moved fairly parallel with perceived risk, suggesting that such drinking (and very likely the drunk-driving behavior associated with it) became increasingly unacceptable in the peer group. Note that the rates of disapproval and perceived risk for binge drinking are higher in the lower grades than in 12th grade. As with perceived risk, disapproval increased appreciably in all grades, though it leveled after 2012 among 8th graders and after 2016 in 10th and 12th grades.

Availability

Perceived availability of alcohol, which until 1999 was asked only of 8th and 10th graders, was very high and mostly steady in the early 1990s. Since 1996, however, there have been substantial declines in 8th and 10th grades. For 12th grade, availability has declined only modestly with 87% in 2017 still saying that alcohol would be fairly or very easy to get. Overall, it appears that states, communities, and parents have been successful in reducing adolescents' access to alcohol, particularly among the younger teens. Much room for further declines in availability still remains, however.

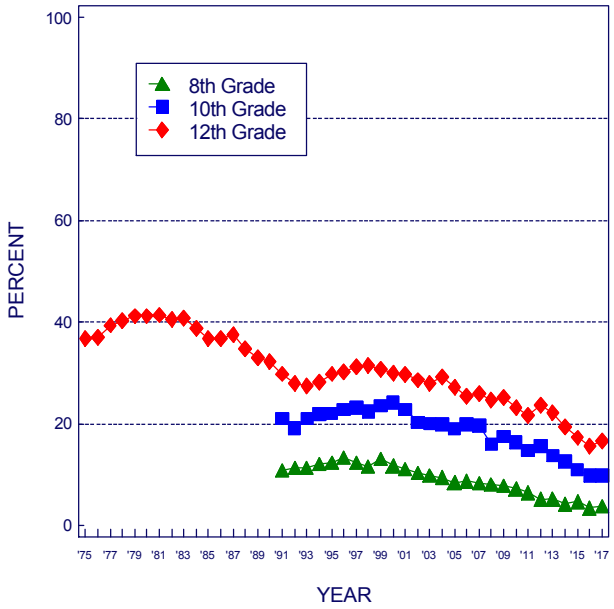
[13] O'Malley, P. M., & Wagenaar, A. C. (1991). Effects of minimum drinking age laws on alcohol use, related behaviors, and traffic crash involvement among American youth: 1976-1987. *Journal of Studies on Alcohol, 52*, 478-491.

Alcohol: Trends in Binge Drinking, Risk, Disapproval, and Availability

Grades 8, 10, 12

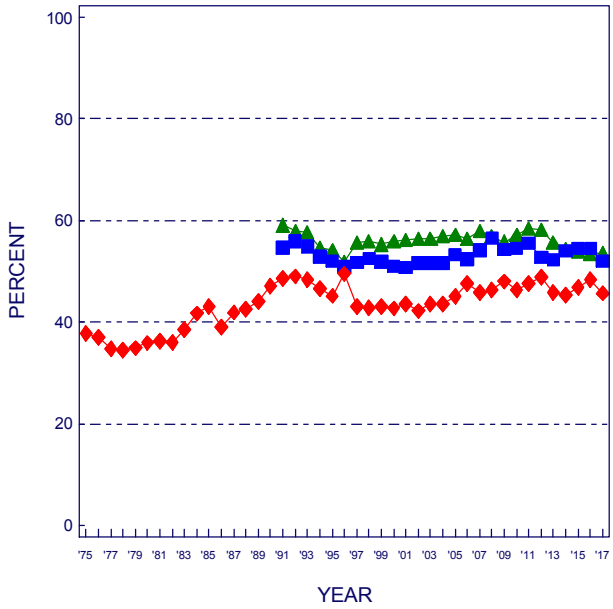
Use

% who had 5+ drinks in a row at least once in past two weeks



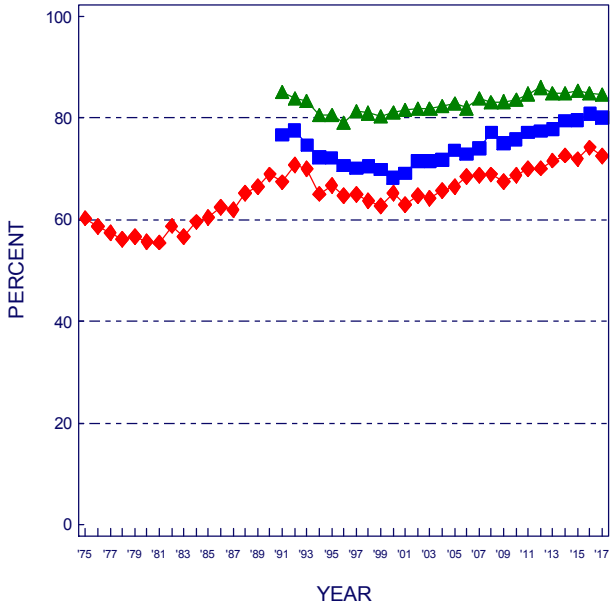
Risk

% seeing "great risk" in having 5+ drinks in a row once or twice each weekend



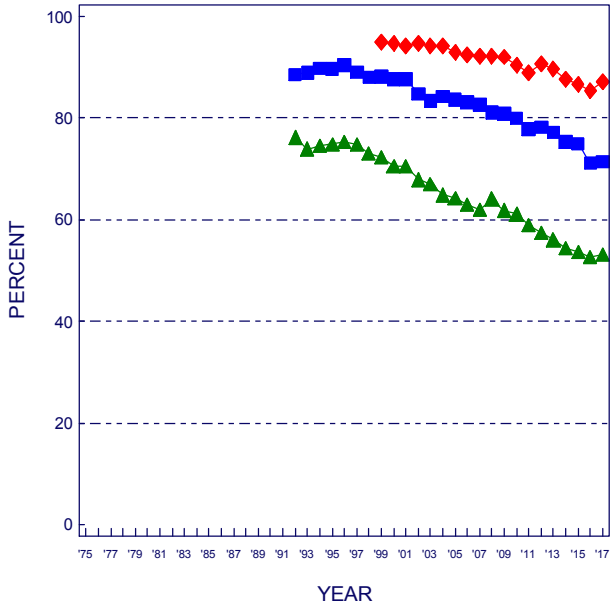
Disapproval

% disapproving of having 5+ drinks in a row once or twice each weekend



Availability

% saying "fairly easy" or "very easy" to get



Source. The Monitoring the Future study, the University of Michigan.

Cigarettes

Cigarette smoking is the leading cause of preventable disease and mortality in the United States, and is usually initiated in adolescence. That makes what happens with cigarette smoking in adolescence particularly important to study.

Trends in Use

Differences in smoking rates between various birth cohorts (or, in this case, school class cohorts) tend to stay with those cohorts throughout the life cycle. This means that it is critical to prevent smoking very early. It also means that the trends in a given historical period may differ across various grade levels as changes in use occurring earlier in adolescence work their way up the age spectrum (i.e., as "cohort effects").

Among 12th graders, 30-day prevalence of smoking reached a peak in 1976 at 39% (likely having peaked earlier at lower grade levels as these same class cohorts passed through them in previous years.) After about a one quarter drop in 12th-grade 30-day prevalence between 1976 and 1981, the rate remained remarkably stable until 1992 (28%). In the 1990s, smoking began to rise sharply, after 1991 among 8th and 10th graders and after 1992 among 12th graders. Over the next four to five years, smoking rates increased by about one half in the lower two grades and by almost one third in grade 12—very substantial increases, to which MTF drew considerable public attention. Smoking peaked in 1996 for 8th and 10th graders and in 1997 for 12th graders before beginning a fairly steady and substantial decline that continued through 2004 for 8th and 10th graders. Between the peak levels in the mid-1990s and 2004, 30-day prevalence of smoking declined by 56% in 8th grade, 47% in 10th, and 32% in 12th. This important decline in adolescent smoking decelerated after about 2002. *Still, by 2017, 30-day prevalence levels had fallen from peak levels by 91%, 84%, and 74% in grades 8, 10, and 12, respectively.* An increase in 2009 in federal taxes on cigarettes (from $0.39 to $1.01 per pack) may have contributed to the recent decline in use. Of particular importance, smoking initiation by 8th graders declined by four fifths from a peak of 49% in 1996 to 9% by 2017. These changes are of tremendous importance to the eventual health and longevity of this generation of adolescents.

Perceived Risk

Among 12th graders, the proportion seeing great risk in pack-a-day smoking rose before and during the first period of decline in use in the late 1970s. It leveled in 1980 (before use leveled), declined a bit in 1982, but then started to rise again gradually for five years. (It is possible that cigarette advertising effectively offset the influence of rising perceptions of risk during that period.) Perceived risk fell some in the early 1990s at all three grade levels as use increased sharply. Since then, there has generally been an increase (though not entirely consistently over the years) in perceived risk, reaching in 2015 the highest levels yet observed in grades 8 and 10 and close to the highest in grade 12. Risk has fallen back some in 10th and 12th grades over the past two to three years, and has remained fairly level among 8th graders for the past six years. Note the differences in the extent of perceived risk among grade levels. There is a clear age effect: by the time most youngsters fully appreciate the hazards of smoking, many already have initiated the behavior.

Disapproval

Disapproval rates for pack-a-day smoking have been fairly high throughout the study and, unlike perceived risk, have been higher in the lower grade levels, though as risk has risen, the differences have almost been eliminated. Among 12th graders, there was a gradual increase in disapproval of smoking from 1976 to 1986, followed by some erosion over the next decade through 1997. After 1997, disapproval rose for some years in all three grades, but leveled briefly after 2006 or 2007, before rising even more. We measure a number of other smoking-related attitudes; these became increasingly negative, but leveled off seven or eight years ago (see Table 3 in the 2016 MTF press release on teen tobacco use). So, disapproval has leveled in the lower grades, perceived risk is declining in the upper grades, and other attitudes and beliefs about cigarette smoking are no longer moving in a direction that would discourage use. This suggests that external changes in the environment may be required to further reduce youth smoking.

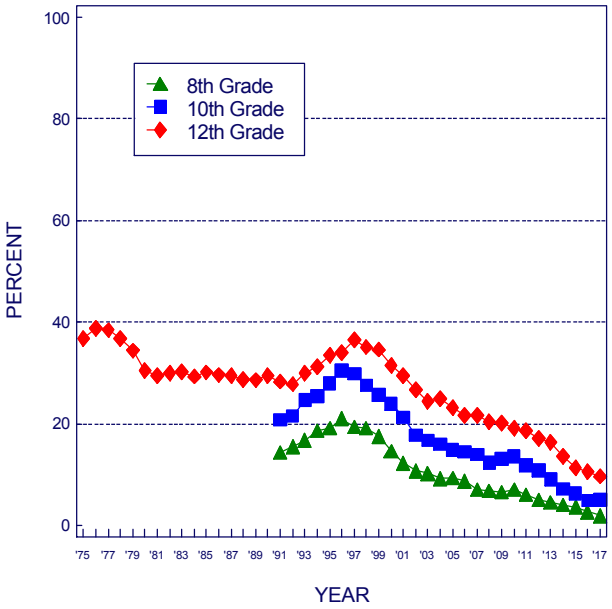
Availability

Since 1996, cigarette availability has declined considerably among 8th and 10th graders, at least until 2017 when both grades leveled. Some 46% of 8th graders and 63% of 10th graders now say that cigarettes would be very easy or fairly easy to get, down from 78% in 1992 among 8th graders and 91% in 1995 among 10th graders.

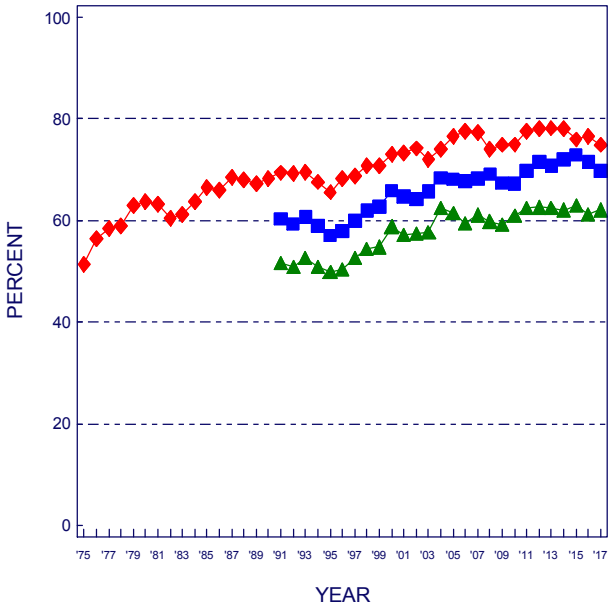
Cigarettes : Trends in 30-Day Use, Risk, Disapproval, and Availability

Grades 8, 10, 12

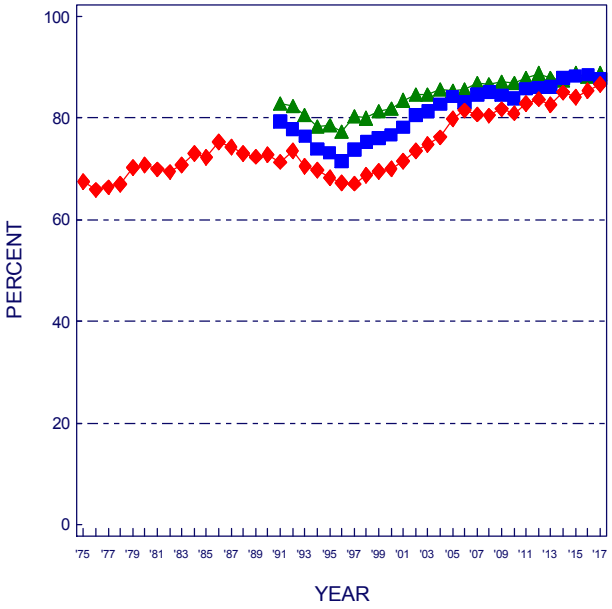
Use
% who used in last 30 days



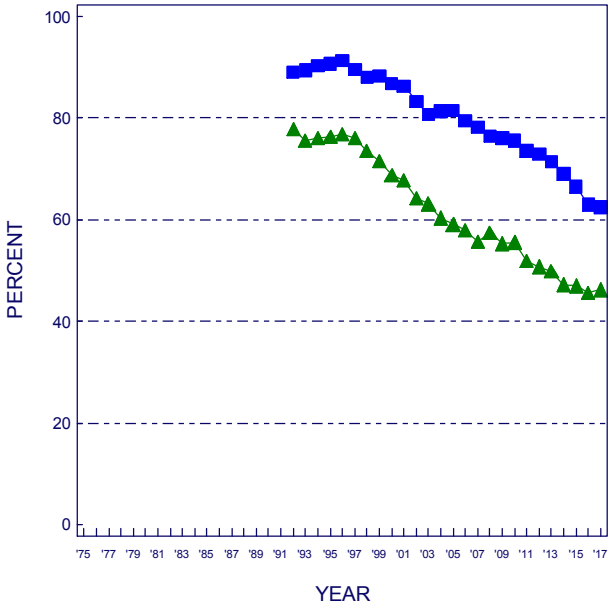
Risk
% seeing "great risk" in smoking a pack or more per day



Disapproval
% disapproving of smoking a pack or more per day



Availability
% saying "fairly easy" or "very easy" to get



Source. The Monitoring the Future study, the University of Michigan.

Smokeless Tobacco

Traditionally, smokeless tobacco has come in two forms: "snuff" and "chew." Snuff is finely ground tobacco usually sold in tins, either loose or in packets. It is held in the mouth between the lip or cheek and the gums. Chew is a leafy form of tobacco, usually sold in pouches. It too is held in the mouth and may, as the name implies, be chewed. In both cases, nicotine is absorbed by the mucous membranes of the mouth. These forms are sometimes called "spit" tobacco because users expectorate the tobacco juices and saliva (stimulated by the tobacco) that accumulate in the mouth. "***Snus***" (rhymes with goose) is a relatively new variation on smokeless tobacco, as are some other ***dissolvable tobacco*** products that literally dissolve in the mouth. Given that snus appeared to be gaining in popularity, separate items regarding the use of snus and dissolvable tobacco in the past 12 months were added to the 12th grade surveys in 2011 and to the 8th and 10th grade surveys in 2012. In addition, in 2011 snus and dissolvable tobacco were added as examples in the long-standing question on smokeless tobacco.

Trends in Use

The use of smokeless tobacco by teens has been decreasing gradually, and 30-day prevalence is now less than half of the recent peak levels in the mid-1990s, though there was a reversal of the declines from about 2007 through 2010. Among 8th graders, 30-day prevalence declined from a 1994 peak of 7.7% to 3.2% in 2007, reached a low of 2.8% in 2013, and then fell even lower to 1.7% by 2017. Among 10th graders, use declined from a 1994 peak of 10.5% to 4.9% by 2004, and then rose to 6.4% in 2013 before dropping again to 3.8% in 2017. Among 12th graders, 30-day use declined from a 1995 peak of 12.2% to 6.1% by 2006 then rose to 8.5% in 2010, before falling back to 4.9% in 2017. Thirty-day prevalence of daily use of smokeless tobacco fell gradually but appreciably for some years. Daily usage rates in 2017 were 0.4%, 0.6%, and 2.0% in grades 8, 10, and 12, respectively—down substantially from peak levels recorded in the 1990s—but most of the declines occurred in the 1990s, not since.

Smokeless tobacco use among American young people is almost exclusively a male behavior. Among males, the 30-day prevalence rates in 2017 were 2.2%, 6.1%, and 9.9% in grades 8, 10, and 12, versus 1.3%, 1.5%, and 0.7% for females. The respective current daily use rates for males were 0.5%, 1.2%, and 4.0% compared to 0.2%, 0.1%, and 0.2% for females.

Annual prevalence in 2017 for ***snus*** was 1.1%, 2.6%, and 4.2% among 8th, 10th, and 12th graders, respectively, reflecting a decline since 2012 in all three grades. For ***dissolvable tobacco***, the corresponding figures were 0.6%, 0.6%, and 1.4%, reflecting little change since 2012. (See Table 6 for trends.)

Perceived Risk

The most recent low point in the level of perceived risk for smokeless tobacco was 1995 in all three grades (though for 12th graders it was considerably lower in the mid-1980s). For a decade following 1995, there was a gradual but substantial increase in proportions saying that there is a great risk in using smokeless tobacco regularly. It thus appears that one important reason for the appreciable declines in smokeless tobacco use during the latter half of the 1990s was that an increasing proportion of young people were persuaded of the dangers of using it. However, the increases in perceived risk ended by 2004 in 12th grade, and it has declined some in the interval since then in all grades. The decline could be due to generational forgetting of the dangers of use, the increased marketing of snus and other smokeless products, and/or public statements about smokeless tobacco use being relatively less dangerous than cigarette smoking. In the last two to three years, perceived risk has leveled in all three grades.

Disapproval

Only 8th and 10th graders are asked about their personal disapproval of using smokeless tobacco regularly. The most recent low points for disapproval in both grades were 1995 and 1996. Disapproval rose among 8th graders from 74% in 1996 to 82% in 2005, about where it was in 2017 (81%). For 10th graders, disapproval rose from 71% in 1996 to 82% in 2008, also about where it was in 2017 (81%).

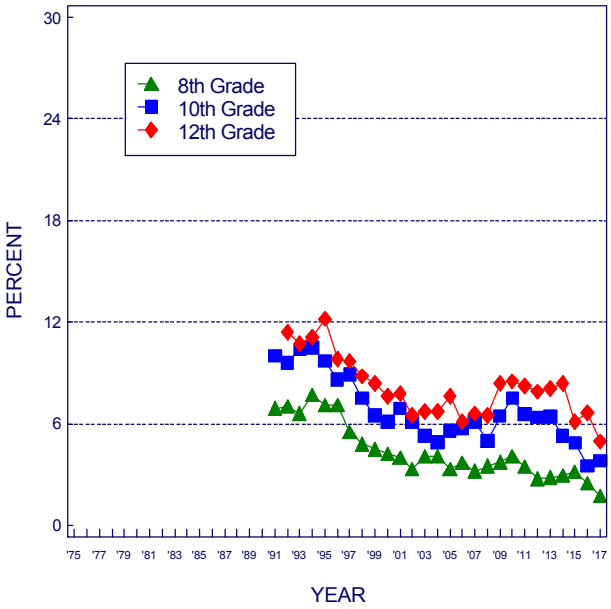
Availability

There are no questions on perceived availability of smokeless tobacco.

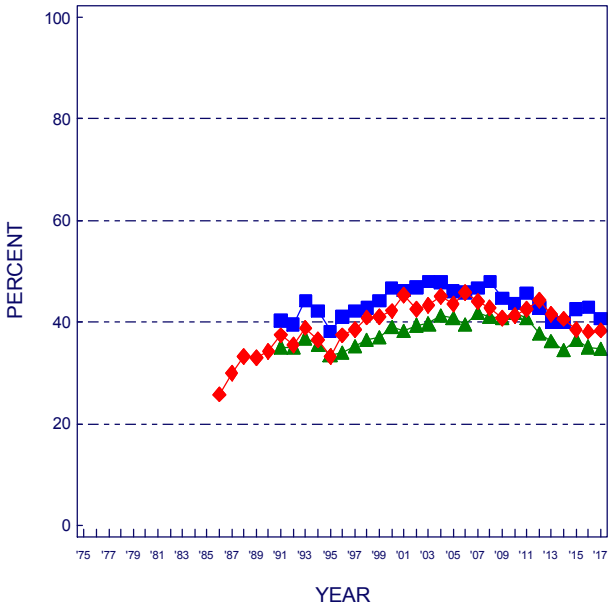
Smokeless Tobacco : Trends in 30-Day Use, Risk, and Disapproval

Grades 8, 10, 12

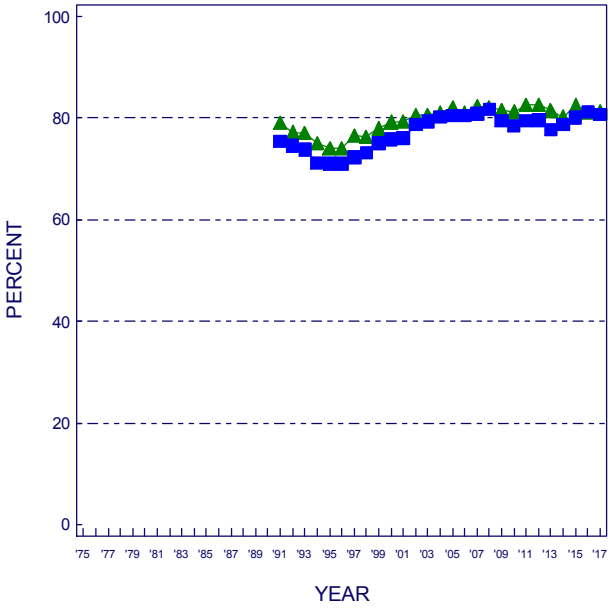
Use
% who used in last 30 days



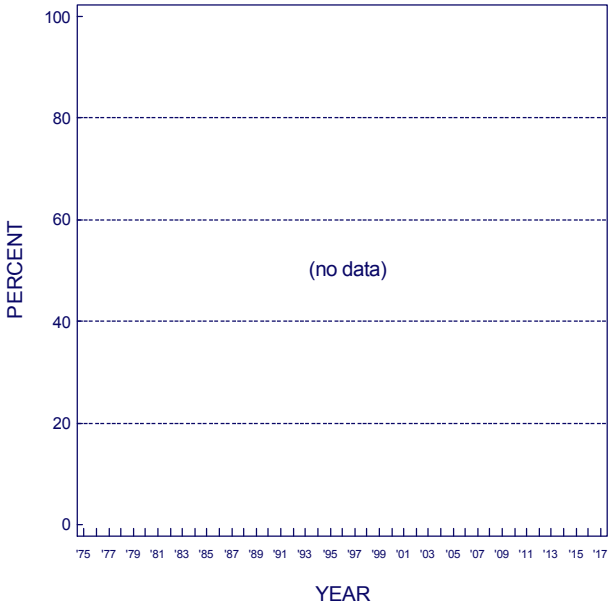
Risk
% seeing "great risk" in using regularly



Disapproval
% disapproving of using regularly



Availability
% saying "fairly easy" or "very easy" to get



Source. The Monitoring the Future study, the University of Michigan.

Vaping

Vaping involves the use of a battery-powered device to heat a liquid or plant material that releases chemicals in an inhalable vapor or aerosol, or mist. Examples of vaping devices include e-cigarettes, "mods," and e-pens. The vapor may contain nicotine, the active ingredients of marijuana, flavored propylene glycol, and/or flavored vegetable glycerin. The liquid that is vaporized comes in hundreds of flavors, many of which (e.g., bubble gum and milk chocolate cream) likely are attractive to teens.

MTF questions on vaping were revised for the 2017 survey. They now include separate questions on vaping of nicotine, marijuana, and "just flavoring." Questions in previous years asked only about vaping in general, and then asked about the substance vaped at last use. With the revised questions we provide the first published estimates for vaping of specific substances in. the past 30 days, past 12 months, and lifetime.

Trends in Use

Levels of ***marijuana vaping*** are considerable. In 2017, 3%, 8%, and 10% of 8th, 10th, and 12th, graders respectively reported vaping marijuana in the past 12 months. These annual levels are only 20% to 25% lower than the levels for *lifetime* prevalence of vaping marijuana, indicating that marijuana vaping is a recent phenomenon.

Levels of ***nicotine vaping*** are also considerable, with 19% of 12th graders vaping nicotine in the past year. The annual prevalence levels were 8% and 16% % for 8th and 10th graders, respectively. Additional students may get nicotine in what they vape without being aware of it, so the estimates should be considered conservative.

"Just flavoring" was the substance most commonly vaped, at levels higher than nicotine and marijuana vaping in each grade. Prevalence was 12%, 19%, and 21%% in, 8th, 10th, and 12th grades, respectively, in the past year.

Levels of ***overall vaping*** in 2017 were similar to 2016 levels, although the measures are not directly comparable. With this caveat, the combined portion of students in 2017 who reported vaping flavoring, marijuana, and/or nicotine was similar to those who reported that they had vaped anything in 2016, with the two respective percentages for use in the past 30 days at 17% in 2017 and 13% in 2016 among 12th graders, 13% and 11% for 10th graders, and 7% and 6% for 8th graders.

Evidence is accumulating, including from MTF, that vaping predicts cigarette experimentation.[14,15] Thus high levels of vaping may offset some of the progress made in reducing smoking among U.S. adolescents. We are closely following these developments.

Perceived Risk

E-cigarettes are by far the most common vaping device, and the percentage of adolescents who believe that regular e-cigarette use poses a risk of harm increased from 14.5% in 2015 to 20.3% in 2017 in 8th grade, from 14.1% to 19.4% in 10th grade, and from 14.2% to 16.1% (ns) in 12th grade. Still, e-cigarettes have one of the lowest levels of perceived risk for regular use of all drugs, including alcohol.

Adolescents see much different risk for "e-cigarette use" as compared to "vaping nicotine." The percentage of 12th graders who considered "great risk" in regular use of e-cigarettes was 16% as compared to 27% for vaping of nicotine on a regular basis. In 10th grade the parallel numbers were 19% and 33%, and in 8th grade they were 20% and 38%. These results suggest that many adolescents consider "e-cigarette use" to include vaping of e-liquids that do not contain nicotine.

Note that perceived risk of vaping nicotine on a regular basis *declines* at the higher grades, which is the opposite pattern for perceived risk of cigarette smoking.

Disapproval

Disapproval of regular use of e-cigarettes also has been relatively low compared to most other substances. However, it did rise in 2016 from 65% to 67% in 8th and grade and from 60% to 65% in 10th grade (the increase was statistically significant in 10th grade but not in 8th grade; the question is not asked of 12th graders.) In 2017 these questions were replaced with questions about disapproval of vaping an e-liquid with nicotine. Such vaping on a regular basis was disapproved by 80%, 75%, and 72% in 8th, 10th, and 12th grades.

Availability

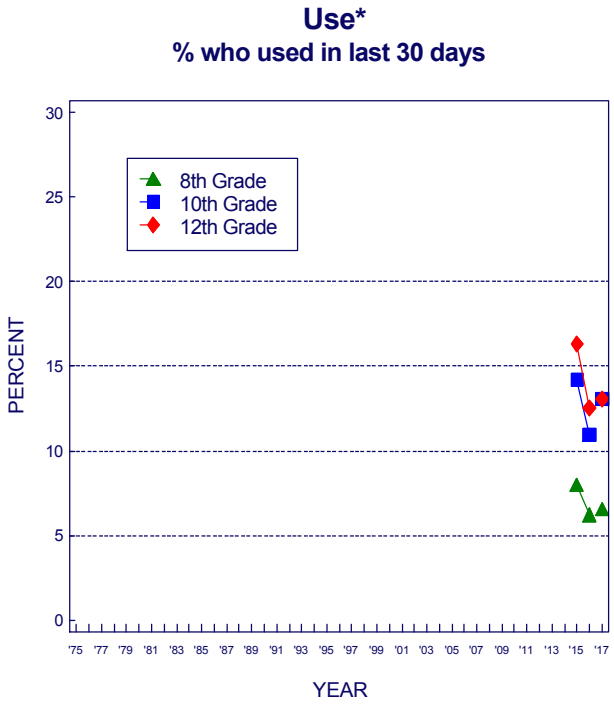
Data on availability of vaping devices or e-cigarettes have not been gathered.

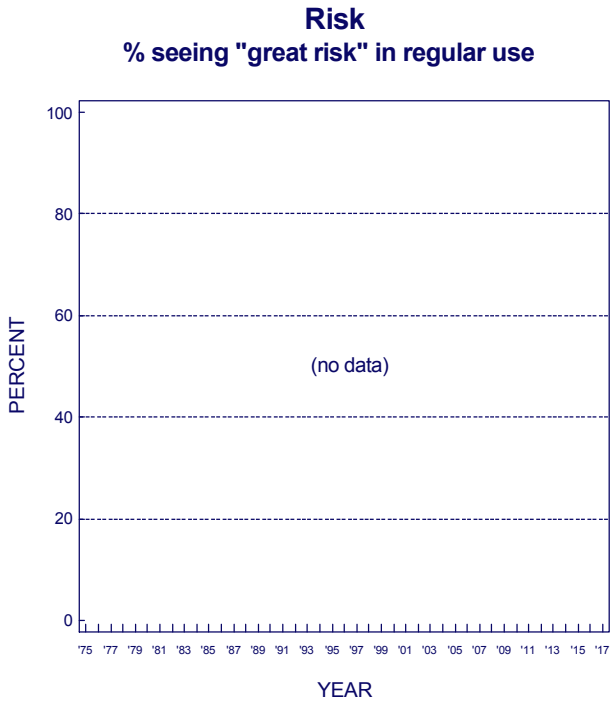
[14] Miech, R. A., Patrick, M. E., O'Malley, P. M., & Johnston, L. D. (2017). E-cigarette use as a predictor of cigarette smoking: Results from a 1-year follow-up of a national sample of 12th grade students. *Tobacco Control*, *26*(e2), e106-e111.

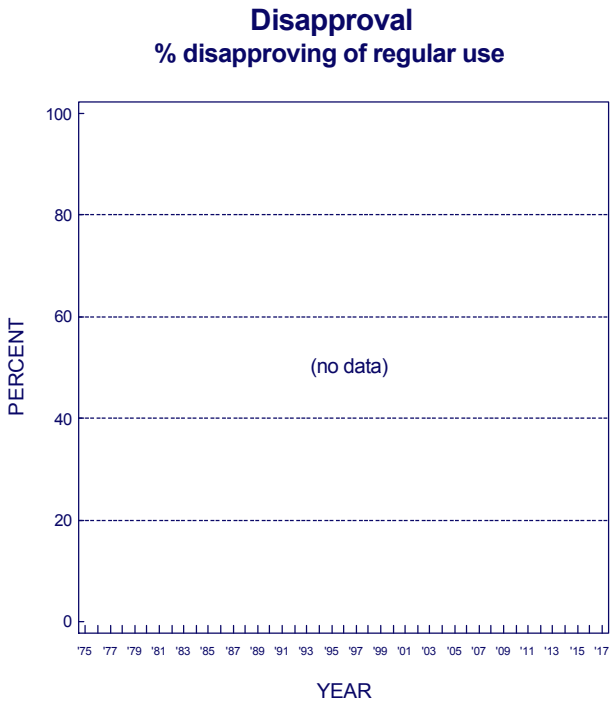
[15] Soneji, S., Barrington-Trimis, J. L., Wills, T. A., Leventhal, A. M., Unger, J. B., Gibson, L. A., . . . Sargent, J. D. (2017). Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: A systematic review and meta-analysis. *JAMA Pediatrics*, *171*(8), 788-797.

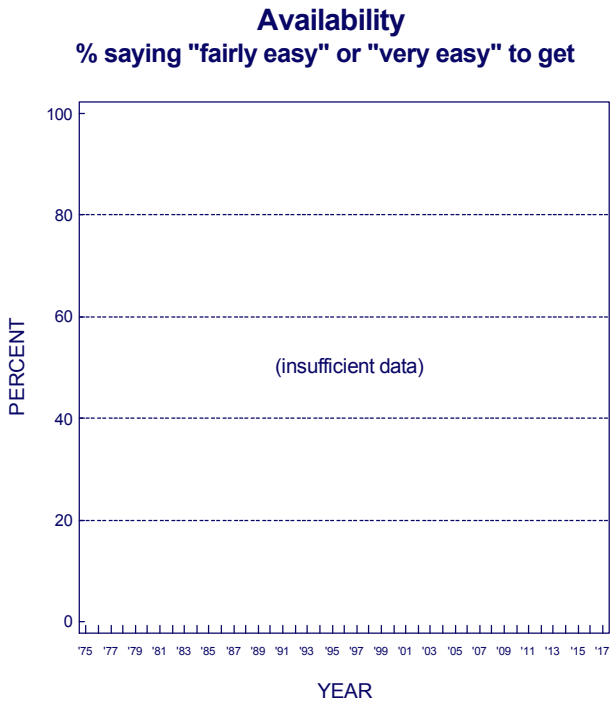
Any Vaping: Trends in 30-Day Use

Grades 8, 10, 12









Source. The Monitoring the Future study, the University of Michigan.

*In 2017, the surveys switched from asking about vaping in general to asking separately about vaping nicotine, marijuana, and just flavoring. Beginning in 2017, data presented for any vaping are based on these new questions.

Other Tobacco Products

Twelfth graders were first asked about smoking small cigars and smoking tobacco using a hookah (water pipe) in 2010. These questions were not asked of 8th and 10th graders initially, but are now. Only the prevalence and frequency of use in the past 12 months were reported; we use this prevalence period, requiring only a single question (which we call a "tripwire" question) to determine whether additional questions on the substance may be warranted in future surveys. Small cigar and hookah use are charted separately on the facing page.

Smoking Tobacco Using a Hookah. The past 12 months prevalence of hookah use had been rising since it was first measured in 2010, from 17.1% in 2010 to 22.9% in 2014; but it then declined sharply to 10.1% in 2017, including a significant decline in all three years. Only about 6% of the 12th grade students in 2017 indicated use on more than two occasions during the prior 12 months, suggesting that a considerable amount of hookah use is light or experimental. (Males had been slightly more likely than females to use hookahs, but currently females are slightly more likely.)

Small Cigars. Small or little cigars are the approximate size and shape of a cigarette, but they are classified as cigars because they are wrapped in brown paper, which contains some tobacco leaf, rather than in white paper. In 2017, the annual prevalence for small or little cigars (our question uses the term "small cigars") was 13%. Smoking small cigars has declined significantly since 2010, when annual prevalence was 23%. Unlike hookah smoking, use of small cigars shows a sizable gender difference: the 2017 annual prevalence for 12th grade males was 19% compared to 8% for females. The increases in the federal taxes on tobacco products, instituted in 2009, may well have played a role in decreasing the use of small cigars. The tax increase on a pack of small cigars fell under the same regulations as regular cigarettes (rising from $0.39 to $1.01 per pack). Some producers of small cigars subsequently increased the weight of their cigars slightly (taxation is based on weight, with cigars falling into a higher weight class with a lower tax rate) in order to avoid the higher taxes placed on cigarettes and to remove them from FDA control under current law. Seven percent of 12th graders indicated having used small cigars on more than two occasions during the past year, and only 1% on more than 20 occasions, so they tend to be smoked much less frequently than regular cigarettes. Some small cigars are flavored, which is likely to make them more attractive to young people. A concern in the public health community is that these products will have the effect of reversing the hard-won gains in reducing cigarette smoking among youth. Small cigars contain nicotine and combustible tobacco as do cigarettes, and therefore carry similar dangers.

Small (Little) Cigars and Cigarillos. In a set of questions introduced in 2014 we asked about the use in the prior 30 days of little cigars OR cigarillos. (Cigarillos lie between little cigars and large cigars in size—length and thickness—and are wrapped in tobacco leaf like large cigars. They fall into the lower federal taxation bracket than cigarettes.) The distinction is made between flavored and unflavored (regular) little cigars or cigarillos, and it shows that the flavored ones are more widely used by teens. There was no significant change between 2014 and 2015 in the 30-day prevalence of either type, but in 2016 there were declines in all 3 grades, significant in 8th and 12th grades, followed by little change in 2017 (Table 7). Thirty-day prevalence in 2017 was 2.6%, 4.0%, and 10.1% for flavored and 1.6%, 3.0%, and 6.6% for regular small cigars or cigarillos in grades 8, 10, and 12, respectively.

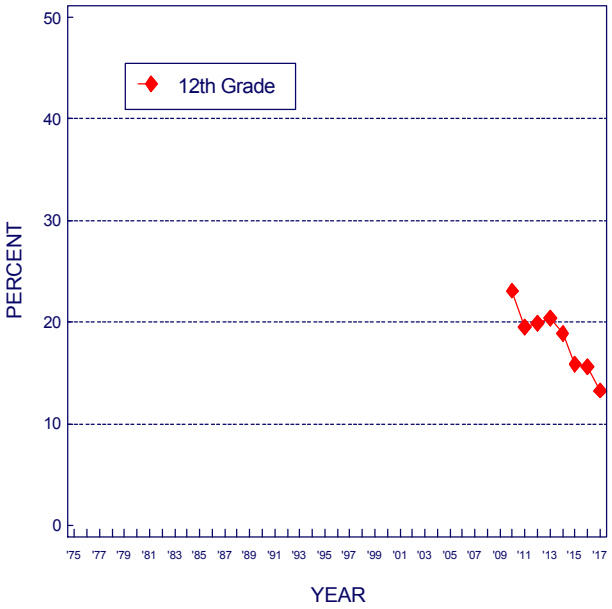
Large Cigars. A question on the 30-day prevalence of smoking large cigars also was added in 2014. The rates were 1.5%, 2.6%, and 5.6% in 2017—with all three grades showing declines in 2016 (significant in 8th and 10th grades) but no significant changes in 2017 (see Table 7).

Small Cigars and Tobacco using a Hookah : Trends in Annual Use

Grade 12

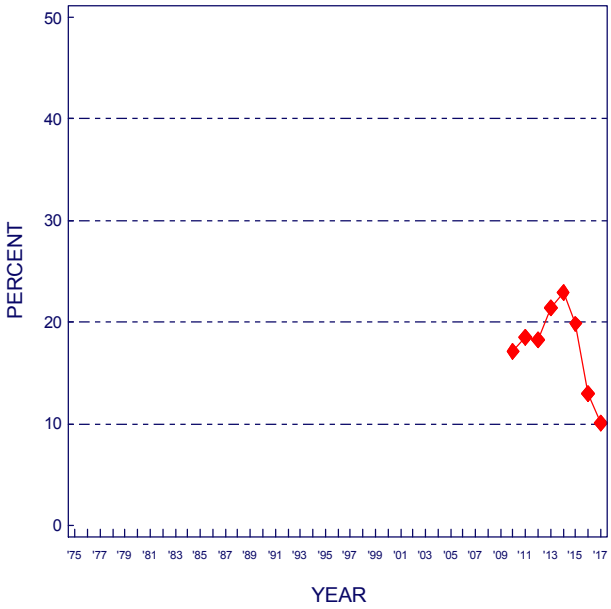
Small Cigar Use

% who used in last 12 months



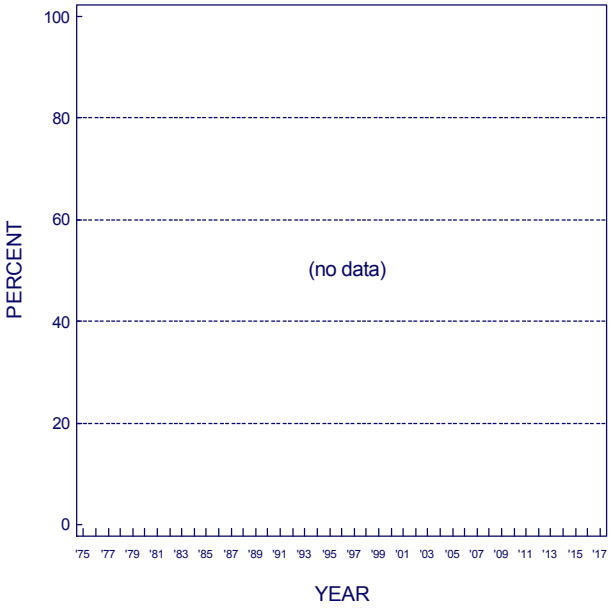
Use of Tobacco with a Hookah

% who used in last 12 months



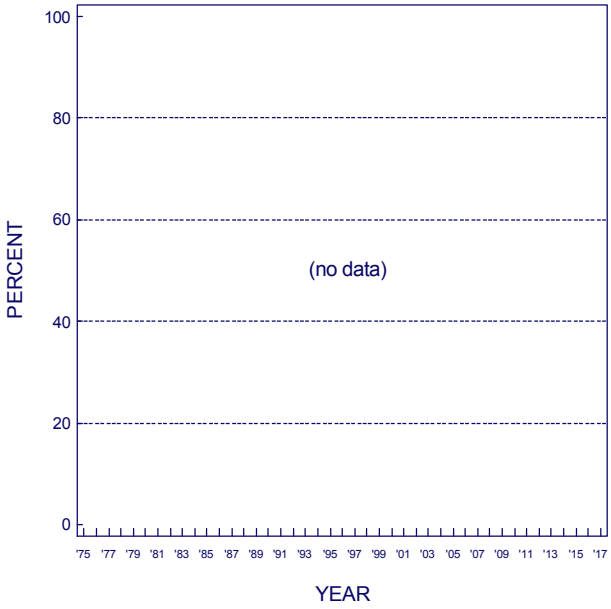
Disapproval

% disapproving of using once or twice



Availability

% saying "fairly easy" or "very easy" to get



Source. The Monitoring the Future study, the University of Michigan.

Steroids

Unlike many other drugs discussed in this Overview, anabolic steroids are not usually taken for their psychoactive effects, though they may have some, but rather for muscle and strength development. However, they are similar to most other drugs studied here in two respects: they are controlled substances for which there is an illicit market, and they can have adverse consequences for the user. Questions about steroid use were added beginning in 1989. Respondents are asked: "Steroids, or anabolic steroids, are sometimes prescribed by doctors to promote healing from certain types of injuries. Some athletes, and others, have used them to try to increase muscle development. The question asks, "On how many occasions (if any) have you taken steroids on your own—that is, without a doctor telling you to take them?" In 2006, the question text was changed slightly in some questionnaire forms—the phrase "to promote healing from certain types of injuries" was replaced by "to treat certain conditions." The resulting data did not show any effect from this rewording. In 2007, the remaining forms were changed in the same manner.

Trends in Use

Anabolic steroids have been used predominately by males; therefore, data based on all respondents can mask the higher rates and larger fluctuations that occur among males. (For example, in 2017, annual prevalence rates were 0.6%, 0.8%, and 1.4% for boys in grades 8, 10, and 12, compared with 0.6%, 0.5%, and 0.5% for girls.) Between 1991 and 1998, the overall annual prevalence rate was fairly stable among 8th and 10th graders, ranging between 0.9% and 1.2% (as use among 12th graders increased). In 1999, however, use among both 8th and 10th graders increased from 1.2% to 1.7%. (Almost all of that increase occurred among boys, increasing from 1.6% in 1998 to 2.5% in 1999 in 8th grade and from 1.9% to 2.8% in 10th grade.) Thus, rates among boys increased by about half in a single year. The fact that it was the year following Mark McGwire hitting a record number of home runs and admitting using androstenedione (a steroid precursor) is likely not a coincidence. By 2017 among all 8th graders, steroid use had declined by about two thirds to 0.6%. Among 10th graders, use continued to increase, reaching 2.2% in 2002, but then declined by about two thirds to 0.7% by 2017. In 12th grade, there was a different trend story. With data going back to 1989, we can see that steroid use first fell from 1.9% overall in 1989 to 1.1% in 1992—the low point. From 1992 to 2000, there was a more gradual increase in use, reaching 1.7% in 2000. In 2001, use rose significantly among 12th graders to 2.4% (possibly reflecting a cohort effect). Twelfth graders' use decreased significantly in 2005 to 1.5%, then stayed fairly level through 2015 (1.7%), and then declined significantly in 2016 to 1.1% with little change in 2017. Use is now down from recent peak levels by about two thirds among 8th and 10th graders, and about six tenths among 12th graders. (The use of androstenedione—a steroid precursor—has also declined sharply since 2001, most sharply through 2007. It was classified as a Schedule II controlled substance in 2005 by the DEA.)

Perceived Risk

Perceived risk and disapproval were asked of 8th and 10th graders for only a few years. All grades seemed to have a peak in perceived risk around 1993. The longer-term data from 12th graders show a ten percentage-point drop between 1998 and 2000. A change this sharp is quite unusual and highly significant, suggesting that some particular event or events in 1998—quite possibly publicity about use of androstenedione by a famous home-run-hitting baseball player—made steroids seem less risky. It seems likely that perceived risk dropped substantially in the lower grades as well, consistent with the sharp upturn in their use that year. By 2006, perceived risk for 12th graders was up to 60%, with little change until 2013 when it showed a significant 4.4 percentage point decline. Another significant decline in 2017 of 5.4 percentage points brought it down to 49%, a record low.

Disapproval

Among 12th graders, disapproval of steroid use has been quite high for some years. Between 1998 and 2003, there was a modest decrease, though not as dramatic as the drop in perceived risk. From 2003 to 2008, disapproval rose some—as perceived risk rose and use declined—then leveled and declined from 2012 through 2014, before leveling.

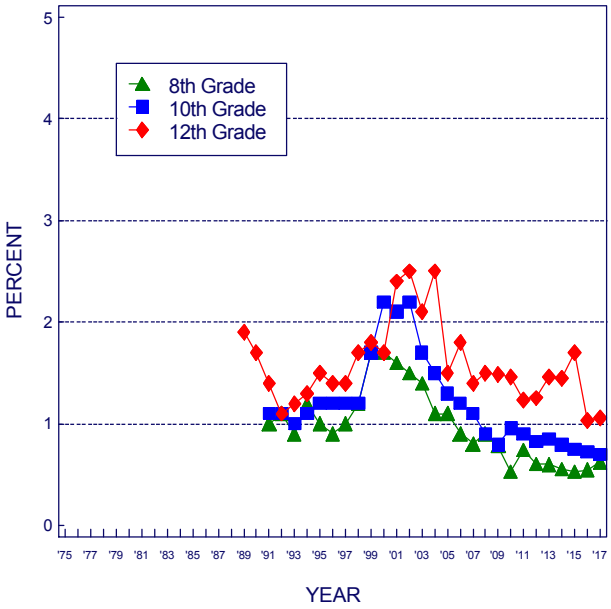
Availability

Perceived availability of steroids was relatively high prior to 2001 or 2002, but it has declined appreciably at all grades through 2017 reaching the lowest levels recorded by the study. A number of steroids have been scheduled by the DEA, no doubt contributing to the drop in availability.

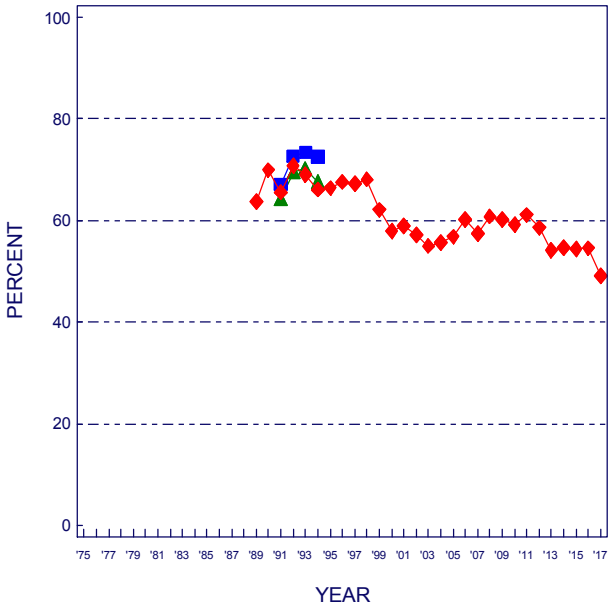
Steroids: Trends in Annual Use, Risk, Disapproval, and Availability

Grades 8, 10, 12

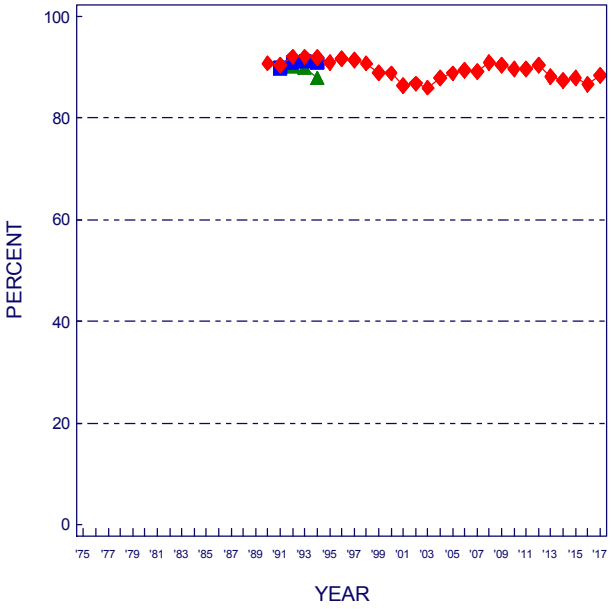
Use
% who used in last 12 months



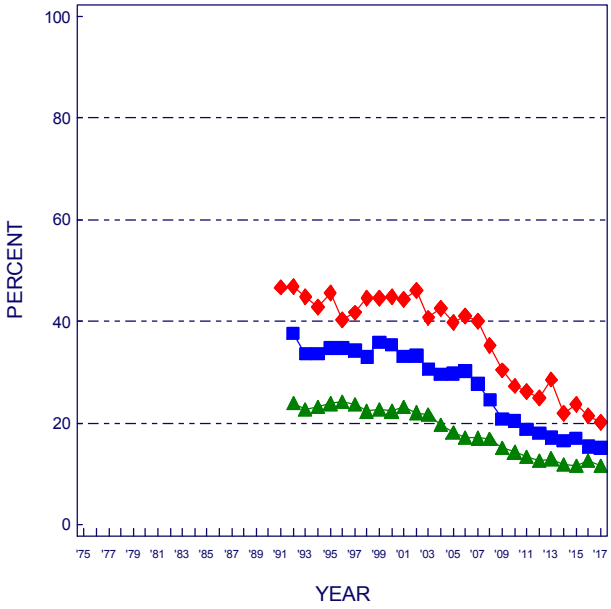
Risk*
% seeing "great risk" in using once or twice



Disapproval*
% disapproving of using once or twice



Availability
% saying "fairly easy" or "very easy" to get



Source. The Monitoring the Future study, the University of Michigan.
*Question discontinued in 8th- and 10th-grade questionnaires in 1995.

Subgroup Differences

Understanding the important subgroup variations in substance use among the nation's youth allows for more informed considerations of substance use epidemiology, etiology and prevention. It also helps to prioritize prevention and treatment efforts. In this section, we present a brief overview of some of the major demographic subgroup differences.

Space does not permit a full discussion or documentation of the many subgroup differences of the drugs covered in this report. However, the forthcoming *Volume I* in this series contains tables providing subgroup prevalence levels for all of the classes of drugs discussed here in 2017, specifically. Chapters 4 and 5 in *Volume I* have in-depth discussion and interpretation of those subgroup differences. Comparisons are made by gender, college plans, region of the country, population density, socioeconomic level (as measured by educational level of the parents), and race/ethnicity. In addition, an annual Monitoring the Future Occasional Paper provides tables giving *cross-time trends* in the subgroup prevalence levels for all of the classes of drugs discussed here and, importantly, charts showing the subgroup trends for all drugs. This Occasional Paper, *Demographic subgroup trends among adolescents in the use of various licit and illicit drugs 1975-2017*, is Number 90 in the series and contains data through 2017. The graphs in the occasional paper present easily accessible views of trends and comparisons while its tables provide the specific numbers behind the figures.

Gender

Generally, males have somewhat higher rates of illicit drug use than females (especially higher rates of frequent use), most notably by 12th grade.

There have been some important changes over the years, however. Specifically, a long-standing gender difference in annual marijuana use (with males somewhat higher than females in their use), was virtually eliminated among 8th graders by 2013 and among 10th graders by 2016.Among 12th graders the gap nearly closed by 2017. The convergence is largely due to sharper declines among males in all grades in the past few years, and some increase in use among females in grade 12.

Males in all three grades have much higher rates of smokeless tobacco use and, until recent years, steroid use. In the upper grades, males have higher rates of use of small cigars, large cigars, dissolvable tobacco, and snus specifically. The primary exception may be found in the misuse of prescription drugs like amphetamines, sedatives, and tranquilizers, where females have tended to have higher rates of use than males in the early grades. One important exception has been misuse of prescription narcotic drugs, which is reported only at grade 12: Males have consistently had higher rates of use. For most drugs, though, the gender differences among 8th graders are very small, with females fairly consistently reporting slightly higher rates than males through 2015; in 2016 and 2017 males were equal to or higher than females in the use of several drugs. Among 10th graders, males have generally, though not always, reported higher rates than females.

Alcohol has tended to show a narrowing of gender differences over the life of the study. Among 12th graders, for many years males consistently reported distinctly higher 30-day alcohol usage rates than females; however, the difference has been narrowing, and by 2014 females had only a slightly lower prevalence. In 8th grade there had been almost no gender difference, as has been true among 10th graders since about 2002; but in the last couple of years females have come to have a higher 30-day prevalence of use. Gender differences in *binge drinking* have followed a similar pattern—females reporting the same rates as males in 8th grade, the genders converging in recent years in 10th grade, and now females having significantly higher rates of binge drinking in both 10th and 12th grades. This continued narrowing of gender differences among teens, with some recent evidence of cross-over, deserves attention.

Gender differences in 30-day cigarette smoking among 8th and 10th graders have generally been minimal. Tenth grade males reported slightly higher rates than females from about 2006 through 2014, but this disparity has since dissipated. Among 12th graders, females generally had higher rates of smoking than males through 1990, but since then males have generally had the higher rates (11% vs. 8% in 2017) due to smoking declining more rapidly among females (though both genders have shown very substantial declines).

The gender differences in substance use appear to emerge for many drugs as students grow older. In 8th grade, females have higher rates of use for some drugs, such as inhalants and amphetamines. Prevalence rates for both genders then increase with age (with the single exception of inhalants), but the increase is often sharper among males. At each grade level, usage rates for both genders generally tend to move much in parallel across time for the various substances, and the absolute differences between the genders tend to be largest in the historical periods in which overall prevalence rates are highest.

Race/Ethnicity

Among the most dramatic and interesting subgroup differences are those found among the three largest racial/ethnic groups—Whites, African Americans, and Hispanics. For a number of years White students had substantially higher rates of using any illicit drug than did African American students, but the differences have narrowed in recent years as a result of increasing marijuana use among African American students and a decline among White students. (Marijuana use tends to drive the overall index of any illicit drug use and in 2017 marijuana use was significantly higher among African American students than among White students in 8th grade and somewhat higher in 10th grade.) Still, African American students have tended to have lower levels of use for certain licit and illicit drugs at all three grade levels—in particular for hallucinogens, synthetic marijuana, and all forms of prescription drugs used without a doctor's orders. For 12th graders heroin use among African Americans has been higher than among Whites in recent years, and previously crack use was also higher; in all three grades African American use of bath salts generally has been higher than Whites or Hispanics.

African American students' use of alcohol and cigarettes tends to be significantly lower than Whites in all three grades. In fact, African Americans' use of cigarettes has been dramatically lower than Whites' use—a difference that emerged largely during the life of the study (i.e., since 1975).

Hispanic students generally have had rates of use that place them between the other two groups in 12th grade—usually closer to the rates for Whites than for African Americans. In the last few years, however, Hispanics have attained the highest reported rates of use of any illicit drug in all three grades—in large part due to their increase in marijuana use. Indeed, both African Americans and Hispanics have shown a considerably greater increase in marijuana use than Whites, at least until 2014 when Hispanics' use began to decline in both grades 8 and 10; this decline has continued into 2017. In 12th grade Hispanics have the highest use rates for a number of substances: synthetic marijuana, cocaine, crack, cocaine other than crack, OxyContin, methamphetamine, and crystal methamphetamine. In 8th grade, Hispanics have tended to report the highest rates of the three racial/ethnic groups on nearly all classes of drugs. Like African American students, Hispanic students generally have lower rates than White students of misusing any of the prescription drugs, particularly in the upper grades.

Again, we refer the reader to Occasional Paper 90 for a detailed picture of these complex subgroup differences and how they have changed over the years.

College Plans

While in high school, those students who are not college-bound (a decreasing proportion of the total youth population over the longer term) are considerably more likely to be at risk for using illicit drugs, drinking heavily, and particularly smoking cigarettes. Again, these differences are largest in periods of highest prevalence. In the lower grades, the college-bound had a greater increase in cigarette smoking than did their non-college-bound peers in the early to mid-1990s; but the college-bound also showed a considerably larger decline since then, leaving them with dramatically lower smoking rates at present than they had in the 1990s.

Region of the Country

The differences associated with region of the country are so sufficiently varied and complex that we cannot do justice to them here. In the past, the Northeast and West tended to have the highest proportions of students using any illicit drug, and the South, the lowest; however, these rankings have not applied to many of the specific drugs and do not apply to all grades today. The cocaine epidemic of the early 1980s was much more pronounced in the West and Northeast than in the other two regions, although the differences decreased as the overall epidemic subsided. The upsurge of ecstasy use in 1999 occurred primarily in the Northeast, but that drug's newfound popularity then spread to the three other regions of the country. While the South and West have generally had lower rates of drinking among students than the Northeast and the Midwest, those differences have narrowed somewhat in recent years and are now fairly small in all three grades. Cigarette smoking rates have generally been lowest in the West; but in 2017, after substantial declines in cigarette smoking in all three grades, the regional differences are smaller.

Population Density

There have not been very large or consistent differences in overall illicit drug use associated with population density since MTF began, helping to demonstrate just how universal the illicit drug phenomenon has been in this country. Use of any illicit drug has tended to be lowest in the more rural areas at 12th grade over most of the life of the study; and use of any illicit drug other than marijuana generally has been lower in large cities in 12th grade. Crack and heroin use have generally not been concentrated in urban areas, as is commonly believed, meaning that no parents and schools should assume that their children are immune to these threats simply because they do not live in a city. Since the late 1990s, students in non-urban areas have emerged with much higher smoking rates than others. For alcohol use there have not been large differences as a function of population density.

Socioeconomic Level

The average level of education of the student's parents, as reported by the student, is used as a proxy for socioeconomic status of the family. For many drugs the differences in use by socioeconomic class are very small, and the trends have been highly parallel. One very interesting difference occurred for cocaine, the use of which was *positively* associated with socioeconomic level in the early 1980s, meaning that higher parental education levels were associated with higher prevalence of cocaine use. However, with the advent of crack, which offered cocaine at a lower price, that association nearly disappeared by 1986.

Cigarette smoking showed a similar narrowing of class differences, but in this case a large *negative* association with socioeconomic level diminished considerably between roughly 1985 and 1993. In more recent years, that negative association has re-emerged in the lower grades as use declined faster among students from more educated families. We believe that the removal of the Joe Camel ad campaign, which seemed to reach males from educated families in particular, may have played a role in this.

With regard to alcohol, in recent years there has been essentially no association between parental education and binge drinking among 12th graders, nor among 10th graders in 2017; however, a negative correlation among 8th graders has been fairly consistent, albeit small. Similarly, while binge drinking in 8th and 10th grades is negatively correlated with parental education, in 12th grade there is virtually no association.

Implications for Prevention

The wide divergence in historical trajectories of the various drugs over time helps to illustrate that, to a considerable degree, the determinants of use are often specific to each drug. These determinants include both perceived benefits and perceived adverse outcomes that young people come to associate with each drug, as well as peer norms about their use and the availability of each drug.

The "Honeymoon Period" for New Drugs

Unfortunately, word of the supposed benefits of using a drug usually spreads much faster than information about the adverse consequences. Supposed benefits take only rumor and a few testimonials, the spread of which have been hastened and expanded greatly by the media in general, and in particular the Internet and social media. It usually takes much longer for the evidence of adverse consequences (e.g., adverse reactions, death, disease, overdose, addiction) to cumulate, be recognized, and then be disseminated. Thus, when a new drug comes onto the scene, it has a considerable "honeymoon period" during which its benefits are alleged and its consequences are not yet known. We believe that cocaine and ecstasy both illustrated this dynamic. Synthetic marijuana and so-called "bath salts" are two more recent examples. "Vaping" may be in a honeymoon period today.

Although encouraging the avoidance or delay of *any* type of substance use is likely beneficial, especially at young ages, prevention efforts also need to be drug-specific. That is, to a considerable degree, prevention must occur drug by drug because people will not necessarily generalize the adverse consequences of the use of one drug to the use of others. Many beliefs and attitudes held by young people are drug specific. The figures in this *Overview* on perceived risk and disapproval for the various drugs—attitudes and beliefs that we have shown to be important in explaining many drug trends over the years—amply illustrate this assertion. These attitudes and beliefs are at quite different levels for the various drugs and, more importantly, often trend quite differently over time.

Marijuana is one drug that is affected by some very specific policies, including medicalization and legalization of recreational use by adults. The effects on youth behaviors and attitudes of recent changes in a number of states will need to be carefully evaluated and monitored to determine their longer-term effects. Currently, marijuana does not hold the same appeal for youth as it did in the past, and today's annual prevalence among 12th graders of 37% is considerably lower than rates exceeding 50% observed in the 1970s. However, if states that legalize recreational marijuana allow advertising and promotion of marijuana, then prevalence could rebound and approach or even surpass previous levels.

"Generational Forgetting" Helps Keep the Drug Epidemic Going

Another point worth keeping in mind is that there tends to be a continuous flow of new drugs onto the scene and of older ones being rediscovered by young people. Many drugs have made a comeback years after they first fell from popularity, often because knowledge among youth of their adverse consequences faded as generational replacement took place. We call this process "generational forgetting." Examples include LSD and methamphetamine, two drugs used widely in the 1960s that made a comeback in the 1990s after their initial popularity faded as a result of their adverse consequences becoming widely recognized during periods of high use. Heroin, cocaine, PCP, and crack are some others that have followed a similar pattern. LSD, inhalants, and ecstasy have all shown some effects of generational forgetting in recent years—that is, perceived risk has declined appreciably for those drugs, particularly among the younger students—which puts future cohorts at greater risk of having a resurgence in use. In the case of LSD, perceived risk among 8th graders has declined substantially, and more students are saying that they are not familiar with the drug. It would appear that a resurgence in availability (which declined very sharply after about 2001, likely due to the DEA closing a major lab in 2000) could generate another resurgence of LSD use.

As for newly emerging drugs, examples include nitrite inhalants and PCP in the 1970s; crack and crystal methamphetamine in the 1980s; Rohypnol, GHB, and ecstasy in the 1990s; dextromethorphan and salvia in the early 2000s; and more recently "bath salts," "synthetic marijuana," and "vaping." The frequent introduction of new drugs (or new forms or new modes of administration of older drugs, as illustrated by crack, crystal meth-amphetamine, and non-injected heroin) helps keep this nation's drug problem alive. Because of the lag times described previously, the forces of containment are always playing catch-up with the forces of encouragement and exploitation. Organized efforts to reduce the grace period experienced by new drugs would seem to be among the most promising responses for minimizing the damage they will cause. Such efforts

regarding ecstasy by the National Institute on Drug Abuse and others appeared to pay off.

As for other approaches to prevention, it may be useful to emphasize that almost new drugs should be considered dangerous because such drugs are made and sold by people totally unconcerned with adverse consequences for their users. Those who manufacture synthetic drugs regularly change the chemical formulations in order to skirt laws prohibiting their sale, and they make no effort to assess the safety of each new formulation, which may differ dramatically from the safety of previous formulations. Dealers at the distribution level, in an effort to build a reputation for selling powerful drugs, may mix highly potent drugs (e.g., fentanyl) into other drugs (e.g., heroin or other narcotics, marijuana) not attending to the danger that carries for the user. Some such drugs are extemely potent. As a result there are many drugs on the market with little or no information about their adverse effects, and many injuries and deaths resulting from their use. If young people understood this, they might be less likely to use drugs on the illicit market.

TABLE 1

Trends in Lifetime Prevalence of Use of Various Drugs for Grades 8, 10, and 12 Combined

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Any Illicit Drug[b]	30.4	29.8	32.1	35.7	38.9	42.2	*43.3*	42.3	41.9	41.0	40.9	39.5	37.5	36.4	35.7
Any Illicit Drug other than Marijuana[b]	19.7	19.7	21.2	22.0	23.6	*24.2*	24.0	23.1	22.7	22.1‡	*23.2*	21.1	19.8	19.3	18.6
Any Illicit Drug including Inhalants[b]	36.8	36.3	38.8	41.9	44.9	47.4	*48.2*	47.4	46.9	46.2	45.5	43.7	41.9	41.3	41.0
Marijuana/Hashish	22.7	21.1	23.4	27.8	31.6	35.6	**37.8**	36.5	36.4	35.3	35.3	34.0	32.4	31.4	30.8
Inhalants	17.0	16.9	18.2	18.6	**19.4**	19.1	18.6	18.1	17.5	16.4	15.3	13.6	13.4	13.7	14.1
Hallucinogens	6.1	6.3	7.0	7.7	8.9	10.0	*10.2*	9.5	9.0	8.5‡	**9.2**	7.6	6.9	6.3	5.9
LSD	5.5	5.7	6.5	6.9	8.1	8.9	**9.1**	8.3	7.9	7.2	6.5	5.0	3.7	3.0	2.6
Hallucinogens other than LSD	2.4	2.5	2.7	3.6	3.9	4.8	*4.9*	4.8	4.4	4.5‡	**6.7**	6.0	5.8	5.6	5.4
Ecstasy (MDMA)[c], original	—	—	—	—	—	4.9	5.2	4.5	5.3	7.2	**8.0**	6.9	5.4	4.7	4.0
Revised	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cocaine	4.6	4.0	4.1	4.5	5.1	6.0	6.6	7.0	**7.2**	6.5	5.9	5.7	5.3	5.5	5.5
Crack	2.0	1.9	2.0	2.5	2.8	3.2	3.4	**3.8**	**3.8**	3.5	3.2	3.2	2.9	2.9	2.8
Other cocaine	4.1	3.5	3.6	3.9	4.2	5.2	5.9	6.1	**6.3**	5.6	5.1	4.8	4.5	4.7	4.7
Heroin	1.1	1.3	1.3	1.6	1.9	2.1	2.1	**2.2**	**2.2**	2.1	1.7	1.7	1.5	1.5	1.5
With a needle	—	—	—	—	1.1	1.2	1.1	1.1	**1.3**	1.0	0.9	0.9	0.9	0.9	0.9
Without a needle	—	—	—	—	1.3	1.7	1.7	1.6	1.6	**1.8**	1.3	1.3	1.3	1.2	1.1
Amphetamines[b]	12.9	12.5	13.8	14.3	15.2	*15.5*	15.2	14.5	14.0	13.5	13.9	13.1	11.8	11.2	10.3
Methamphetamine	—	—	—	—	—	—	—	—	**6.5**	6.2	5.8	5.3	5.0	4.5	3.9
Tranquilizers	5.5	5.3	5.4	5.5	5.8	6.5	6.6	6.9	*7.0*	6.9‡	**7.9**	**7.9**	7.3	7.1	6.8
Alcohol	*80.1*	79.2‡	68.4	68.4	68.2	68.4	**68.8**	67.4	66.4	66.6	65.5	62.7	61.7	60.5	58.6
Been drunk	**46.3**	44.9	44.6	44.3	44.5	45.1	45.7	44.0	43.7	44.0	43.4	40.5	38.9	39.4	38.4
Flavored alcoholic beverages	—	—	—	—	—	—	—	—	—	—	—	—	—	**54.7**	**54.7**
Cigarettes	53.5	53.0	54.0	54.6	55.8	**57.8**	57.4	56.0	54.5	51.8	49.1	44.2	40.8	39.6	37.4
Smokeless tobacco	—	26.2	25.6	**26.3**	26.0	25.7	22.7	21.1	19.4	17.9	16.6	15.2	14.1	13.6	13.8
Any Vaping[d]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vaping nicotine	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vaping marijuana	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vaping just flavoring	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Steroids	1.9	1.8	1.8	2.1	2.1	1.8	2.1	2.3	2.8	3.0	**3.3**	**3.3**	3.0	2.5	2.1

Table continued on next page.

TABLE 1 (continued)
Trends in Lifetime Prevalence of Use of Various Drugs for Grades 8, 10, and 12 Combined

(Entries are percentages.)

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change	Peak year–2017 change: Absolute change	Peak year–2017 change: Proportional change (%) [a]	Low year–2017 change: Absolute change	Low year–2017 change: Proportional change
Any Illicit Drug[b]	34.0	32.7	32.6	33.2	34.4	34.7	34.1	36.0‡	**34.9**	34.3	32.6	33.4	+0.8	-1.5	-4.4	+0.8	+2.3
Any Illicit Drug other than Marijuana[b]	18.2	17.7	16.8	16.5	16.8	16.1	15.5	16.8‡	**15.8**	15.1	14.3	14.0	-0.3	-1.8 s	-11.5	—	—
Any Illicit Drug including Inhalants[b]	39.3	38.0	37.9	37.9	38.8	38.7	37.9	39.3‡	**37.9**	37.4	34.9	36.5	+1.6 s	-1.5	-3.9	+1.6 s	+4.6
Marijuana/Hashish	28.9	27.9	27.9	29.0	30.4	31.0	30.7	32.0	30.5	30.0	28.6	29.3	+0.7	-8.5 sss	-22.4	+1.4	+5.1
Inhalants	13.7	13.5	13.1	12.5	12.1	10.6	10.0	8.9	8.8	7.5	6.5	6.7	+0.2	-12.7 sss	-65.7	+0.2	+2.7
Hallucinogens	5.7	5.8	5.6	5.3	5.8	5.7	5.0	5.0	4.3	4.3	4.3	4.2	-0.1	-5.0 sss	-54.2	—	—
LSD	2.5	2.6	2.7	2.5	2.8	2.7	2.5	2.6	2.4	2.8	3.1	3.1	0.0	-6.0 sss	-66.2	+0.7 s	+27.0
Hallucinogens other than LSD	5.2	5.1	4.8	4.7	5.0	4.9	4.3	4.1	3.5	3.1	3.0	2.9	-0.1	-3.7 sss	-56.2	—	—
Ecstasy (MDMA)[c], original	4.3	4.5	4.1	4.6	5.5	5.5	4.6	4.7	3.5	—	—	—	—	—	—	—	—
Revised	—	—	—	—	—	—	—	—	**5.0**	4.0	3.1	3.0	-0.1	-2.0 sss	-40.3	—	—
Cocaine	5.3	5.2	4.8	4.2	3.8	3.4	3.3	3.1	2.9	2.7	2.3	2.5	+0.1	-4.7 sss	-65.7	+0.1	+5.5
Crack	2.6	2.5	2.2	2.0	1.9	1.6	1.5	1.5	1.3	1.3	1.0	1.1	+0.1	-2.8 sss	-71.7	+0.1	+6.2
Other cocaine	4.7	4.6	4.1	3.7	3.4	3.1	2.9	2.7	2.5	2.3	2.1	2.1	0.0	-4.2 sss	-66.6	0.0	+0.8
Heroin	1.4	1.4	1.3	1.4	1.4	1.2	1.0	1.0	0.9	0.7	0.6	0.6	0.0	-1.6 sss	-73.4	—	—
With a needle	0.9	0.8	0.8	0.8	0.9	0.8	0.6	0.7	0.7	0.5	0.4	0.4	0.0	-0.9 sss	-70.8	—	—
Without a needle	1.0	1.0	0.9	0.9	1.0	0.9	0.7	0.7	0.6	0.5	0.4	0.4	0.0	-1.4 sss	-77.8	—	—
Amphetamines[b]	10.1	9.5	8.6	8.6	8.9	8.6	8.3	10.5‡	**9.7**	9.1	8.1	7.7	-0.5	-2.0 sss	-20.9	—	—
Methamphetamine	3.4	2.5	2.5	2.2	2.2	1.8	1.6	1.5	1.4	1.1	0.8	0.9	0.0	-5.7 sss	-86.6	0.0	+5.0
Tranquilizers	7.0	6.7	6.3	6.5	6.6	6.0	5.8	5.2	5.3	5.2	5.5	5.6	+0.1	-2.2 sss	-28.5	+0.4	-28.5
Alcohol	57.0	56.3	55.1	54.6	53.6	51.5	50.0	48.4	46.4	45.2	41.9	41.7	-0.2	-27.0 sss	-39.3	—	—
Been drunk	37.6	36.6	35.1	35.9	34.2	32.5	32.8	31.7	29.2	28.2	26.4	26.0	-0.4	-20.3 sss	-43.9	—	—
Flavored alcoholic beverages	53.1	51.3	49.3	47.9	46.7	44.5	42.7	41.1	38.8	37.4	33.8	33.5	-0.3	-21.1 sss	-38.7	—	—
Cigarettes	35.0	33.3	31.3	31.2	30.9	28.7	27.0	25.6	22.9	21.1	18.2	17.0	-1.2 s	-40.8 sss	-70.5	—	—
Smokeless tobacco	13.3	12.9	12.3	13.5	14.5	13.8	13.5	12.8	12.1	11.3	10.3	8.7	-1.6 s	-17.6 sss	-66.9	—	—
Any Vaping[d]	—	—	—	—	—	—	—	—	—	*29.9*	26.6‡	28.2	—	—	—	—	—
Vaping nicotine	—	—	—	—	—	—	—	—	—	—	—	18.9	—	—	—	—	—
Vaping marijuana	—	—	—	—	—	—	—	—	—	—	—	8.5	—	—	—	—	—
Vaping just flavoring	—	—	—	—	—	—	—	—	—	—	—	24.9	—	—	—	—	—
Steroids	2.0	1.8	1.6	1.5	1.5	1.5	1.4	1.5	1.4	1.5	1.3	1.2	0.0	-2.0 sss	-62.0	—	—

Source. The Monitoring the Future study, the University of Michigan.

Notes. ' – ' indicates data not available. ' ‡ ' indicates a change in the question text. When a question change occurs, peak levels after that change are used to calculate the peak year to current year difference.

Values in bold equal peak levels since 1991. Values in italics equal peak level before wording change. Underlined values equal lowest level since recent peak level.

Level of significance of difference between classes: s = .05, ss = .01, sss = .001.

Any apparent inconsistency between the change estimate and the prevalence estimates for the two most recent years is due to rounding.

[a]The proportional change is the percent by which the most recent year deviates from the peak year [or the low year] for the drug in question. So, if a drug was at 20% prevalence in the peak year and declined to 10% prevalence in the most recent year, that would reflect a proportional decline of 50%.

[b]In 2013, for the questions on the use of amphetamines, the text was changed on two of the questionnaire forms for 8th and 10th graders and four of the questionnaire forms for 12th graders. This change also impacted the any illicit drug indices. Data presented here include only the changed forms beginning in 2013.

[c]In 2014, the text was changed on one of the questionnaire forms for 8th, 10th, and 12th graders to include "molly" in the description. The remaining forms were changed in 2015. Data for both versions of the question are presented here.

[d]In 2017, the surveys switched from asking about vaping in general to asking separately about vaping nicotine, marijuana, and just flavoring. Beginning in 2017, data presented for any vaping are based on these new questions.

TABLE 2
Trends in Annual Prevalence of Use of Various Drugs for Grades 8, 10, and 12 Combined

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Any Illicit Drug[c]	20.2	19.7	23.2	27.6	31.0	33.6	*34.1*	32.2	31.9	31.4	31.8	30.2	28.4	27.6	27.1
Any Illicit Drug other than Marijuana[c]	12.0	12.0	13.6	14.6	16.4	*17.0*	16.8	15.8	15.6	15.3‡	*16.3*	14.6	13.7	13.5	13.1
Any Illicit Drug including Inhalants[c]	23.5	23.2	26.7	31.1	34.1	36.6	*36.7*	35.0	34.6	34.1	34.3	32.3	30.8	30.1	30.1
Marijuana/Hashish	15.0	14.3	17.7	22.5	26.1	29.0	**30.1**	28.2	27.9	27.2	27.5	26.1	24.6	23.8	23.4
Synthetic marijuana	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Inhalants	7.6	7.8	8.9	9.6	**10.2**	9.9	9.1	8.5	7.9	7.7	6.9	6.1	6.2	6.7	7.0
Hallucinogens	3.8	4.1	4.8	5.2	6.6	*7.2*	6.9	6.3	6.1	5.4‡	**6.0**	4.5	4.1	4.0	3.9
LSD	3.4	3.8	4.3	4.7	5.9	**6.3**	6.0	5.3	5.3	4.5	4.1	2.4	1.6	1.6	1.5
Hallucinogens other than LSD	1.3	1.4	1.7	2.2	2.7	*3.2*	*3.2*	3.1	2.9	2.8‡	**4.0**	3.7	3.6	3.6	3.4
Ecstasy (MDMA)[d], original	—	—	—	—	—	3.1	3.4	2.9	3.7	5.3	**6.0**	4.9	3.1	2.6	2.4
Revised	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Salvia	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cocaine	2.2	2.1	2.3	2.8	3.3	4.0	4.3	**4.5**	**4.5**	3.9	3.5	3.7	3.3	3.5	3.5
Crack	1.0	1.1	1.2	1.5	1.8	2.0	2.1	**2.4**	2.2	2.1	1.8	2.0	1.8	1.7	1.6
Other cocaine	2.0	1.8	2.0	2.3	2.8	3.4	3.7	3.7	**4.0**	3.3	3.0	3.1	2.8	3.1	3.0
Heroin	0.5	0.6	0.6	0.9	1.2	**1.3**	**1.3**	1.2	**1.3**	**1.3**	0.9	1.0	0.8	0.9	0.8
With a needle	—	—	—	—	**0.7**	**0.7**	**0.7**	**0.7**	**0.7**	0.5	0.5	0.5	0.5	0.5	0.5
Without a needle	—	—	—	—	0.9	0.9	1.0	0.9	1.0	**1.1**	0.7	0.7	0.6	0.7	0.7
OxyContin	—	—	—	—	—	—	—	—	—	—	—	2.7	3.2	3.3	3.4
Vicodin	—	—	—	—	—	—	—	—	—	—	—	6.0	**6.6**	5.8	5.7
Amphetamines[c]	7.5	7.3	8.4	9.1	10.0	10.4	10.1	9.3	9.0	9.2	9.6	8.9	8.0	7.6	7.0
Ritalin	—	—	—	—	—	—	—	—	—	—	**4.2**	3.8	3.5	3.6	3.3
Adderall	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Methamphetamine	—	—	—	—	—	—	—	—	**4.1**	3.5	3.4	3.2	3.0	2.6	2.4
Bath salts (synthetic stimulants)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Tranquilizers	2.8	2.8	2.9	3.1	3.7	4.1	4.1	4.4	4.4	*4.5*‡	**5.5**	5.3	4.8	4.8	4.7
OTC Cough/Cold Medicines	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Rohypnol	—	—	—	—	—	*1.1*	*1.1*	*1.1*	0.8	0.7	0.9‡	0.8	0.8	**0.9**	0.8
GHB[b]	—	—	—	—	—	—	—	—	—	**1.4**	1.2	1.2	1.2	1.1	0.8
Ketamine [b]	—	—	—	—	—	—	—	—	—	**2.0**	1.9	**2.0**	1.7	1.3	1.0
Alcohol	67.4	66.3‡	59.7	60.5	60.4	60.9	**61.4**	59.7	59.0	59.3	58.2	55.3	54.4	54.0	51.9
Been drunk	35.8	34.3	34.3	35.0	35.9	36.7	**36.9**	35.5	36.0	35.9	35.0	32.1	31.2	32.5	30.8
Flavored alcoholic beverages	—	—	—	—	—	—	—	—	—	—	—	—	—	**44.5**	43.9
Alcoholic beverages containing caffeine	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Any Vaping	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vaping nicotine	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vaping marijuana	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vaping just flavoring	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Dissolvable tobacco products	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Snus	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Steroids	1.2	1.1	1.0	1.2	1.3	1.1	1.2	1.3	1.7	1.9	**2.0**	**2.0**	1.7	1.6	1.3

Table continued on next page.

TABLE 2 (continued)
Trends in Annual Prevalence of Use of Various Drugs for Grades 8, 10, and 12 Combined

(Entries are percentages.)

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change	Peak year–2017 change: Absolute change	Peak year–2017 change: Proportional change (%) [a]	Low year–2017 change: Absolute change	Low year–2017 change: Proportional change
Any Illicit Drug[c]	25.8	24.8	24.9	25.9	27.3	27.6	27.1	28.6‡	**27.2**	26.8	25.3	26.5	+1.2	-0.7	-2.6	+1.2	+4.6
Any Illicit Drug other than Marijuana[c]	12.7	12.4	11.9	11.6	11.8	11.3	10.8	11.4‡	**10.9**	10.5	9.7	9.4	-0.3	-1.5 ss	-14.2	—	—
Any Illicit Drug including Inhalants[c]	28.7	27.6	27.6	28.5	29.7	29.8	29.0	30.5‡	**28.5**	28.4	26.3	28.3	+2.0 ss	-0.2	-0.6	+2.0 ss	+7.7
Marijuana/Hashish	22.0	21.4	21.5	22.9	24.5	25.0	24.7	25.8	24.2	23.7	22.6	23.9	+1.3 s	-6.2 sss	-20.6	+2.5 sss	+11.8
Synthetic marijuana	—	—	—	—	—	—	**8.0**	6.4	4.8	4.2	3.1	2.8	-0.4 s	-5.2 sss	-65.4	—	—
Inhalants	6.9	6.4	6.4	6.1	6.0	5.0	4.5	3.8	3.6	3.2	2.6	2.9	+0.2	-7.3 sss	-71.9	+0.2	+8.1
Hallucinogens	3.6	3.8	3.8	3.5	3.8	3.7	3.2	3.1	2.8	2.8	2.8	2.7	0.0	-3.2 sss	-54.1	—	—
LSD	1.4	1.7	1.9	1.6	1.8	1.8	1.6	1.6	1.7	1.9	2.0	2.1	+0.1	-4.3 sss	-67.5	+0.6 ss	+46.1
Hallucinogens other than LSD	3.3	3.3	3.2	3.0	3.3	3.1	2.7	2.5	2.1	1.9	1.8	1.8	0.0	-2.3 sss	-56.3	—	—
Ecstasy (MDMA)[d], original	2.7	3.0	2.9	3.0	3.8	3.7	2.5	2.8	2.2	—	—	—	—	—	—	—	—
Revised	—	—	—	—	—	—	—	—	**3.4**	2.4	1.8	1.7	-0.1	-1.6 sss	-48.9	—	—
Salvia	—	—	—	—	3.5	**3.6**	2.7	2.3	1.4	1.2	1.2	0.9	-0.3 ss	-2.7 sss	-74.2	—	—
Cocaine	3.5	3.4	2.9	2.5	2.2	2.0	1.9	1.8	1.6	1.7	1.4	1.6	+0.2	-2.9 sss	-64.5	+0.2	+12.2
Crack	1.5	1.5	1.3	1.2	1.1	1.0	0.9	0.8	0.7	0.8	0.6	0.7	+0.1	-1.7 sss	-70.7	+0.1	+20.1
Other cocaine	3.1	2.9	2.6	2.1	1.9	1.7	1.7	1.5	1.5	1.5	1.2	1.3	+0.1	-2.7 sss	-66.3	+0.1	+8.8
Heroin	0.8	0.8	0.8	0.8	0.8	0.7	0.6	0.6	0.5	0.4	0.3	0.3	0.0	-1.0 sss	-75.4	0.0	+8.9
With a needle	0.5	0.5	0.5	0.5	0.6	0.5	0.4	0.4	0.4	0.3	0.3	0.2	0.0	-0.5 sss	-69.5	—	—
Without a needle	0.6	0.7	0.6	0.5	0.6	0.5	0.4	0.4	0.3	0.3	0.2	0.2	0.0	-0.9 sss	-81.4	0.0	+6.5
OxyContin	3.5	3.5	3.4	**3.9**	3.8	3.4	2.9	2.9	2.4	2.3	2.1	1.9	-0.2	-2.0 sss	-51.6	—	—
Vicodin	6.3	6.2	6.1	6.5	5.9	5.1	4.3	3.7	3.0	2.5	1.8	1.3	-0.5	-5.2 sss	-79.6	—	—
Amphetamines[c]	6.8	6.5	5.8	5.9	6.2	5.9	5.6	7.0‡	**6.6**	6.2	5.4	5.0	-0.4	-1.6 sss	-24.1	—	—
Ritalin	3.5	2.8	2.6	2.5	2.2	2.1	1.7	1.7	1.5	1.4	1.1	0.8	-0.2	-3.4 sss	-80.5	—	—
Adderall	—	—	—	4.3	**4.5**	4.1	4.4	4.4	4.1	4.5	3.9	3.5	-0.3	-0.5 s	-10.3	—	—
Methamphetamine	2.0	1.4	1.3	1.3	1.3	1.2	1.0	1.0	0.8	0.6	0.5	0.5	0.0	-3.6 sss	-88.2	—	—
Bath salts (synthetic stimulants)	—	—	—	—	—	—	0.9	**0.9**	0.8	0.7	0.8	0.5	-0.3 s	-0.4 s	-43.6	—	—
Tranquilizers	4.6	4.5	4.3	4.5	4.4	3.9	3.7	3.3	3.4	3.4	3.5	3.6	+0.1	-1.9 sss	-35.1	+0.2	+7.5
OTC Cough/Cold Medicines	**5.4**	5.0	4.7	5.2	4.8	4.4	4.4	4.0	3.2	3.1	3.2	3.0	-0.2	-2.4 sss	-44.4	—	—
Rohypnol	0.7	0.8	0.7	0.6	0.8	0.9	0.7	0.6	0.5	0.5	0.7	0.5	-0.2 s	-0.5 sss	-50.4	—	—
GHB[b]	0.9	0.7	0.9	0.9	0.8	0.8	—	—	—	—	—	—	—	—	—	—	—
Ketamine [b]	1.1	1.0	1.2	1.3	1.2	1.2	—	—	—	—	—	—	—	—	—	—	—
Alcohol	50.7	50.2	48.7	48.4	47.4	45.3	44.3	42.8	40.7	39.9	36.7	36.7	0.0	-24.7 sss	-40.2	0.0	+0.1
Been drunk	30.7	29.7	28.1	28.7	27.1	25.9	26.4	25.4	23.6	22.5	20.7	20.4	-0.3	-16.5 sss	-44.8	—	—
Flavored alcoholic beverages	42.4	40.8	39.0	37.8	35.9	33.7	32.5	31.3	29.4	28.8	25.3	25.9	+0.5	-18.6 sss	-41.9	+0.5	+2.1
Alcoholic beverages containing caffeine	—	—	—	—	—	**19.7**	18.6	16.6	14.3	13.0	11.2	10.6	-0.6	-9.1 sss	-46.1	—	—
Any Vaping	—	—	—	—	—	—	—	—	—	—	—	21.5	—	—	—	—	—
Vaping nicotine	—	—	—	—	—	—	—	—	—	—	—	13.9	—	—	—	—	—
Vaping marijuana	—	—	—	—	—	—	—	—	—	—	—	6.8	—	—	—	—	—
Vaping just flavoring	—	—	—	—	—	—	—	—	—	—	—	17.2	—	—	—	—	—
Dissolvable tobacco products	—	—	—	—	—	—	**1.4**	1.4	1.2	1.1	0.9	0.9	0.0	-0.5	-35.1	—	—
Snus	—	—	—	—	—	—	**5.6**	4.8	4.1	3.8	3.6	2.6	-1.0 sss	-3.0 sss	-53.9	—	—
Steroids	1.3	1.1	1.1	1.0	0.9	0.9	0.9	0.9	0.9	1.0	0.8	0.8	0.0	-1.2 sss	-61.3	0.0	+2.9

Source. The Monitoring the Future study, the University of Michigan.

Notes. ' – ' indicates data not available. ' ‡ ' indicates a change in the question text. When a question change occurs, peak levels after that change are used to calculate the peak year to current year difference.

Values in bold equal peak levels since 1991. Values in italics equal peak level before wording change. Underlined values equal lowest level since recent peak level.

Level of significance of difference between classes: s = .05, ss = .01, sss = .001.

Any apparent inconsistency between the change estimate and the prevalence estimates for the two most recent years is due to rounding.

[a]The proportional change is the percent by which the most recent year deviates from the peak year [or the low year] for the drug in question. So, if a drug was at 20% prevalence in the peak year and declined to 10% prevalence in the most recent year, that would reflect a proportional decline of 50%.

[b]Question was discontinued among 8th and 10th graders in 2012.

[c]In 2013, for the questions on the use of amphetamines, the text was changed on two of the questionnaire forms for 8th and 10th graders and four of the questionnaire forms for 12th graders. This change also impacted the any illicit drug indices. Data presented here include only the changed forms beginning in 2013.

[d]In 2014, the text was changed on one of the questionnaire forms for 8th, 10th, and 12th graders to include "molly" in the description. The remaining forms were changed in 2015. Data for both versions of the question are presented here.

TABLE 3
Trends in 30-Day Prevalence of Use of Various Drugs for Grades 8, 10, and 12 Combined

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Any Illicit Drug[b]	10.9	10.5	13.3	16.8	18.6	*20.6*	20.5	19.5	19.5	19.2	19.4	18.2	17.3	16.2	15.8
Any Illicit Drug other than Marijuana[b]	5.4	5.5	6.5	7.1	*8.4*	*8.4*	*8.4*	8.2	7.9	8.0‡	*8.2*	7.7	7.1	7.0	6.7
Any Illicit Drug including Inhalants[b]	13.0	12.5	15.4	18.9	20.7	*22.4*	22.2	21.1	21.1	21.0	20.8	19.5	18.6	17.5	17.5
Marijuana/Hashish	8.3	7.7	10.2	13.9	15.6	17.7	**17.9**	16.9	16.9	16.3	16.6	15.3	14.8	13.6	13.4
Inhalants	3.2	3.3	3.8	4.0	**4.3**	3.9	3.7	3.4	3.3	3.2	2.8	2.7	2.7	2.9	2.9
Hallucinogens	1.5	1.6	1.9	2.2	*3.1*	2.7	3.0	2.8	2.5	2.0‡	**2.3**	1.7	1.5	1.5	1.5
LSD	1.3	1.5	1.6	1.9	**2.8**	2.1	2.4	2.3	2.0	1.4	1.5	0.7	0.6	0.6	0.6
Hallucinogens other than LSD	0.5	0.5	0.7	1.0	1.0	*1.2*	*1.2*	*1.2*	1.1	1.1‡	**1.4**	1.4	1.2	1.3	1.2
Ecstasy (MDMA)[c], original	—	—	—	—	—	1.5	1.3	1.2	1.6	**2.4**	2.4	1.8	1.0	0.9	0.9
Revised	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cocaine	0.8	0.9	0.9	1.2	1.5	1.7	1.8	**1.9**	1.9	1.7	1.5	1.6	1.4	1.6	1.6
Crack	0.4	0.5	0.5	0.7	0.8	0.9	0.8	**1.0**	0.9	0.9	0.9	1.0	0.8	0.8	0.8
Other cocaine	0.7	0.7	0.8	1.1	1.2	1.3	1.5	1.6	**1.7**	1.4	1.3	1.3	1.2	1.4	1.3
Heroin	0.2	0.3	0.3	0.4	0.6	0.6	0.6	**0.6**	0.6	0.6	0.4	0.5	0.4	0.5	0.5
With a needle	—	—	—	—	0.3	**0.4**	0.3	0.4	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Without a needle	—	—	—	—	0.4	0.4	**0.5**	0.4	0.4	0.4	0.3	0.4	0.3	0.3	0.3
Amphetamines[b]	3.0	3.3	3.9	4.0	4.5	*4.8*	4.5	4.3	4.2	4.5	4.7	4.4	3.9	3.6	3.3
Methamphetamine	—	—	—	—	—	—	—	—	1.5	**1.5**	1.4	1.5	1.4	1.1	0.9
Tranquilizers	1.1	1.1	1.1	1.3	1.6	1.7	1.7	1.9	1.9	*2.1*‡	2.3	**2.4**	2.2	2.1	2.1
Alcohol	*39.8*	38.4‡	36.3	37.6	37.8	**38.8**	38.6	37.4	37.2	36.6	35.5	33.3	33.2	32.9	31.4
Been drunk	19.2	17.8	18.2	19.3	20.3	20.4	**21.2**	20.4	20.6	20.3	19.7	17.4	17.7	18.1	17.0
Flavored alcoholic beverages	—	—	—	—	—	—	—	—	—	—	—	—	—	**23.0**	21.6
Cigarettes	20.7	21.2	23.4	24.7	26.6	28.3	**28.3**	27.0	25.2	22.6	20.2	17.7	16.6	16.1	15.3
Smokeless tobacco	—	9.2	9.1	**9.7**	9.6	8.5	8.0	7.0	6.3	5.8	6.1	5.2	5.3	5.1	5.3
Any Vaping[d]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vaping nicotine	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vaping marijuana	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vaping just flavoring	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Large Cigars	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Flavored Little Cigars	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Regular Little Cigars	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Tobacco using a hookah	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Steroids	0.6	0.6	0.6	0.7	0.6	0.5	0.7	0.7	0.9	0.9	0.9	**1.0**	0.9	0.9	0.7

Table continued on next page.

TABLE 3 (continued)
Trends in 30-Day Prevalence of Use of Various Drugs for Grades 8, 10, and 12 Combined

(Entries are percentages.)

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change	Peak year–2017 change: Absolute change	Peak year–2017 change: Proportional change (%) [a]	Low year–2017 change: Absolute change	Low year–2017 change: Proportional change
Any Illicit Drug[b]	14.9	14.8	14.6	15.8	16.7	17.0	16.8	17.3‡	**16.5**	15.9	15.5	16.1	+0.6	-0.4	-2.4	+0.6	+3.9
Any Illicit Drug other than Marijuana[b]	6.4	6.4	5.9	5.7	5.7	5.7	5.2	5.4‡	**5.4**	5.1	4.6	4.4	-0.1	-1.0 sss	-18.2	—	—
Any Illicit Drug including Inhalants[b]	16.5	16.5	16.1	17.3	18.0	18.3	17.6	18.4‡	**17.3**	16.8	16.0	17.2	+1.2 s	-0.1	-0.7	+1.2 s	+7.2
Marijuana/Hashish	12.5	12.4	12.5	13.8	14.8	15.2	15.1	15.6	14.4	14.0	13.7	14.5	+0.7	-3.4 sss	-19.2	+2.1 sss	+17.0
Inhalants	2.7	2.6	2.6	2.5	2.4	2.1	1.7	1.5	1.4	1.3	1.2	1.3	+0.2	-3.0 sss	-68.9	+0.2	+14.3
Hallucinogens	1.3	1.4	1.4	1.3	1.4	1.3	1.1	1.1	1.0	1.0	1.0	1.0	+0.1	-1.2 sss	-54.5	+0.1	+6.6
LSD	0.6	0.6	0.7	0.5	0.7	0.7	0.5	0.6	0.6	0.7	0.7	0.8	+0.1	-2.0 sss	-72.1	+0.2 s	+40.8
Hallucinogens other than LSD	1.1	1.1	1.1	1.0	1.2	1.0	0.9	0.8	0.7	0.6	0.5	0.6	+0.1	-0.8 sss	-56.9	+0.1	+16.1
Ecstasy (MDMA)[c], original	1.0	1.1	1.2	1.2	1.5	1.4	0.8	1.0	0.8	—	—	—	—	—	—	—	—
Revised	—	—	—	—	—	—	—	—	**1.1**	0.8	0.6	0.6	0.0	-0.5 s	-46.1	0.0	+5.8
Cocaine	1.6	1.4	1.3	1.0	0.9	0.8	0.8	0.8	0.7	0.8	0.5	0.7	+0.1	-1.2 sss	-64.0	+0.1	+27.6
Crack	0.7	0.7	0.6	0.5	0.5	0.5	0.4	0.4	0.4	0.4	0.3	0.4	+0.1	-0.6 sss	-64.2	+0.1	28.6
Other cocaine	1.4	1.1	1.1	0.8	0.8	0.7	0.7	0.6	0.6	0.7	0.4	0.6	+0.2 s	-1.1 sss	-65.7	+0.2 s	+42.3
Heroin	0.4	0.4	0.4	0.4	0.4	0.4	0.3	0.3	0.3	0.2	0.2	0.2	0.0	-0.4 sss	-63.5	0.0	+2.7
With a needle	0.3	0.3	0.3	0.2	0.3	0.3	0.2	0.2	0.3	0.1	0.2	0.1	0.0	-0.2 sss	-63.2	0.0	+0.3
Without a needle	0.3	0.3	0.2	0.2	0.3	0.3	0.2	0.2	0.2	0.2	0.1	0.1	0.0	-0.3 sss	-73.0	0.0	+6.9
Amphetamines[b]	3.0	3.2	2.6	2.7	2.7	2.8	2.5	3.2‡	**3.2**	2.7	2.5	2.2	-0.2	-0.9 sss	-29.2	—	—
Methamphetamine	0.7	0.5	0.7	0.5	0.6	0.5	0.5	0.4	0.3	0.3	0.3	0.2	-0.1	-1.3 sss	-87.2	—	—
Tranquilizers	2.1	2.0	1.9	1.9	1.9	1.7	1.5	1.5	1.5	1.5	1.4	1.4	+0.1	-1.0 sss	-40.4	+0.1	+4.5
Alcohol	31.0	30.1	28.1	28.4	26.8	25.5	25.9	24.3	22.6	21.8	19.8	19.9	+0.1	-18.9 sss	-48.7	+0.1	+0.7
Been drunk	17.4	16.5	14.9	15.2	14.6	13.5	14.7	13.5	11.9	11.0	10.1	9.8	-0.3	-11.4 sss	-53.8	—	—
Flavored alcoholic beverages	21.7	20.4	18.6	17.9	17.0	15.2	14.9	14.0	12.9	12.8	10.9	12.3	+1.4 ss	-10.7 sss	-46.6	+1.4 ss	+13.1
Cigarettes	14.4	13.6	12.6	12.7	12.8	11.7	10.6	9.6	8.0	7.0	5.9	5.4	-0.5	-22.9 sss	-80.9	—	—
Smokeless tobacco	5.1	5.2	4.9	6.0	6.5	5.9	5.6	5.7	5.4	4.7	4.1	3.5	-0.7	-6.2 sss	-64.3	—	—
Any Vaping[d]	—	—	—	—	—	—	—	—	—	*12.8*	9.9‡	12.0	—	—	—	—	—
Vaping nicotine	—	—	—	—	—	—	—	—	—	—	—	7.5	—	—	—	—	—
Vaping marijuana	—	—	—	—	—	—	—	—	—	—	—	3.6	—	—	—	—	—
Vaping just flavoring	—	—	—	—	—	—	—	—	—	—	—	8.0	—	—	—	—	—
Large Cigars	—	—	—	—	—	—	—	—	3.9	**4.2**	**3.3**	3.2	-0.1	-1.0 sss	-24.4	—	—
Flavored Little Cigars	—	—	—	—	—	—	—	—	**7.4**	7.1	5.6	5.4	-0.2	-2.0 sss	-27.4	—	—
Regular Little Cigars	—	—	—	—	—	—	—	—	4.5	**4.9**	3.6	3.6	+0.1	-1.3 sss	-25.9	+0.1	+1.5
Tobacco using a hookah	—	—	—	—	—	—	—	—	—	—	**4.3**	3.4	-0.8	-0.8	-18.6	—	—
Steroids	0.7	0.6	0.6	0.6	0.6	0.5	0.5	0.6	0.5	0.5	0.4	0.4	0.0	-0.6 sss	-58.8	—	—

Source. The Monitoring the Future study, the University of Michigan.

Notes. ' – ' indicates data not available. ' ‡ ' indicates a change in the question text. When a question change occurs, peak levels after that change are used to calculate the peak year to current year difference.

Values in bold equal peak levels since 1991. Values in italics equal peak level before wording change. Underlined values equal lowest level since recent peak level.

Level of significance of difference between classes: s = .05, ss = .01, sss = .001.

Any apparent inconsistency between the change estimate and the prevalence estimates for the two most recent years is due to rounding.

[a]The proportional change is the percent by which the most recent year deviates from the peak year [or the low year] for the drug in question. So, if a drug was at 20% prevalence in the peak year and declined to 10% prevalence in the most recent year, that would reflect a proportional decline of 50%.

[b]In 2013, for the questions on the use of amphetamines, the text was changed on two of the questionnaire forms for 8th and 10th graders and four of the questionnaire forms for 12th graders. This change also impacted the any illicit drug indices. Data presented here include only the changed forms beginning in 2013.

[c]In 2014, the text was changed on one of the questionnaire forms for 8th, 10th, and 12th graders to include "molly" in the description. The remaining forms were changed in 2015. Data for both versions of the question are presented here.

[d]In 2017, the surveys switched from asking about vaping in general to asking separately about vaping nicotine, marijuana, and just flavoring. Beginning in 2017, data presented for any vaping are based on these new questions.

TABLE 4
Trends in Daily Prevalence of Use of Selected Drugs and Heavy Use of Alcohol and Tobacco for Grades 8, 10, and 12 Combined

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Marijuana	0.9	0.9	1.2	2.1	2.7	3.2	3.4	3.4	3.5	3.5	**3.7**	3.5	3.4	3.0	2.9
Alcohol	*1.7*	1.6‡	2.0	1.8	1.9	2.0	2.1	**2.2**	2.0	1.7	2.0	1.9	1.7	1.5	1.5
5+ drinks in a row in last 2 weeks	20.0	19.0	19.5	20.3	21.1	21.9	**21.9**	21.5	21.7	21.2	20.4	18.9	18.6	18.8	17.5
Been drunk	0.4	0.4	0.5	0.6	0.7	0.7	0.9	0.8	**0.9**	0.8	0.7	0.6	0.7	0.7	0.6
Cigarettes	12.4	11.9	13.5	14.0	15.5	16.8	**16.9**	15.4	15.0	13.4	11.6	10.2	9.3	9.0	8.0
1/2 pack+/day	6.5	6.1	6.9	7.2	7.9	**8.7**	8.6	7.9	7.6	6.4	5.7	4.9	4.5	4.1	3.7
Smokeless tobacco	—	**3.0**	2.7	2.9	2.5	2.3	2.5	2.1	1.7	1.9	2.0	1.4	1.6	1.7	1.6

Table continued on next page.

TABLE 4 (continued)
Trends in Daily Prevalence of Use of Selected Drugs and Heavy Use of Alcohol and Tobacco for Grades 8, 10, and 12 Combined

(Entries are percentages.)

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change	Peak year–2017 change: Absolute change	Peak year–2017 change: Proportional change (%) [a]	Low year–2017 change: Absolute change	Low year–2017 change: Proportional change
Marijuana	2.8	2.7	2.8	2.8	3.4	3.6	3.6	3.7	3.3	3.3	3.0	3.1	+0.1	-0.5 ss	-14.9	+0.4 s	+15.0
Alcohol	1.5	1.6	1.4	1.3	1.4	1.0	1.2	1.1	1.0	0.8	0.7	0.7	+0.1	-1.4 sss	-65.9	+0.1	+11.5
5+ drinks in a row in last 2 weeks	17.4	17.2	15.5	16.1	14.9	13.6	14.3	13.2	11.7	10.7	9.4	9.9	+0.5	-12.1 sss	-55.1	+0.5	+5.0
Been drunk	0.7	0.6	0.6	0.5	0.6	0.5	0.6	0.5	0.5	0.3	0.3	0.4	+0.1 s	-0.5 sss	-54.4	+0.1 s	+36.8
Cigarettes	7.6	7.1	6.4	6.4	6.4	5.7	5.2	4.7	3.6	3.2	2.5	2.3	-0.2	-14.6 sss	-86.4	—	—
1/2 pack+/day	3.4	3.0	2.7	2.6	2.5	2.1	1.9	1.8	1.4	1.1	0.9	0.8	-0.1	-7.9 sss	-90.6	—	—
Smokeless tobacco	1.5	1.6	1.6	1.8	2.1	1.8	1.9	1.7	1.8	1.7	1.4	1.0	-0.4	-2.0 sss	-67.2	—	—

Source. The Monitoring the Future study, the University of Michigan.

Notes. ' – ' indicates data not available. ' ‡ ' indicates a change in the question text. When a question change occurs, peak levels after that change are used to calculate the peak year to current year difference.

Values in bold equal peak levels since 1991. Values in italics equal peak level before wording change. Underlined values equal lowest level since recent peak level.

Level of significance of difference between classes: s = .05, ss = .01, sss = .001.

Any apparent inconsistency between the change estimate and the prevalence estimates for the two most recent years is due to rounding.

[a]The proportional change is the percent by which the most recent year deviates from the peak year [or the low year] for the drug in question. So, if a drug was at 20% prevalence in the peak year and declined to 10% prevalence in the most recent year, that would reflect a proportional decline of 50%.

TABLE 5
Trends in Lifetime Prevalence of Use of Various Drugs in Grades 8, 10, and 12

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
Any Illicit Drug [a]																												
8th Grade	18.7	20.6	22.5	25.7	28.5	31.2	29.4	29.0	28.3	26.8	26.8	24.5	22.8	21.5	21.4	20.9	19.0	19.6	19.9	21.4	20.1	18.5‡	21.1	20.3	20.5	17.2	18.2	+1.0
10th Grade	30.6	29.8	32.8	37.4	40.9	45.4	47.3	44.9	46.2	45.6	45.6	44.6	41.4	39.8	38.2	36.1	35.6	34.1	36.0	37.0	37.7	36.8‡	39.1	37.4	34.7	33.7	34.3	+0.7
12th Grade	44.1	40.7	42.9	45.6	48.4	50.8	54.3	54.1	54.7	54.0	53.9	53.0	51.1	51.1	50.4	48.2	46.8	47.4	46.7	48.2	49.9	49.1‡	49.8	49.1	48.9	48.3	48.9	+0.6
Any Illicit Drug other than Marijuana [a,b]																												
8th Grade	14.3	15.6	16.8	17.5	18.8	19.2	17.7	16.9	16.3	15.8‡	17.0	13.7	13.6	12.2	12.1	12.2	11.1	11.2	10.4	10.6	9.8	8.7‡	10.4	10.0	10.3	8.9	9.3	+0.4
10th Grade	19.1	19.2	20.9	21.7	24.3	25.5	25.0	23.6	24.0	23.1‡	23.6	22.1	19.7	18.8	18.0	17.5	18.2	15.9	16.7	16.8	15.6	14.9‡	16.4	15.9	14.6	14.0	13.7	-0.3
12th Grade	26.9	25.1	26.7	27.6	28.1	28.5	30.0	29.4	29.4	29.0‡	30.7	29.5	27.7	28.7	27.4	26.9	25.5	24.9	24.0	24.7	24.9	24.1‡	24.8	22.6	21.1	20.7	19.5	-1.2
Any Illicit Drug including Inhalants [a,c]																												
8th Grade	28.5	29.6	32.3	35.1	38.1	39.4	38.1	37.8	37.2	35.1	34.5	31.6	30.3	30.2	30.0	29.2	27.7	28.3	27.9	28.6	26.4	25.1‡	25.9	25.2	24.9	20.6	23.3	+2.7 s
10th Grade	36.1	36.2	38.7	42.7	45.9	49.8	50.9	49.3	49.9	49.3	48.8	47.7	44.9	43.1	42.1	40.1	39.8	38.7	40.0	40.6	40.8	40.0‡	41.6	40.4	37.2	35.9	37.0	+1.1
12th Grade	47.6	44.4	46.6	49.1	51.5	53.5	56.3	56.1	56.3	57.0	56.0	54.6	52.8	53.0	53.5	51.2	49.1	49.3	48.4	49.9	51.8	50.3‡	52.3	49.9	51.4	49.3	50.3	+1.1
Marijuana/Hashish																												
8th Grade	10.2	11.2	12.6	16.7	19.9	23.1	22.6	22.2	22.0	20.3	20.4	19.2	17.5	16.3	16.5	15.7	14.2	14.6	15.7	17.3	16.4	15.2	16.5	15.6	15.5	12.8	13.5	+0.6
10th Grade	23.4	21.4	24.4	30.4	34.1	39.8	42.3	39.6	40.9	40.3	40.1	38.7	36.4	35.1	34.1	31.8	31.0	29.9	32.3	33.4	34.5	33.8	35.8	33.7	31.1	29.7	30.7	+1.0
12th Grade	36.7	32.6	35.3	38.2	41.7	44.9	49.6	49.1	49.7	48.8	49.0	47.8	46.1	45.7	44.8	42.3	41.8	42.6	42.0	43.8	45.5	45.2	45.5	44.4	44.7	44.5	45.0	+0.5
Inhalants [c,d]																												
8th Grade	17.6	17.4	19.4	19.9	21.6	21.2	21.0	20.5	19.7	17.9	17.1	15.2	15.8	17.3	17.1	16.1	15.6	15.7	14.9	14.5	13.1	11.8	10.8	10.8	9.4	7.7	8.9	+1.2 s
10th Grade	15.7	16.6	17.5	18.0	19.0	19.3	18.3	18.3	17.0	16.6	15.2	13.5	12.7	12.4	13.1	13.3	13.6	12.8	12.3	12.0	10.1	9.9	8.7	8.7	7.2	6.6	6.1	-0.5
12th Grade	17.6	16.6	17.4	17.7	17.4	16.6	16.1	15.2	15.4	14.2	13.0	11.7	11.2	10.9	11.4	11.1	10.5	9.9	9.5	9.0	8.1	7.9	6.9	6.5	5.7	5.0	4.9	-0.2
Hallucinogens [b,f]																												
8th Grade	3.2	3.8	3.9	4.3	5.2	5.9	5.4	4.9	4.8	4.6‡	5.2	4.1	4.0	3.5	3.8	3.4	3.1	3.3	3.0	3.4	3.3	2.8	2.5	2.0	2.0	1.9	1.9	0.0
10th Grade	6.1	6.4	6.8	8.1	9.3	10.5	10.5	9.8	9.7	8.9‡	8.9	7.8	6.9	6.4	5.8	6.1	6.4	5.5	6.1	6.1	6.0	5.2	5.4	5.0	4.6	4.4	4.2	-0.2
12th Grade	9.6	9.2	10.9	11.4	12.7	14.0	15.1	14.1	13.7	13.0‡	14.7	12.0	10.6	9.7	8.8	8.3	8.4	8.7	7.4	8.6	8.3	7.5	7.6	6.3	6.4	6.7	6.7	0.0

(Table continued on next page.)

TABLE 5 (cont.)
Trends in Lifetime Prevalence of Use of Various Drugs in Grades 8, 10, and 12

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
LSD [b]																												
8th Grade	2.7	3.2	3.5	3.7	4.4	5.1	4.7	4.1	4.1	3.9	3.4	2.5	2.1	1.8	1.9	1.6	1.6	1.9	1.7	1.8	1.7	1.3	1.4	1.1	1.3	1.2	1.3	+0.1
10th Grade	5.6	5.8	6.2	7.2	8.4	9.4	9.5	8.5	8.5	7.6	6.3	5.0	3.5	2.8	2.5	2.7	3.0	2.6	3.0	3.0	2.8	2.6	2.7	2.6	3.0	3.2	3.0	-0.2
12th Grade	8.8	8.6	10.3	10.5	11.7	12.6	13.6	12.6	12.2	11.1	10.9	8.4	5.9	4.6	3.5	3.3	3.4	4.0	3.1	4.0	4.0	3.8	3.9	3.7	4.3	4.9	5.0	+0.1
Hallucinogens other than LSD [b]																												
8th Grade	1.4	1.7	1.7	2.2	2.5	3.0	2.6	2.5	2.4	2.3‡	3.9	3.3	3.2	3.0	3.3	2.8	2.6	2.5	2.4	2.7	2.8	2.3	1.9	1.5	1.2	1.3	1.2	0.0
10th Grade	2.2	2.5	2.8	3.8	3.9	4.7	4.8	5.0	4.7	4.8‡	6.6	6.3	5.9	5.8	5.2	5.5	5.7	4.8	5.4	5.3	5.2	4.5	4.4	4.1	3.3	3.1	2.9	-0.2
12th Grade	3.7	3.3	3.9	4.9	5.4	6.8	7.5	7.1	6.7	6.9‡	10.4	9.2	9.0	8.7	8.1	7.8	7.7	7.8	6.8	7.7	7.3	6.6	6.4	5.1	4.8	4.7	4.8	+0.1
Ecstasy (MDMA) [g]																												
8th Grade, original	—	—	—	—	—	3.4	3.2	2.7	2.7	4.3	5.2	4.3	3.2	2.8	2.8	2.5	2.3	2.4	2.2	3.3	2.6	2.0	1.8	1.4	—	—	—	—
Revised	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2.4	2.3	1.7	1.5	-0.1
10th Grade,original	—	—	—	—	—	5.6	5.7	5.1	6.0	7.3	8.0	6.6	5.4	4.3	4.0	4.5	5.2	4.3	5.5	6.4	6.6	5.0	5.7	3.7	—	—	—	—
Revised	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5.2	3.8	2.8	2.8	0.0
12th Grade, original	—	—	—	—	—	6.1	6.9	5.8	8.0	11.0	11.7	10.5	8.3	7.5	5.4	6.5	6.5	6.2	6.5	7.3	8.0	7.2	7.1	5.6	—	—	—	—
Revised	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	7.9	5.9	4.9	4.9	0.0
Cocaine																												
8th Grade	2.3	2.9	2.9	3.6	4.2	4.5	4.4	4.6	4.7	4.5	4.3	3.6	3.6	3.4	3.7	3.4	3.1	3.0	2.6	2.6	2.2	1.9	1.7	1.8	1.6	1.4	1.3	-0.1
10th Grade	4.1	3.3	3.6	4.3	5.0	6.5	7.1	7.2	7.7	6.9	5.7	6.1	5.1	5.4	5.2	4.8	5.3	4.5	4.6	3.7	3.3	3.3	3.3	2.6	2.7	2.1	2.1	0.0
12th Grade	7.8	6.1	6.1	5.9	6.0	7.1	8.7	9.3	9.8	8.6	8.2	7.8	7.7	8.1	8.0	8.5	7.8	7.2	6.0	5.5	5.2	4.9	4.5	4.6	4.0	3.7	4.2	+0.5
Crack																												
8th Grade	1.3	1.6	1.7	2.4	2.7	2.9	2.7	3.2	3.1	3.1	3.0	2.5	2.5	2.4	2.4	2.3	2.1	2.0	1.7	1.5	1.5	1.0	1.2	1.2	1.0	0.9	0.8	-0.1
10th Grade	1.7	1.5	1.8	2.1	2.8	3.3	3.6	3.9	4.0	3.7	3.1	3.6	2.7	2.6	2.5	2.2	2.3	2.0	2.1	1.8	1.6	1.4	1.5	1.0	1.1	0.8	0.8	0.0
12th Grade	3.1	2.6	2.6	3.0	3.0	3.3	3.9	4.4	4.6	3.9	3.7	3.8	3.6	3.9	3.5	3.5	3.2	2.8	2.4	2.4	1.9	2.1	1.8	1.8	1.7	1.4	1.7	+0.3
Cocaine other than Crack [h]																												
8th Grade	2.0	2.4	2.4	3.0	3.4	3.8	3.5	3.7	3.8	3.5	3.3	2.8	2.7	2.6	2.9	2.7	2.6	2.4	2.1	2.1	1.8	1.6	1.4	1.4	1.3	1.1	1.0	-0.1
10th Grade	3.8	3.0	3.3	3.8	4.4	5.5	6.1	6.4	6.8	6.0	5.0	5.2	4.5	4.8	4.6	4.3	4.8	4.0	4.1	3.4	3.0	3.0	2.9	2.2	2.3	1.9	1.9	-0.1
12th Grade	7.0	5.3	5.4	5.2	5.1	6.4	8.2	8.4	8.8	7.7	7.4	7.0	6.7	7.3	7.1	7.9	6.8	6.5	5.3	5.1	4.9	4.4	4.2	4.1	3.4	3.3	3.5	+0.2

(Table continued on next page.)

TABLE 5 (cont.)
Trends in Lifetime Prevalence of Use of Various Drugs in Grades 8, 10, and 12

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
Heroin [i,j]																												
8th Grade	1.2	1.4	1.4	2.0	2.3	2.4	2.1	2.3	2.3	1.9	1.7	1.6	1.6	1.6	1.5	1.4	1.3	1.4	1.3	1.3	1.2	0.8	1.0	0.9	0.5	0.5	0.7	+0.2
10th Grade	1.2	1.2	1.3	1.5	1.7	2.1	2.1	2.3	2.3	2.2	1.7	1.8	1.5	1.5	1.5	1.4	1.5	1.2	1.5	1.3	1.2	1.1	1.0	0.9	0.7	0.6	0.4	-0.2
12th Grade	0.9	1.2	1.1	1.2	1.6	1.8	2.1	2.0	2.0	2.4	1.8	1.7	1.5	1.5	1.5	1.4	1.5	1.3	1.2	1.6	1.4	1.1	1.0	1.0	0.8	0.7	0.7	0.0
With a Needle [j]																												
8th Grade	—	—	—	—	1.5	1.6	1.3	1.4	1.6	1.1	1.2	1.0	1.0	1.1	1.0	1.0	0.9	0.9	0.9	0.9	0.8	0.6	0.6	0.8	0.3	0.3	0.4	+0.1
10th Grade	—	—	—	—	1.0	1.1	1.1	1.2	1.3	1.0	0.8	1.0	0.9	0.8	0.8	0.9	0.9	0.7	0.9	0.8	0.8	0.7	0.7	0.6	0.5	0.5	0.3	-0.2
12th Grade	—	—	—	—	0.7	0.8	0.9	0.8	0.9	0.8	0.7	0.8	0.7	0.7	0.9	0.8	0.7	0.7	0.6	1.1	0.9	0.7	0.7	0.8	0.6	0.5	0.4	0.0
Without a Needle [j]																												
8th Grade	—	—	—	—	1.5	1.6	1.4	1.5	1.4	1.3	1.1	1.0	1.1	1.0	0.9	0.9	0.7	0.9	0.8	0.7	0.7	0.5	0.5	0.4	0.3	0.4	0.5	+0.1
10th Grade	—	—	—	—	1.1	1.7	1.7	1.7	1.6	1.7	1.3	1.3	1.0	1.1	1.1	1.0	1.1	0.8	1.0	0.9	0.8	0.8	0.7	0.5	0.4	0.3	0.3	0.0
12th Grade	—	—	—	—	1.4	1.7	2.1	1.6	1.8	2.4	1.5	1.6	1.8	1.4	1.3	1.1	1.4	1.1	0.9	1.4	1.3	0.8	0.9	0.7	0.7	0.6	0.4	-0.2
Narcotics other than Heroin [k,l]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	6.6	6.1	6.4	6.6	7.2	8.2	9.7	9.8	10.2	10.6	9.9‡	13.5	13.2	13.5	12.8	13.4	13.1	13.2	13.2	13.0	13.0	12.2	11.1	9.5	8.4	7.8	6.8	-1.0
Amphetamines [k,m]																												
8th Grade	10.5	10.8	11.8	12.3	13.1	13.5	12.3	11.3	10.7	9.9	10.2	8.7	8.4	7.5	7.4	7.3	6.5	6.8	6.0	5.7	5.2	4.5‡	6.9	6.7	6.8	5.7	5.7	-0.1
10th Grade	13.2	13.1	14.9	15.1	17.4	17.7	17.0	16.0	15.7	15.7	16.0	14.9	13.1	11.9	11.1	11.2	11.1	9.0	10.3	10.6	9.0	8.9‡	11.2	10.6	9.7	8.8	8.2	-0.6
12th Grade	15.4	13.9	15.1	15.7	15.3	15.3	16.5	16.4	16.3	15.6	16.2	16.8	14.4	15.0	13.1	12.4	11.4	10.5	9.9	11.1	12.2	12.0‡	13.8	12.1	10.8	10.0	9.2	-0.8
Methamphetamine [n,o]																												
8th Grade	—	—	—	—	—	—	—	—	4.5	4.2	4.4	3.5	3.9	2.5	3.1	2.7	1.8	2.3	1.6	1.8	1.3	1.3	1.4	1.0	0.8	0.6	0.7	0.0
10th Grade	—	—	—	—	—	—	—	—	7.3	6.9	6.4	6.1	5.2	5.3	4.1	3.2	2.8	2.4	2.8	2.5	2.1	1.8	1.6	1.4	1.3	0.7	0.9	+0.2
12th Grade	—	—	—	—	—	—	—	—	8.2	7.9	6.9	6.7	6.2	6.2	4.5	4.4	3.0	2.8	2.4	2.3	2.1	1.7	1.5	1.9	1.0	1.2	1.1	-0.1

(Table continued on next page.)

TABLE 5 (cont.)
Trends in Lifetime Prevalence of Use of Various Drugs in Grades 8, 10, and 12

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
Crystal Methamphetamine (Ice) [o]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	3.3	2.9	3.1	3.4	3.9	4.4	4.4	5.3	4.8	4.0	4.1	4.7	3.9	4.0	4.0	3.4	3.4	2.8	2.1	1.8	2.1	1.7	2.0	1.3	1.2	1.4	1.5	+0.1
Sedatives (Barbiturates) [k,p]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	6.2	5.5	6.3	7.0	7.4	7.6	8.1	8.7	8.9	9.2	8.7	9.5	8.8	9.9	10.5	10.2	9.3	8.5	8.2	7.5	7.0	6.9	7.5	6.8	5.9	5.2	4.5	-0.7
Tranquilizers [b,k]																												
8th Grade	3.8	4.1	4.4	4.6	4.5	5.3	4.8	4.6	4.4	4.4‡	5.0	4.3	4.4	4.0	4.1	4.3	3.9	3.9	3.9	4.4	3.4	3.0	2.9	2.9	3.0	3.0	3.4	+0.4
10th Grade	5.8	5.9	5.7	5.4	6.0	7.1	7.3	7.8	7.9	8.0‡	9.2	8.8	7.8	7.3	7.1	7.2	7.4	6.8	7.0	7.3	6.8	6.3	5.5	5.8	5.8	6.1	6.0	0.0
12th Grade	7.2	6.0	6.4	6.6	7.1	7.2	7.8	8.5	9.3	8.9‡	10.3	11.4	10.2	10.6	9.9	10.3	9.5	8.9	9.3	8.5	8.7	8.5	7.7	7.4	6.9	7.6	7.5	-0.1
Any Prescription Drug [q]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	24.0	23.9	22.2	21.5	20.9	21.6	21.7	21.2‡	22.2	19.9	18.3	18.0	16.5	-1.6
Rohypnol [r]																												
8th Grade	—	—	—	—	—	1.5	1.1	1.4	1.3	1.0	1.1	0.8	1.0	1.0	1.1	1.0	1.0	0.7	0.7	0.9	2.0	1.0	0.7	0.6	0.8	0.9	0.6	-0.3
10th Grade	—	—	—	—	—	1.5	1.7	2.0	1.8	1.3	1.5	1.3	1.0	1.2	1.0	0.8	1.3	0.9	0.7	1.4	1.2	0.8	1.1	1.0	0.5	1.0	0.7	-0.3
12th Grade	—	—	—	—	—	1.2	1.8	3.0	2.0	1.5	1.7	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Alcohol [s]																												
Any Use																												
8th Grade	70.1	69.3‡	55.7	55.8	54.5	55.3	53.8	52.5	52.1	51.7	50.5	47.0	45.6	43.9	41.0	40.5	38.9	38.9	36.6	35.8	33.1	29.5	27.8	26.8	26.1	22.8	23.1	+0.3
10th Grade	83.8	82.3‡	71.6	71.1	70.5	71.8	72.0	69.8	70.6	71.4	70.1	66.9	66.0	64.2	63.2	61.5	61.7	58.3	59.1	58.2	56.0	54.0	52.1	49.3	47.1	43.4	42.2	-1.2
12th Grade	88.0	87.5‡	80.0	80.4	80.7	79.2	81.7	81.4	80.0	80.3	79.7	78.4	76.6	76.8	75.1	72.7	72.2	71.9	72.3	71.0	70.0	69.4	68.2	66.0	64.0	61.2	61.5	+0.3

(Table continued on next page.)

TABLE 5 (cont.)
Trends in Lifetime Prevalence of Use of Various Drugs in Grades 8, 10, and 12

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
Been Drunk [o]																												
8th Grade	26.7	26.8	26.4	25.9	25.3	26.8	25.2	24.8	24.8	25.1	23.4	21.3	20.3	19.9	19.5	19.5	17.9	18.0	17.4	16.3	14.8	12.8	12.2	10.8	10.9	8.6	9.2	+0.6
10th Grade	50.0	47.7	47.9	47.2	46.9	48.5	49.4	46.7	48.9	49.3	48.2	44.0	42.4	42.3	42.1	41.4	41.2	37.2	38.6	36.9	35.9	34.6	33.5	30.2	28.6	26.0	25.1	-1.0
12th Grade	65.4	63.4	62.5	62.9	63.2	61.8	64.2	62.4	62.3	62.3	63.9	61.6	58.1	60.3	57.5	56.4	55.1	54.7	56.5	54.1	51.0	54.2	52.3	49.8	46.7	46.3	45.3	-0.9
Flavored Alcoholic Beverages [e,n]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	37.9	35.5	35.5	34.0	32.8	29.4	30.0	27.0	23.5	21.9	19.2	19.3	16.3	16.0	-0.3
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	58.6	58.8	58.1	55.7	53.5	51.4	51.3	48.4	46.7	44.9	42.3	38.7	33.3	34.8	+1.5
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	71.0	73.6	69.9	68.4	65.5	67.4	62.6	62.4	60.5	58.9	57.5	55.6	53.6	51.2	-2.4
Cigarettes																												
Any Use																												
8th Grade	44.0	45.2	45.3	46.1	46.4	49.2	47.3	45.7	44.1	40.5	36.6	31.4	28.4	27.9	25.9	24.6	22.1	20.5	20.1	20.0	18.4	15.5	14.8	13.5	13.3	9.8	9.4	-0.4
10th Grade	55.1	53.5	56.3	56.9	57.6	61.2	60.2	57.7	57.6	55.1	52.8	47.4	43.0	40.7	38.9	36.1	34.6	31.7	32.7	33.0	30.4	27.7	25.7	22.6	19.9	17.5	15.9	-1.6
12th Grade	63.1	61.8	61.9	62.0	64.2	63.5	65.4	65.3	64.6	62.5	61.0	57.2	53.7	52.8	50.0	47.1	46.2	44.7	43.6	42.2	40.0	39.5	38.1	34.4	31.1	28.3	26.6	-1.7
Smokeless Tobacco [t]																												
8th Grade	22.2	20.7	18.7	19.9	20.0	20.4	16.8	15.0	14.4	12.8	11.7	11.2	11.3	11.0	10.1	10.2	9.1	9.8	9.6	9.9	9.7	8.1	7.9	8.0	8.6	6.9	6.2	-0.7
10th Grade	28.2	26.6	28.1	29.2	27.6	27.4	26.3	22.7	20.4	19.1	19.5	16.9	14.6	13.8	14.5	15.0	15.1	12.2	15.2	16.8	15.6	15.4	14.0	13.6	12.3	10.2	9.1	-1.0
12th Grade	—	32.4	31.0	30.7	30.9	29.8	25.3	26.2	23.4	23.1	19.7	18.3	17.0	16.7	17.5	15.2	15.1	15.6	16.3	17.6	16.9	17.4	17.2	15.1	13.2	14.2	11.0	-3.2 s
Any Vaping [bb]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	21.7	17.5‡	18.5	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	32.8	29.0‡	30.9	—
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	35.5	33.8‡	35.8	—
Vaping Nicotine [bb]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	10.6	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	21.4	—
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	25.0	—

(Table continued on next page.)

TABLE 5 (cont.)
Trends in Lifetime Prevalence of Use of Various Drugs in Grades 8, 10, and 12

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
Vaping Marijuana[bb]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4.0	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	9.8	—
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	11.9	—
Vaping Just Flavoring[bb]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	17.0	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	27.5	—
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	30.7	—
Steroids [k,u]																												
8th Grade	1.9	1.7	1.6	2.0	2.0	1.8	1.8	2.3	2.7	3.0	2.8	2.5	2.5	1.9	1.7	1.6	1.5	1.4	1.3	1.1	1.2	1.2	1.1	1.0	1.0	0.9	1.1	+0.1
10th Grade	1.8	1.7	1.7	1.8	2.0	1.8	2.0	2.0	2.7	3.5	3.5	3.5	3.0	2.4	2.0	1.8	1.8	1.4	1.3	1.6	1.4	1.3	1.3	1.4	1.2	1.3	1.1	-0.2
12th Grade	2.1	2.1	2.0	2.4	2.3	1.9	2.4	2.7	2.9	2.5	3.7	4.0	3.5	3.4	2.6	2.7	2.2	2.2	2.2	2.0	1.8	1.8	2.1	1.9	2.3	1.6	1.6	0.0
Previously surveyed drugs that have been dropped.																												
Nitrites [e]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	1.6	1.5	1.4	1.7	1.5	1.8	2.0	2.7	1.7	0.8	1.9	1.5	1.6	1.3	1.1	1.2	1.2	0.6	1.1	—	—	—	—	—	—	—	—	—
PCP [e]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	2.9	2.4	2.9	2.8	2.7	4.0	3.9	3.9	3.4	3.4	3.5	3.1	2.5	1.6	2.4	2.2	2.1	1.8	1.7	1.8	2.3	1.6	1.3	—	—	—	—	—
Methaqualone [e,k]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	1.3	1.6	0.8	1.4	1.2	2.0	1.7	1.6	1.8	0.8	1.1	1.5	1.0	1.3	1.3	1.2	1.0	0.8	0.7	0.4	0.6	0.8	—	—	—	—	—	—

Source. The Monitoring the Future study, the University of Michigan.

Note: See footnotes following Table 5-5d.

TABLE 6
Trends in Annual Prevalence of Use of Various Drugs in Grades 8, 10, and 12

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
Any Illicit Drug [a]																												
8th Grade	11.3	12.9	15.1	18.5	21.4	23.6	22.1	21.0	20.5	19.5	19.5	17.7	16.1	15.2	15.5	14.8	13.2	14.1	14.5	16.0	14.7	13.4‡	15.2	14.6	14.8	12.0	12.9	+0.9
10th Grade	21.4	20.4	24.7	30.0	33.3	37.5	38.5	35.0	35.9	36.4	37.2	34.8	32.0	31.1	29.8	28.7	28.1	26.9	29.4	30.2	31.1	30.1‡	32.1	29.9	27.9	26.8	27.8	+1.0
12th Grade	29.4	27.1	31.0	35.8	39.0	40.2	42.4	41.4	42.1	40.9	41.4	41.0	39.3	38.8	38.4	36.5	35.9	36.6	36.5	38.3	40.0	39.7‡	40.1	38.7	38.6	38.3	39.9	+1.6
Any Illicit Drug other than Marijuana [a,b]																												
8th Grade	8.4	9.3	10.4	11.3	12.6	13.1	11.8	11.0	10.5	10.2‡	10.8	8.8	8.8	7.9	8.1	7.7	7.0	7.4	7.0	7.1	6.4	5.5‡	6.3	6.4	6.3	5.4	5.8	+0.3
10th Grade	12.2	12.3	13.9	15.2	17.5	18.4	18.2	16.6	16.7	16.7‡	17.9	15.7	13.8	13.5	12.9	12.7	13.1	11.3	12.2	12.1	11.2	10.8‡	11.2	11.2	10.5	9.8	9.4	-0.4
12th Grade	16.2	14.9	17.1	18.0	19.4	19.8	20.7	20.2	20.7	20.4‡	21.6	20.9	19.8	20.5	19.7	19.2	18.5	18.3	17.0	17.3	17.6	17.0‡	17.8	15.9	15.2	14.3	13.3	-1.0
Any Illicit Drug including Inhalants [a,c]																												
8th Grade	16.7	18.2	21.1	24.2	27.1	28.7	27.2	26.2	25.3	24.0	23.9	21.4	20.4	20.2	20.4	19.7	18.0	19.0	18.8	20.3	18.2	17.0‡	17.6	16.8	17.0	13.5	15.8	+2.3 ss
10th Grade	23.9	23.5	27.4	32.5	35.6	39.6	40.3	37.1	37.7	38.0	38.7	36.1	33.5	32.9	31.7	30.7	30.2	28.8	31.2	31.8	32.5	31.5‡	33.2	31.0	28.9	27.7	29.1	+1.4
12th Grade	31.2	28.8	32.5	37.6	40.2	41.9	43.3	42.4	42.8	42.5	42.6	42.1	40.5	39.1	40.3	38.0	37.0	37.3	37.6	39.2	41.5	40.2‡	42.3	39.2	40.2	38.7	41.2	+2.5
Marijuana/Hashish																												
8th Grade	6.2	7.2	9.2	13.0	15.8	18.3	17.7	16.9	16.5	15.6	15.4	14.6	12.8	11.8	12.2	11.7	10.3	10.9	11.8	13.7	12.5	11.4	12.7	11.7	11.8	9.4	10.1	+0.8
10th Grade	16.5	15.2	19.2	25.2	28.7	33.6	34.8	31.1	32.1	32.2	32.7	30.3	28.2	27.5	26.6	25.2	24.6	23.9	26.7	27.5	28.8	28.0	29.8	27.3	25.4	23.9	25.5	+1.6
12th Grade	23.9	21.9	26.0	30.7	34.7	35.8	38.5	37.5	37.8	36.5	37.0	36.2	34.9	34.3	33.6	31.5	31.7	32.4	32.8	34.8	36.4	36.4	36.4	35.1	34.9	35.6	37.1	+1.5
Synthetic Marijuana [n,o]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4.4	4.0	3.3	3.1	2.7	2.0	-0.7 s
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	8.8	7.4	5.4	4.3	3.3	2.7	-0.6
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	11.4	11.3	7.9	5.8	5.2	3.5	3.7	+0.2
Inhalants [c,d]																												
8th Grade	9.0	9.5	11.0	11.7	12.8	12.2	11.8	11.1	10.3	9.4	9.1	7.7	8.7	9.6	9.5	9.1	8.3	8.9	8.1	8.1	7.0	6.2	5.2	5.3	4.6	3.8	4.7	+0.9 s
10th Grade	7.1	7.5	8.4	9.1	9.6	9.5	8.7	8.0	7.2	7.3	6.6	5.8	5.4	5.9	6.0	6.5	6.6	5.9	6.1	5.7	4.5	4.1	3.5	3.3	2.9	2.4	2.3	-0.1
12th Grade	6.6	6.2	7.0	7.7	8.0	7.6	6.7	6.2	5.6	5.9	4.5	4.5	3.9	4.2	5.0	4.5	3.7	3.8	3.4	3.6	3.2	2.9	2.5	1.9	1.9	1.7	1.5	-0.1

(Table continued on next page.)

TABLE 6 (cont.)
Trends in Annual Prevalence of Use of Various Drugs in Grades 8, 10, and 12

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
Hallucinogens [b,f]																												
8th Grade	1.9	2.5	2.6	2.7	3.6	4.1	3.7	3.4	2.9	2.8‡	3.4	2.6	2.6	2.2	2.4	2.1	1.9	2.1	1.9	2.2	2.2	1.6	1.6	1.3	1.3	1.2	1.1	-0.1
10th Grade	4.0	4.3	4.7	5.8	7.2	7.8	7.6	6.9	6.9	6.1‡	6.2	4.7	4.1	4.1	4.0	4.1	4.4	3.9	4.1	4.2	4.1	3.5	3.4	3.3	3.1	2.9	2.8	-0.1
12th Grade	5.8	5.9	7.4	7.6	9.3	10.1	9.8	9.0	9.4	8.1‡	9.1	6.6	5.9	6.2	5.5	4.9	5.4	5.9	4.7	5.5	5.2	4.8	4.5	4.0	4.2	4.3	4.4	+0.1
LSD [b]																												
8th Grade	1.7	2.1	2.3	2.4	3.2	3.5	3.2	2.8	2.4	2.4	2.2	1.5	1.3	1.1	1.2	0.9	1.1	1.3	1.1	1.2	1.1	0.8	1.0	0.7	0.9	0.8	0.9	+0.1
10th Grade	3.7	4.0	4.2	5.2	6.5	6.9	6.7	5.9	6.0	5.1	4.1	2.6	1.7	1.6	1.5	1.7	1.9	1.8	1.9	1.9	1.8	1.7	1.7	1.9	2.0	2.1	2.1	-0.1
12th Grade	5.2	5.6	6.8	6.9	8.4	8.8	8.4	7.6	8.1	6.6	6.6	3.5	1.9	2.2	1.8	1.7	2.1	2.7	1.9	2.6	2.7	2.4	2.2	2.5	2.9	3.0	3.3	+0.3
Hallucinogens other than LSD [b]																												
8th Grade	0.7	1.1	1.0	1.3	1.7	2.0	1.8	1.6	1.5	1.4‡	2.4	2.1	2.1	1.9	2.0	1.8	1.6	1.6	1.5	1.8	1.8	1.3	1.2	1.0	0.8	0.8	0.7	-0.1
10th Grade	1.3	1.4	1.9	2.4	2.8	3.3	3.3	3.4	3.2	3.1‡	4.3	4.0	3.6	3.7	3.5	3.7	3.8	3.3	3.5	3.5	3.5	3.0	2.7	2.6	1.9	2.0	1.8	-0.2
12th Grade	2.0	1.7	2.2	3.1	3.8	4.4	4.6	4.6	4.3	4.4‡	5.9	5.4	5.4	5.6	5.0	4.6	4.8	5.0	4.2	4.8	4.3	4.0	3.7	3.0	2.9	2.7	2.9	+0.2
PCP [e]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	1.4	1.4	1.4	1.6	1.8	2.6	2.3	2.1	1.8	2.3	1.8	1.1	1.3	0.7	1.3	0.7	0.9	1.1	1.0	1.0	1.3	0.9	0.7	0.8	1.4	1.3	1.0	-0.3
Ecstasy (MDMA) [g]																												
8th Grade, original		—	—	—	—	2.3	2.3	1.8	1.7	3.1	3.5	2.9	2.1	1.7	1.7	1.4	1.5	1.7	1.3	2.4	1.7	1.1	1.1	0.9	—	—	—	—
Revised		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1.5	1.4	1.0	0.9	-0.1
10th Grade,original		—	—	—	—	4.6	3.9	3.3	4.4	5.4	6.2	4.9	3.0	2.4	2.6	2.8	3.5	2.9	3.7	4.7	4.5	3.0	3.6	2.3	—	—	—	—
Revised		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3.8	2.4	1.8	1.7	-0.0
12th Grade, original		—	—	—	—	4.6	4.0	3.6	5.6	8.2	9.2	7.4	4.5	4.0	3.0	4.1	4.5	4.3	4.3	4.5	5.3	3.8	4.0	3.6	—	—	—	—
Revised		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5.0	3.6	2.7	2.6	-0.1
Salvia [n,o]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1.7	1.6	1.4	1.2	0.6	0.7	0.9	0.4	-0.6 s
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3.7	3.9	2.5	2.3	1.8	1.2	0.9	0.9	0.0
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5.7	5.5	5.9	4.4	3.4	1.8	1.9	1.8	1.5	-0.2

(Table continued on next page.)

TABLE 6 (cont.)
Trends in Annual Prevalence of Use of Various Drugs in Grades 8, 10, and 12

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
Cocaine																												
8th Grade	1.1	1.5	1.7	2.1	2.6	3.0	2.8	3.1	2.7	2.6	2.5	2.3	2.2	2.0	2.2	2.0	2.0	1.8	1.6	1.6	1.4	1.2	1.0	1.0	0.9	0.8	0.8	0.0
10th Grade	2.2	1.9	2.1	2.8	3.5	4.2	4.7	4.7	4.9	4.4	3.6	4.0	3.3	3.7	3.5	3.2	3.4	3.0	2.7	2.2	1.9	2.0	1.9	1.5	1.8	1.3	1.4	+0.1
12th Grade	3.5	3.1	3.3	3.6	4.0	4.9	5.5	5.7	6.2	5.0	4.8	5.0	4.8	5.3	5.1	5.7	5.2	4.4	3.4	2.9	2.9	2.7	2.6	2.6	2.5	2.3	2.7	+0.5
Crack																												
8th Grade	0.7	0.9	1.0	1.3	1.6	1.8	1.7	2.1	1.8	1.8	1.7	1.6	1.6	1.3	1.4	1.3	1.3	1.1	1.1	1.0	0.9	0.6	0.6	0.7	0.5	0.5	0.5	0.0
10th Grade	0.9	0.9	1.1	1.4	1.8	2.1	2.2	2.5	2.4	2.2	1.8	2.3	1.6	1.7	1.7	1.3	1.3	1.3	1.2	1.0	0.9	0.8	0.8	0.5	0.7	0.4	0.6	+0.2
12th Grade	1.5	1.5	1.5	1.9	2.1	2.1	2.4	2.5	2.7	2.2	2.1	2.3	2.2	2.3	1.9	2.1	1.9	1.6	1.3	1.4	1.0	1.2	1.1	1.1	1.1	0.8	1.0	+0.2
Cocaine other than Crack [h]																												
8th Grade	1.0	1.2	1.3	1.7	2.1	2.5	2.2	2.4	2.3	1.9	1.9	1.8	1.6	1.6	1.7	1.6	1.5	1.4	1.3	1.3	1.1	1.0	0.8	0.8	0.8	0.6	0.6	0.0
10th Grade	2.1	1.7	1.8	2.4	3.0	3.5	4.1	4.0	4.4	3.8	3.0	3.4	2.8	3.3	3.0	2.9	3.1	2.6	2.3	1.9	1.7	1.8	1.6	1.3	1.5	1.1	1.2	+0.1
12th Grade	3.2	2.6	2.9	3.0	3.4	4.2	5.0	4.9	5.8	4.5	4.4	4.4	4.2	4.7	4.5	5.2	4.5	4.0	3.0	2.6	2.6	2.4	2.4	2.4	2.1	2.0	2.3	+0.3
Heroin [I,j]																												
8th Grade	0.7	0.7	0.7	1.2	1.4	1.6	1.3	1.3	1.4	1.1	1.0	0.9	0.9	1.0	0.8	0.8	0.8	0.9	0.7	0.8	0.7	0.5	0.5	0.5	0.3	0.3	0.3	+0.1
10th Grade	0.5	0.6	0.7	0.9	1.1	1.2	1.4	1.4	1.4	1.4	0.9	1.1	0.7	0.9	0.9	0.9	0.8	0.8	0.9	0.8	0.8	0.6	0.6	0.5	0.5	0.3	0.2	-0.1
12th Grade	0.4	0.6	0.5	0.6	1.1	1.0	1.2	1.0	1.1	1.5	0.9	1.0	0.8	0.9	0.8	0.8	0.9	0.7	0.7	0.9	0.8	0.6	0.6	0.6	0.5	0.3	0.4	+0.1
With a Needle [j]																												
8th Grade	—	—	—	—	0.9	1.0	0.8	0.8	0.9	0.6	0.7	0.6	0.6	0.7	0.6	0.5	0.6	0.5	0.5	0.6	0.5	0.4	0.3	0.4	0.2	0.2	0.2	0.0
10th Grade	—	—	—	—	0.6	0.7	0.7	0.8	0.6	0.5	0.4	0.6	0.5	0.5	0.5	0.5	0.5	0.5	0.6	0.5	0.5	0.4	0.5	0.4	0.2	0.3	0.2	-0.1
12th Grade	—	—	—	—	0.5	0.5	0.5	0.4	0.4	0.4	0.3	0.4	0.4	0.4	0.5	0.5	0.4	0.4	0.3	0.7	0.6	0.4	0.4	0.5	0.3	0.3	0.2	0.0
Without a Needle [j]																												
8th Grade	—	—	—	—	0.8	1.0	0.8	0.8	0.9	0.7	0.6	0.6	0.6	0.6	0.5	0.5	0.5	0.6	0.4	0.5	0.4	0.3	0.3	0.2	0.2	0.2	0.3	+0.1
10th Grade	—	—	—	—	0.8	0.9	1.1	1.0	1.1	1.1	0.7	0.8	0.5	0.7	0.7	0.6	0.6	0.6	0.6	0.6	0.5	0.4	0.4	0.3	0.3	0.2	0.1	0.0
12th Grade	—	—	—	—	1.0	1.0	1.2	0.8	1.0	1.6	0.8	0.8	0.8	0.7	0.8	0.6	1.0	0.5	0.6	0.8	0.7	0.4	0.4	0.5	0.4	0.3	0.2	-0.1

(Table continued on next page.)

TABLE 6 (cont.)
Trends in Annual Prevalence of Use of Various Drugs in Grades 8, 10, and 12

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
Narcotics other than Heroin [k,l]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	3.5	3.3	3.6	3.8	4.7	5.4	6.2	6.3	6.7	7.0	6.7‡	9.4	9.3	9.5	9.0	9.0	9.2	9.1	9.2	8.7	8.7	7.9	7.1	6.1	5.4	4.8	4.2	-0.5
OxyContin [k,n,v]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	1.3	1.7	1.7	1.8	2.6	1.8	2.1	2.0	2.1	1.8	1.6	2.0	1.0	0.8	0.9	0.8	-0.1
10th Grade	—	—	—	—	—	—	—	—	—	—	—	3.0	3.6	3.5	3.2	3.8	3.9	3.6	5.1	4.6	3.9	3.0	3.4	3.0	2.6	2.1	2.2	+0.1
12th Grade	—	—	—	—	—	—	—	—	—	—	—	4.0	4.5	5.0	5.5	4.3	5.2	4.7	4.9	5.1	4.9	4.3	3.6	3.3	3.7	3.4	2.7	-0.7
Vicodin [k,n,v]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	2.5	2.8	2.5	2.6	3.0	2.7	2.9	2.5	2.7	2.1	1.3	1.4	1.0	0.9	0.8	0.7	-0.2
10th Grade	—	—	—	—	—	—	—	—	—	—	—	6.9	7.2	6.2	5.9	7.0	7.2	6.7	8.1	7.7	5.9	4.4	4.6	3.4	2.5	1.7	1.5	-0.3
12th Grade	—	—	—	—	—	—	—	—	—	—	—	9.6	10.5	9.3	9.5	9.7	9.6	9.7	9.7	8.0	8.1	7.5	5.3	4.8	4.4	2.9	2.0	-1.0 ss
Amphetamines [k,m]																												
8th Grade	6.2	6.5	7.2	7.9	8.7	9.1	8.1	7.2	6.9	6.5	6.7	5.5	5.5	4.9	4.9	4.7	4.2	4.5	4.1	3.9	3.5	2.9‡	4.2	4.3	4.1	3.5	3.5	0.0
10th Grade	8.2	8.2	9.6	10.2	11.9	12.4	12.1	10.7	10.4	11.1	11.7	10.7	9.0	8.5	7.8	7.9	8.0	6.4	7.1	7.6	6.6	6.5‡	7.9	7.6	6.8	6.1	5.6	-0.5
12th Grade	8.2	7.1	8.4	9.4	9.3	9.5	10.2	10.1	10.2	10.5	10.9	11.1	9.9	10.0	8.6	8.1	7.5	6.8	6.6	7.4	8.2	7.9‡	9.2	8.1	7.7	6.7	5.9	-0.8
Ritalin [k,n,o]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	2.9	2.8	2.6	2.5	2.4	2.6	2.1	1.6	1.8	1.5	1.3	0.7	1.1	0.9	0.6	0.8	0.4	-0.4 s
10th Grade	—	—	—	—	—	—	—	—	—	—	4.8	4.8	4.1	3.4	3.4	3.6	2.8	2.9	3.6	2.7	2.6	1.9	1.8	1.8	1.6	1.2	0.8	-0.4
12th Grade	—	—	—	—	—	—	—	—	—	—	5.1	4.0	4.0	5.1	4.4	4.4	3.8	3.4	2.1	2.7	2.6	2.6	2.3	1.8	2.0	1.2	1.3	+0.1
Adderall [k,n,o]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2.0	2.3	1.7	1.7	1.8	1.3	1.0	1.5	1.3	-0.3
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5.7	5.3	4.6	4.5	4.4	4.6	5.2	4.2	4.0	-0.2
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5.4	6.5	6.5	7.6	7.4	6.8	7.5	6.2	5.5	-0.6

(Table continued on next page.)

TABLE 6 (cont.)
Trends in Annual Prevalence of Use of Various Drugs in Grades 8, 10, and 12

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
Methamphetamine [n,o]																												
8th Grade	—	—	—	—	—	—	—	—	3.2	2.5	2.8	2.2	2.5	1.5	1.8	1.8	1.1	1.2	1.0	1.2	0.8	1.0	1.0	0.6	0.5	0.4	0.5	+0.1
10th Grade	—	—	—	—	—	—	—	—	4.6	4.0	3.7	3.9	3.3	3.0	2.9	1.8	1.6	1.5	1.6	1.6	1.4	1.0	1.0	0.8	0.8	0.4	0.4	-0.1
12th Grade	—	—	—	—	—	—	—	—	4.7	4.3	3.9	3.6	3.2	3.4	2.5	2.5	1.7	1.2	1.2	1.0	1.4	1.1	0.9	1.0	0.6	0.6	0.6	-0.1
Crystal Methamphetamine (Ice) [o]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	1.4	1.3	1.7	1.8	2.4	2.8	2.3	3.0	1.9	2.2	2.5	3.0	2.0	2.1	2.3	1.9	1.6	1.1	0.9	0.9	1.2	0.8	1.1	0.8	0.5	0.8	0.8	0.0
Bath salts (synthetic stimulants) [n,o]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.8	1.0	0.5	0.4	0.9	0.5	-0.4
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.6	0.9	0.9	0.7	0.8	0.4	-0.3
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1.3	0.9	0.9	1.0	0.8	0.6	-0.1
Sedatives (Barbiturates) [k,p]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	3.4	2.8	3.4	4.1	4.7	4.9	5.1	5.5	5.8	6.2	5.7	6.7	6.0	6.5	7.2	6.6	6.2	5.8	5.2	4.8	4.3	4.5	4.8	4.3	3.6	3.0	2.9	-0.1
Tranquilizers [b,k]																												
8th Grade	1.8	2.0	2.1	2.4	2.7	3.3	2.9	2.6	2.5	2.6‡	2.8	2.6	2.7	2.5	2.8	2.6	2.4	2.4	2.6	2.8	2.0	1.8	1.8	1.7	1.7	1.7	2.0	+0.3
10th Grade	3.2	3.5	3.3	3.3	4.0	4.6	4.9	5.1	5.4	5.6‡	7.3	6.3	5.3	5.1	4.8	5.2	5.3	4.6	5.0	5.1	4.5	4.3	3.7	3.9	3.9	4.1	4.1	0.0
12th Grade	3.6	2.8	3.5	3.7	4.4	4.6	4.7	5.5	5.8	5.7‡	6.9	7.7	6.7	7.3	6.8	6.6	6.2	6.2	6.3	5.6	5.6	5.3	4.6	4.7	4.7	4.9	4.7	-0.2
Any Prescription Drug [q]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	17.1	16.8	15.8	15.4	14.4	15.0	15.2	14.8‡	15.9	13.9	12.9	12.0	10.9	-1.0

(Table continued on next page.)

TABLE 6 (cont.)
Trends in Annual Prevalence of Use of Various Drugs in Grades 8, 10, and 12

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
OTC Cough/Cold Medicines [n,o]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4.2	4.0	3.6	3.8	3.2	2.7	3.0	2.9	2.0	1.6	2.6	2.1	-0.5
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5.3	5.4	5.3	6.0	5.1	5.5	4.7	4.3	3.7	3.3	3.0	3.6	+0.6
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	6.9	5.8	5.5	5.9	6.6	5.3	5.6	5.0	4.1	4.6	4.0	3.2	-0.8
Rohypnol [r]																												
8th Grade	—	—	—	—	—	1.0	0.8	0.8	0.5	0.5	0.7	0.3	0.5	0.6	0.7	0.5	0.7	0.5	0.4	0.5	0.8	0.4	0.4	0.3	0.3	0.5	0.4	-0.1
10th Grade	—	—	—	—	—	1.1	1.3	1.2	1.0	0.8	1.0	0.7	0.6	0.7	0.5	0.5	0.7	0.4	0.4	0.6	0.6	0.5	0.6	0.5	0.2	0.5	0.3	-0.3
12th Grade	—	—	—	—	—	1.1	1.2	1.4	1.0	0.8	0.9‡	1.6	1.3	1.6	1.2	1.1	1.0	1.3	1.0	1.5	1.3	1.5	0.9	0.7	1.0	1.1	0.8	-0.4
GHB [n,w]																												
8th Grade	—	—	—	—	—	—	—	—	—	1.2	1.1	0.8	0.9	0.7	0.5	0.8	0.7	1.1	0.7	0.6	0.6	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	1.1	1.0	1.4	1.4	0.8	0.8	0.7	0.6	0.5	1.0	0.6	0.5	—	—	—	—	—	—	—
12th Grade	—	—	—	—	—	—	—	—	—	1.9	1.6	1.5	1.4	2.0	1.1	1.1	0.9	1.2	1.1	1.4	1.4	1.4	1.0	1.0	0.7	0.9	0.4	-0.5
Ketamine [n,x]																												
8th Grade	—	—	—	—	—	—	—	—	—	1.6	1.3	1.3	1.1	0.9	0.6	0.9	1.0	1.2	1.0	1.0	0.8	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	2.1	2.1	2.2	1.9	1.3	1.0	1.0	0.8	1.0	1.3	1.1	1.2	—	—	—	—	—	—	—
12th Grade	—	—	—	—	—	—	—	—	—	2.5	2.5	2.6	2.1	1.9	1.6	1.4	1.3	1.5	1.7	1.6	1.7	1.5	1.4	1.5	1.4	1.2	1.2	-0.1
Alcohol [s]																												
Any Use																												
8th Grade	54.0	53.7‡	45.4	46.8	45.3	46.5	45.5	43.7	43.5	43.1	41.9	38.7	37.2	36.7	33.9	33.6	31.8	32.1	30.3	29.3	26.9	23.6	22.1	20.8	21.0	17.6	18.2	+0.6
10th Grade	72.3	70.2‡	63.4	63.9	63.5	65.0	65.2	62.7	63.7	65.3	63.5	60.0	59.3	58.2	56.7	55.8	56.3	52.5	52.8	52.1	49.8	48.5	47.1	44.0	41.9	38.3	37.7	-0.6
12th Grade	77.7	76.8‡	72.7	73.0	73.7	72.5	74.8	74.3	73.8	73.2	73.3	71.5	70.1	70.6	68.6	66.5	66.4	65.5	66.2	65.2	63.5	63.5	62.0	60.2	58.2	55.6	55.7	+0.2
Been Drunk [o]																												
8th Grade	17.5	18.3	18.2	18.2	18.4	19.8	18.4	17.9	18.5	18.5	16.6	15.0	14.5	14.5	14.1	13.9	12.6	12.7	12.2	11.5	10.5	8.6	8.4	7.3	7.7	5.7	6.4	+0.7
10th Grade	40.1	37.0	37.8	38.0	38.5	40.1	40.7	38.3	40.9	41.6	39.9	35.4	34.7	35.1	34.2	34.5	34.4	30.0	31.2	29.9	28.8	28.2	27.1	24.6	23.4	20.5	20.4	-0.1
12th Grade	52.7	50.3	49.6	51.7	52.5	51.9	53.2	52.0	53.2	51.8	53.2	50.4	48.0	51.8	47.7	47.9	46.1	45.6	47.0	44.0	42.2	45.0	43.5	41.4	37.7	37.3	35.6	-1.7

(Table continued on next page.)

TABLE 6 (cont.)
Trends in Annual Prevalence of Use of Various Drugs in Grades 8, 10, and 12

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
Flavored Alcoholic Beverages [e,n,y]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	30.4	27.9	26.8	26.0	25.0	22.2	21.9	19.2	17.0	15.7	13.4	13.4	11.2	10.8	-0.5
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	49.7	48.5	48.8	45.9	43.4	41.5	41.0	38.3	37.8	35.6	33.2	31.4	26.1	28.3	+2.3
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	55.2	55.8	58.4	54.7	53.6	51.8	53.4	47.9	47.0	44.4	44.2	43.6	42.8	40.0	39.6	-0.4
Alcoholic Beverages containing Caffeine [n,o,z]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	11.8	10.9	10.2	9.5	8.4	6.5	5.6	-0.9
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	22.5	19.7	16.9	14.3	12.8	10.6	9.9	-0.8
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	26.4	26.4	23.5	20.0	18.3	17.0	16.9	-0.1
Tobacco using a Hookah [e]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	17.1	18.5	18.3	21.4	22.9	19.8	13.0	10.1	-2.9 s
Small cigars [e]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	23.1	19.5	19.9	20.4	18.9	15.9	15.6	13.3	-2.4
Dissolvable Tobacco Products [e,n]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1.0	1.1	1.1	0.9	0.7	0.6	0.0
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1.6	1.2	1.3	1.1	0.9	0.6	-0.3
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1.5	1.6	1.9	1.1	1.4	1.1	1.4	+0.3
Snus [e,n]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2.4	2.0	2.2	1.9	2.2	1.1	-1.0 ss
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	6.9	5.2	4.5	4.0	3.0	2.6	-0.4
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	7.9	7.9	7.7	5.8	5.8	5.8	4.2	-1.6

(Table continued on next page.)

TABLE 6 (cont.)
Trends in Annual Prevalence of Use of Various Drugs in Grades 8, 10, and 12

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
Any Vaping[bb]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	13.3	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	23.9	—
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	27.8	—
Vaping Nicotine[bb]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	7.5	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	15.8	—
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	18.8	—
Vaping Marijuana[bb]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3.0	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	8.1	—
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	9.5	—
Vaping Just Flavoring[bb]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	11.8	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	19.3	—
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	20.6	—
Steroids [k,u]																												
8th Grade	1.0	1.1	0.9	1.2	1.0	0.9	1.0	1.2	1.7	1.7	1.6	1.5	1.4	1.1	1.1	0.9	0.8	0.9	0.8	0.5	0.7	0.6	0.6	0.6	0.5	0.5	0.6	+0.1
10th Grade	1.1	1.1	1.0	1.1	1.2	1.2	1.2	1.2	1.7	2.2	2.1	2.2	1.7	1.5	1.3	1.2	1.1	0.9	0.8	1.0	0.9	0.8	0.8	0.8	0.7	0.7	0.7	0.0
12th Grade	1.4	1.1	1.2	1.3	1.5	1.4	1.4	1.7	1.8	1.7	2.4	2.5	2.1	2.5	1.5	1.8	1.4	1.5	1.5	1.5	1.2	1.3	1.5	1.5	1.7	1.0	1.1	0.0

(Table continued on next page.)

TABLE 6 (cont.)
Trends in Annual Prevalence of Use of Various Drugs in Grades 8, 10, and 12

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
Previously surveyed drugs that have been dropped.																												
Nitrites [e]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	0.9	0.5	0.9	1.1	1.1	1.6	1.2	1.4	0.9	0.6	0.6	1.1	0.9	0.8	0.6	0.5	0.8	0.6	0.9	—	—	—	—	—	—	—	—	—
Provigil [k,o]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1.8	1.3	1.5	—	—	—	—	—	—	—
Methaqualone [e,k]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	0.5	0.6	0.2	0.8	0.7	1.1	1.0	1.1	1.1	0.3	0.8	0.9	0.6	0.8	0.9	0.8	0.5	0.5	0.6	0.3	0.3	0.4	—	—	—	—	—	—
Bidis [n,o]																												
8th Grade	—	—	—	—	—	—	—	—	—	3.9	2.7	2.7	2.0	1.7	1.6	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	6.4	4.9	3.1	2.8	2.1	1.6	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	—	—	—	—	—	—	—	—	—	9.2	7.0	5.9	4.0	3.6	3.3	2.3	1.7	1.9	1.5	1.4	—	—	—	—	—	—	—	—
Kreteks [n,o]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	2.6	2.6	2.0	1.9	1.4	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	6.0	4.9	3.8	3.7	2.8	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	—	—	—	—	—	—	—	—	—	—	10.1	8.4	6.7	6.5	7.1	6.2	6.8	6.8	5.5	4.6	2.9	3.0	1.6	1.6	—	—	—	—

Source. The Monitoring the Future study, the University of Michigan.

Note: See footnotes following Table 5-5d.

TABLE 7
Trends in 30-Day Prevalence of Use of Various Drugs in Grades 8, 10, and 12

	Percentage who used in last 30 days																										2016–2017
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	change
Any Illicit Drug [a]																												
8th Grade	5.7	6.8	8.4	10.9	12.4	14.6	12.9	12.1	12.2	11.9	11.7	10.4	9.7	8.4	8.5	8.1	7.4	7.6	8.1	9.5	8.5	7.7‡	8.7	8.3	8.1	6.9	7.0	+0.1
10th Grade	11.6	11.0	14.0	18.5	20.2	23.2	23.0	21.5	22.1	22.5	22.7	20.8	19.5	18.3	17.3	16.8	16.9	15.8	17.8	18.5	19.2	18.6‡	19.2	18.5	16.5	15.9	17.2	+1.3
12th Grade	16.4	14.4	18.3	21.9	23.8	24.6	26.2	25.6	25.9	24.9	25.7	25.4	24.1	23.4	23.1	21.5	21.9	22.3	23.3	23.8	25.2	25.2‡	25.2	23.7	23.6	24.4	24.9	+0.4
Any Illicit Drug other than Marijuana [a,b]																												
8th Grade	3.8	4.7	5.3	5.6	6.5	6.9	6.0	5.5	5.5	5.6‡	5.5	4.7	4.7	4.1	4.1	3.8	3.6	3.8	3.5	3.5	3.4	2.6‡	3.6	3.3	3.1	2.7	2.7	0.0
10th Grade	5.5	5.7	6.5	7.1	8.9	8.9	8.8	8.6	8.6	8.5‡	8.7	8.1	6.9	6.9	6.4	6.3	6.9	5.3	5.7	5.8	5.4	5.0‡	4.9	5.6	4.9	4.4	4.5	+0.1
12th Grade	7.1	6.3	7.9	8.8	10.0	9.5	10.7	10.7	10.4	10.4‡	11.0	11.3	10.4	10.8	10.3	9.8	9.5	9.3	8.6	8.6	8.9	8.4‡	8.2	7.7	7.6	6.9	6.3	-0.6
Any Illicit Drug including Inhalants [a,c]																												
8th Grade	8.8	10.0	12.0	14.3	16.1	17.5	16.0	14.9	15.1	14.4	14.0	12.6	12.1	11.2	11.2	10.9	10.1	10.4	10.6	11.7	10.5	9.5‡	10.0	9.5	9.3	7.9	8.6	+0.8
10th Grade	13.1	12.6	15.5	20.0	21.6	24.5	24.1	22.5	23.1	23.6	23.6	21.7	20.5	19.3	18.4	17.7	18.1	16.8	18.8	19.4	20.1	19.3‡	20.0	19.1	17.1	16.4	18.0	+1.5
12th Grade	17.8	15.5	19.3	23.0	24.8	25.5	26.9	26.6	26.4	26.4	26.5	25.9	24.6	23.3	24.2	22.1	22.8	22.8	24.1	24.5	26.2	25.2‡	26.5	24.3	24.7	24.6	25.7	+1.1
Marijuana/Hashish																												
8th Grade	3.2	3.7	5.1	7.8	9.1	11.3	10.2	9.7	9.7	9.1	9.2	8.3	7.5	6.4	6.6	6.5	5.7	5.8	6.5	8.0	7.2	6.5	7.0	6.5	6.5	5.4	5.5	0.0
10th Grade	8.7	8.1	10.9	15.8	17.2	20.4	20.5	18.7	19.4	19.7	19.8	17.8	17.0	15.9	15.2	14.2	14.2	13.8	15.9	16.7	17.6	17.0	18.0	16.6	14.8	14.0	15.7	+1.7 s
12th Grade	13.8	11.9	15.5	19.0	21.2	21.9	23.7	22.8	23.1	21.6	22.4	21.5	21.2	19.9	19.8	18.3	18.8	19.4	20.6	21.4	22.6	22.9	22.7	21.2	21.3	22.5	22.9	+0.4
Inhalants [c,d]																												
8th Grade	4.4	4.7	5.4	5.6	6.1	5.8	5.6	4.8	5.0	4.5	4.0	3.8	4.1	4.5	4.2	4.1	3.9	4.1	3.8	3.6	3.2	2.7	2.3	2.2	2.0	1.8	2.1	+0.4
10th Grade	2.7	2.7	3.3	3.6	3.5	3.3	3.0	2.9	2.6	2.6	2.4	2.4	2.2	2.4	2.2	2.3	2.5	2.1	2.2	2.0	1.7	1.4	1.3	1.1	1.2	1.0	1.1	+0.1
12th Grade	2.4	2.3	2.5	2.7	3.2	2.5	2.5	2.3	2.0	2.2	1.7	1.5	1.5	1.5	2.0	1.5	1.2	1.4	1.2	1.4	1.0	0.9	1.0	0.7	0.7	0.8	0.8	0.0
Hallucinogens [b,f]																												
8th Grade	0.8	1.1	1.2	1.3	1.7	1.9	1.8	1.4	1.3	1.2‡	1.6	1.2	1.2	1.0	1.1	0.9	1.0	0.9	0.9	1.0	1.0	0.6	0.8	0.5	0.6	0.6	0.5	-0.1
10th Grade	1.6	1.8	1.9	2.4	3.3	2.8	3.3	3.2	2.9	2.3‡	2.1	1.6	1.5	1.6	1.5	1.5	1.7	1.3	1.4	1.6	1.4	1.2	1.1	1.2	0.9	0.9	1.1	+0.2
12th Grade	2.2	2.1	2.7	3.1	4.4	3.5	3.9	3.8	3.5	2.6‡	3.3	2.3	1.8	1.9	1.9	1.5	1.7	2.2	1.6	1.9	1.6	1.6	1.4	1.5	1.6	1.4	1.6	+0.1

(Table continued on next page.)

TABLE 7 (cont.)
Trends in 30-Day Prevalence of Use of Various Drugs in Grades 8, 10, and 12

	Percentage who used in last 30 days																										2016–2017
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	change
LSD [b]																												
8th Grade	0.6	0.9	1.0	1.1	1.4	1.5	1.5	1.1	1.1	1.0	1.0	0.7	0.6	0.5	0.5	0.4	0.5	0.5	0.5	0.6	0.5	0.3	0.5	0.3	0.4	0.4	0.3	-0.1
10th Grade	1.5	1.6	1.6	2.0	3.0	2.4	2.8	2.7	2.3	1.6	1.5	0.7	0.6	0.6	0.6	0.7	0.7	0.7	0.5	0.7	0.7	0.5	0.6	0.6	0.6	0.7	0.8	+0.1
12th Grade	1.9	2.0	2.4	2.6	4.0	2.5	3.1	3.2	2.7	1.6	2.3	0.7	0.6	0.7	0.7	0.6	0.6	1.1	0.5	0.8	0.8	0.8	0.8	1.0	1.1	1.0	1.2	+0.2
Hallucinogens other than LSD [b]																												
8th Grade	0.3	0.4	0.5	0.7	0.8	0.9	0.7	0.7	0.6	0.6‡	1.1	1.0	1.0	0.8	0.9	0.7	0.7	0.7	0.7	0.8	0.7	0.5	0.5	0.4	0.3	0.3	0.3	0.0
10th Grade	0.4	0.5	0.7	1.0	1.0	1.0	1.2	1.4	1.2	1.2‡	1.4	1.4	1.2	1.4	1.3	1.3	1.4	1.0	1.1	1.2	1.1	0.9	0.8	0.8	0.6	0.5	0.6	+0.0
12th Grade	0.7	0.5	0.8	1.2	1.3	1.6	1.7	1.6	1.6	1.7‡	1.9	2.0	1.5	1.7	1.6	1.3	1.4	1.6	1.4	1.5	1.2	1.3	1.0	1.0	0.9	0.7	1.0	+0.2
Ecstasy (MDMA) [g]																												
8th Grade, original	—	—	—	—	1.0	1.0	0.9	0.8	1.4	1.8	1.4	0.7	0.8	0.6	0.7	0.6	0.8	0.6	1.1	0.6	0.5	0.5	0.4	—	—	—	—
Revised	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.7	0.5	0.3	0.4	0.0
10th Grade,original	—	—	—	—	1.8	1.3	1.3	1.8	2.6	2.6	1.8	1.1	0.8	1.0	1.2	1.2	1.1	1.3	1.9	1.6	1.0	1.2	0.8	—	—	—	—
Revised	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1.1	0.9	0.5	0.5	0.0
12th Grade, original	—	—	—	—	2.0	1.6	1.5	2.5	3.6	2.8	2.4	1.3	1.2	1.0	1.3	1.6	1.8	1.8	1.4	2.3	0.9	1.5	1.4	—	—	—	—
Revised	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1.5	1.1	0.9	0.9	0.0
Cocaine																												
8th Grade	0.5	0.7	0.7	1.0	1.2	1.3	1.1	1.4	1.3	1.2	1.2	1.1	0.9	0.9	1.0	1.0	0.9	0.8	0.8	0.6	0.8	0.5	0.5	0.5	0.5	0.3	0.4	+0.1
10th Grade	0.7	0.7	0.9	1.2	1.7	1.7	2.0	2.1	1.8	1.8	1.3	1.6	1.3	1.7	1.5	1.5	1.3	1.2	0.9	0.9	0.7	0.8	0.8	0.6	0.8	0.4	0.5	+0.1
12th Grade	1.4	1.3	1.3	1.5	1.8	2.0	2.3	2.4	2.6	2.1	2.1	2.3	2.1	2.3	2.3	2.5	2.0	1.9	1.3	1.3	1.1	1.1	1.1	1.0	1.1	0.9	1.2	+0.3
Crack																												
8th Grade	0.3	0.5	0.4	0.7	0.7	0.8	0.7	0.9	0.8	0.8	0.8	0.8	0.7	0.6	0.6	0.6	0.6	0.5	0.5	0.4	0.5	0.3	0.3	0.3	0.3	0.2	0.3	+0.1
10th Grade	0.3	0.4	0.5	0.6	0.9	0.8	0.9	1.1	0.8	0.9	0.7	1.0	0.7	0.8	0.7	0.7	0.5	0.5	0.4	0.5	0.4	0.4	0.4	0.3	0.3	0.2	0.3	+0.1
12th Grade	0.7	0.6	0.7	0.8	1.0	1.0	0.9	1.0	1.1	1.0	1.1	1.2	0.9	1.0	1.0	0.9	0.9	0.8	0.6	0.7	0.5	0.6	0.6	0.7	0.6	0.5	0.6	+0.1
Cocaine other than Crack [h]																												
8th Grade	0.5	0.5	0.6	0.9	1.0	1.0	0.8	1.0	1.1	0.9	0.9	0.8	0.7	0.7	0.7	0.7	0.6	0.6	0.7	0.5	0.6	0.3	0.3	0.4	0.4	0.3	0.3	0.0
10th Grade	0.6	0.6	0.7	1.0	1.4	1.3	1.6	1.8	1.6	1.6	1.2	1.3	1.1	1.5	1.3	1.3	1.1	1.0	0.8	0.7	0.6	0.7	0.7	0.5	0.7	0.3	0.4	+0.1
12th Grade	1.2	1.0	1.2	1.3	1.3	1.6	2.0	2.0	2.5	1.7	1.8	1.9	1.8	2.2	2.0	2.4	1.7	1.7	1.1	1.1	1.0	1.0	0.9	0.9	1.1	0.6	1.1	+0.5 ss

(Table continued on next page.)

TABLE 7 (cont.)
Trends in 30-Day Prevalence of Use of Various Drugs in Grades 8, 10, and 12

	Percentage who used in last 30 days																										2016–2017 change
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	
Heroin [l,j]																												
8th Grade	0.3	0.4	0.4	0.6	0.6	0.7	0.6	0.6	0.6	0.5	0.6	0.5	0.4	0.5	0.5	0.3	0.4	0.4	0.4	0.4	0.4	0.2	0.3	0.3	0.1	0.2	0.2	0.0
10th Grade	0.2	0.2	0.3	0.4	0.6	0.5	0.6	0.7	0.7	0.5	0.3	0.5	0.3	0.5	0.5	0.5	0.4	0.4	0.4	0.4	0.4	0.4	0.3	0.4	0.2	0.2	0.1	-0.1
12th Grade	0.2	0.3	0.2	0.3	0.6	0.5	0.5	0.5	0.5	0.7	0.4	0.5	0.4	0.5	0.5	0.4	0.4	0.4	0.4	0.4	0.4	0.3	0.3	0.4	0.3	0.2	0.3	+0.1
With a Needle [j]																												
8th Grade	—	—	—	—	0.4	0.5	0.4	0.5	0.4	0.3	0.4	0.3	0.3	0.3	0.3	0.2	0.3	0.3	0.3	0.3	0.2	0.2	0.2	0.2	0.1	0.1	0.2	0.0
10th Grade	—	—	—	—	0.3	0.3	0.3	0.4	0.3	0.3	0.2	0.3	0.2	0.3	0.3	0.3	0.3	0.2	0.3	0.2	0.2	0.2	0.2	0.3	0.1	0.2	0.1	-0.1
12th Grade	—	—	—	—	0.3	0.4	0.3	0.2	0.2	0.2	0.2	0.3	0.3	0.2	0.3	0.3	0.2	0.2	0.1	0.4	0.4	0.3	0.2	0.3	0.2	0.2	0.2	0.0
Without a Needle [j]																												
8th Grade	—	—	—	—	0.3	0.4	0.4	0.3	0.4	0.3	0.4	0.3	0.3	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.2	0.1	0.1	0.1	0.2	0.0
10th Grade	—	—	—	—	0.3	0.3	0.4	0.5	0.5	0.4	0.2	0.4	0.2	0.3	0.3	0.3	0.2	0.3	0.2	0.3	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.0
12th Grade	—	—	—	—	0.6	0.4	0.6	0.4	0.4	0.7	0.3	0.5	0.4	0.3	0.5	0.3	0.4	0.2	0.3	0.4	0.4	0.2	0.2	0.4	0.3	0.1	0.2	0.0
Narcotics other than Heroin [k,l]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	1.1	1.2	1.3	1.5	1.8	2.0	2.3	2.4	2.6	2.9	3.0‡	4.0	4.1	4.3	3.9	3.8	3.8	3.8	4.1	3.6	3.6	3.0	2.8	2.2	2.1	1.7	1.6	-0.1
Amphetamines [k,m]																												
8th Grade	2.6	3.3	3.6	3.6	4.2	4.6	3.8	3.3	3.4	3.4	3.2	2.8	2.7	2.3	2.3	2.1	2.0	2.2	1.9	1.8	1.8	1.3‡	2.3	2.1	1.9	1.7	1.7	0.0
10th Grade	3.3	3.6	4.3	4.5	5.3	5.5	5.1	5.1	5.0	5.4	5.6	5.2	4.3	4.0	3.7	3.5	4.0	2.8	3.3	3.3	3.1	2.8‡	3.3	3.7	3.1	2.7	2.5	-0.2
12th Grade	3.2	2.8	3.7	4.0	4.0	4.1	4.8	4.6	4.5	5.0	5.6	5.5	5.0	4.6	3.9	3.7	3.7	2.9	3.0	3.3	3.7	3.3‡	4.2	3.8	3.2	3.0	2.6	-0.4
Methamphetamine [n,o]																												
8th Grade	—	—	—	—	—	—	—	—	1.1	0.8	1.3	1.1	1.2	0.6	0.7	0.6	0.6	0.7	0.5	0.7	0.4	0.5	0.4	0.2	0.3	0.3	0.2	-0.1
10th Grade	—	—	—	—	—	—	—	—	1.8	2.0	1.5	1.8	1.4	1.3	1.1	0.7	0.4	0.7	0.6	0.7	0.5	0.6	0.4	0.3	0.3	0.2	0.1	-0.1
12th Grade	—	—	—	—	—	—	—	—	1.7	1.9	1.5	1.7	1.7	1.4	0.9	0.9	0.6	0.6	0.5	0.5	0.6	0.5	0.4	0.5	0.4	0.3	0.3	+0.1

(Table continued on next page.)

TABLE 7 (cont.)
Trends in 30-Day Prevalence of Use of Various Drugs in Grades 8, 10, and 12

	Percentage who used in last 30 days																											2016–2017
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	change
Crystal Methamphetamine (Ice) [o]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	0.6	0.5	0.6	0.7	1.1	1.1	0.8	1.2	0.8	1.0	1.1	1.2	0.8	0.8	0.9	0.7	0.6	0.6	0.5	0.6	0.6	0.4	0.8	0.4	0.3	0.4	0.5	0.0
Sedatives (Barbiturates) [k,p]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	1.4	1.1	1.3	1.7	2.2	2.1	2.1	2.6	2.6	3.0	2.8	3.2	2.9‡	2.9	3.3	3.0	2.7	2.8	2.5	2.2	1.8	2.0	2.2	2.0	1.7	1.5	1.4	0.0
Tranquilizers [b,k]																												
8th Grade	0.8	0.8	0.9	1.1	1.2	1.5	1.2	1.2	1.1	1.4‡	1.2	1.2	1.4	1.2	1.3	1.3	1.1	1.2	1.2	1.2	1.0	0.8	0.9	0.8	0.8	0.8	0.7	0.0
10th Grade	1.2	1.5	1.1	1.5	1.7	1.7	2.2	2.2	2.2	2.5‡	2.9	2.9	2.4	2.3	2.3	2.4	2.6	1.9	2.0	2.2	1.9	1.7	1.6	1.6	1.7	1.5	1.5	0.0
12th Grade	1.4	1.0	1.2	1.4	1.8	2.0	1.8	2.4	2.5	2.6‡	2.9	3.3	2.8	3.1	2.9	2.7	2.6	2.6	2.7	2.5	2.3	2.1	2.0	2.1	2.0	1.9	2.0	+0.2
Any Prescription Drug [q]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	8.6	8.1	7.8	7.2	7.3	6.9	7.2	7.0‡	7.1	6.4	5.9	5.4	4.9	-0.5
Rohypnol [r]																												
8th Grade	—	—	—	—	—	0.5	0.3	0.4	0.3	0.3	0.4	0.2	0.1	0.2	0.2	0.4	0.3	0.1	0.2	0.2	0.6	0.1	0.1	0.2	0.1	0.2	0.1	-0.1
10th Grade	—	—	—	—	—	0.5	0.5	0.4	0.5	0.4	0.2	0.4	0.2	0.3	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.2	0.1	0.4	0.1	0.3	0.0	-0.3 s
12th Grade	—	—	—	—	—	0.5	0.3	0.3	0.3	0.4	0.3	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Alcohol [s]																												
Any Use																												
8th Grade	25.1	26.1‡	24.3	25.5	24.6	26.2	24.5	23.0	24.0	22.4	21.5	19.6	19.7	18.6	17.1	17.2	15.9	15.9	14.9	13.8	12.7	11.0	10.2	9.0	9.7	7.3	8.0	+0.7
10th Grade	42.8	39.9‡	38.2	39.2	38.8	40.4	40.1	38.8	40.0	41.0	39.0	35.4	35.4	35.2	33.2	33.8	33.4	28.8	30.4	28.9	27.2	27.6	25.7	23.5	21.5	19.9	19.7	-0.2
12th Grade	54.0	51.3‡	48.6	50.1	51.3	50.8	52.7	52.0	51.0	50.0	49.8	48.6	47.5	48.0	47.0	45.3	44.4	43.1	43.5	41.2	40.0	41.5	39.2	37.4	35.3	33.2	33.2	-0.1

(Table continued on next page.)

TABLE 7 (cont.)
Trends in 30-Day Prevalence of Use of Various Drugs in Grades 8, 10, and 12

	Percentage who used in last 30 days																										2016–2017
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	change
Been Drunk [o]																												
8th Grade	7.6	7.5	7.8	8.7	8.3	9.6	8.2	8.4	9.4	8.3	7.7	6.7	6.7	6.2	6.0	6.2	5.5	5.4	5.4	5.0	4.4	3.6	3.5	2.7	3.1	1.8	2.2	+0.5 s
10th Grade	20.5	18.1	19.8	20.3	20.8	21.3	22.4	21.1	22.5	23.5	21.9	18.3	18.2	18.5	17.6	18.8	18.1	14.4	15.5	14.7	13.7	14.5	12.8	11.2	10.3	9.0	8.9	-0.1
12th Grade	31.6	29.9	28.9	30.8	33.2	31.3	34.2	32.9	32.9	32.3	32.7	30.3	30.9	32.5	30.2	30.0	28.7	27.6	27.4	26.8	25.0	28.1	26.0	23.5	20.6	20.4	19.1	-1.3
Flavored Alcoholic Beverages [e,n]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	14.6	12.9	13.1	12.2	10.2	9.5	9.4	8.6	7.6	6.3	5.7	5.5	4.0	4.4	+0.4
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	25.1	23.1	24.7	21.8	20.2	19.0	19.4	15.8	16.3	15.5	14.0	12.8	11.0	12.9	+1.9
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	31.1	30.5	29.3	29.1	27.4	27.4	24.1	23.1	21.8	21.0	19.9	20.8	18.3	20.2	+1.9
Cigarettes																												
Any Use																												
8th Grade	14.3	15.5	16.7	18.6	19.1	21.0	19.4	19.1	17.5	14.6	12.2	10.7	10.2	9.2	9.3	8.7	7.1	6.8	6.5	7.1	6.1	4.9	4.5	4.0	3.6	2.6	1.9	-0.7 ss
10th Grade	20.8	21.5	24.7	25.4	27.9	30.4	29.8	27.6	25.7	23.9	21.3	17.7	16.7	16.0	14.9	14.5	14.0	12.3	13.1	13.6	11.8	10.8	9.1	7.2	6.3	4.9	5.0	+0.2
12th Grade	28.3	27.8	29.9	31.2	33.5	34.0	36.5	35.1	34.6	31.4	29.5	26.7	24.4	25.0	23.2	21.6	21.6	20.4	20.1	19.2	18.7	17.1	16.3	13.6	11.4	10.5	9.7	-0.8
Smokeless Tobacco [t]																												
8th Grade	6.9	7.0	6.6	7.7	7.1	7.1	5.5	4.8	4.5	4.2	4.0	3.3	4.1	4.1	3.3	3.7	3.2	3.5	3.7	4.1	3.5	2.8	2.8	3.0	3.2	2.5	1.7	-0.8 s
10th Grade	10.0	9.6	10.4	10.5	9.7	8.6	8.9	7.5	6.5	6.1	6.9	6.1	5.3	4.9	5.6	5.7	6.1	5.0	6.5	7.5	6.6	6.4	6.4	5.3	4.9	3.5	3.8	+0.3
12th Grade	—	11.4	10.7	11.1	12.2	9.8	9.7	8.8	8.4	7.6	7.8	6.5	6.7	6.7	7.6	6.1	6.6	6.5	8.4	8.5	8.3	7.9	8.1	8.4	6.1	6.6	4.9	-1.7 s
Large Cigars [bb]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1.9	2.4	1.5	1.5	0.0
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3.9	3.4	2.3	2.6	+0.4
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	6.4	7.0	6.5	5.6	-0.9
Flavored Little Cigars [bb]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4.1	4.1	2.8	2.6	-0.2
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	6.9	6.1	4.9	4.0	-1.0
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	11.9	11.4	9.5	10.1	+0.6

(Table continued on next page.)

TABLE 7 (cont.)
Trends in 30-Day Prevalence of Use of Various Drugs in Grades 8, 10, and 12

	Percentage who used in last 30 days																											2016–2017
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	change
Regular Little Cigars [bb]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2.5	3.3	1.9	1.6	-0.2
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4.4	3.8	3.0	3.0	0.0
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	7.0	7.8	6.1	6.6	+0.4
Any Vaping [bb]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	8.0	6.2‡	6.6	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	14.2	11.0‡	13.1	—
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	16.3	12.5‡	16.6	—
Vaping Nicotine [bb]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3.5	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	8.2	—
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	11.0	—
Vaping Marijuana [bb]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1.6	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4.3	—
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4.9	—
Vaping Just Flavoring [bb]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5.3	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	9.2	—
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	9.7	—
Tobacco Using a Hookah [bb]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2.8	2.5	-0.4
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4.0	3.0	-0.9 s
12th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	6.1	5.0	-1.1

(Table continued on next page.)

TABLE 7 (cont.)
Trends in 30-Day Prevalence of Use of Various Drugs in Grades 8, 10, and 12

	Percentage who used in last 30 days																										2016–2017
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	change
Steroids [k,u]																												
8th Grade	0.4	0.5	0.5	0.5	0.6	0.4	0.5	0.5	0.7	0.8	0.7	0.8	0.7	0.5	0.5	0.5	0.4	0.5	0.4	0.3	0.4	0.3	0.3	0.2	0.3	0.3	0.3	0.0
10th Grade	0.6	0.6	0.5	0.6	0.6	0.5	0.7	0.6	0.9	1.0	0.9	1.0	0.8	0.8	0.6	0.6	0.5	0.5	0.5	0.5	0.5	0.4	0.4	0.4	0.4	0.3	0.3	-0.1
12th Grade	0.8	0.6	0.7	0.9	0.7	0.7	1.0	1.1	0.9	0.8	1.3	1.4	1.3	1.6	0.9	1.1	1.0	1.0	1.0	1.1	0.7	0.9	1.0	0.9	1.0	0.7	0.8	+0.1
Previously surveyed drugs that have been dropped.																												
Nitrites [e]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	0.4	0.3	0.6	0.4	0.4	0.7	0.7	1.0	0.4	0.3	0.5	0.6	0.7	0.7	0.5	0.3	0.5	0.3	0.6	—	—	—	—	—	—	—	—	—
PCP [e]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	0.5	0.6	1.0	0.7	0.6	1.3	0.7	1.0	0.8	0.9	0.5	0.4	0.6	0.4	0.7	0.4	0.5	0.6	0.5	0.8	0.8	0.5	0.4	—	—	—	—	—
Methaqualone [e,k]																												
8th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10th Grade	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12th Grade	0.2	0.4	0.1	0.4	0.4	0.6	0.3	0.6	0.4	0.2	0.5	0.3	0.4	0.5	0.5	0.4	0.4	0.2	0.3	0.2	0.2	0.3	—	—	—	—	—	—

Source. The Monitoring the Future study, the University of Michigan.

Note: See footnotes following Table 8.

TABLE 8
Trends in 30-Day Prevalence of Daily Use of Various Drugs in Grades 8, 10, and 12

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
Marijuana/Hashish Daily [aa]																												
8th Grade	0.2	0.2	0.4	0.7	0.8	1.5	1.1	1.1	1.4	1.3	1.3	1.2	1.0	0.8	1.0	1.0	0.8	0.9	1.0	1.2	1.3	1.1	1.1	1.0	1.1	0.7	0.8	0.0
10th Grade	0.8	0.8	1.0	2.2	2.8	3.5	3.7	3.6	3.8	3.8	4.5	3.9	3.6	3.2	3.1	2.8	2.8	2.7	2.8	3.3	3.6	3.5	4.0	3.4	3.0	2.5	2.9	+0.4
12th Grade	2.0	1.9	2.4	3.6	4.6	4.9	5.8	5.6	6.0	6.0	5.8	6.0	6.0	5.6	5.0	5.0	5.1	5.4	5.2	6.1	6.6	6.5	6.5	5.8	6.0	6.0	5.9	-0.1
Alcohol [s,aa]																												
Any Daily Use																												
8th Grade	0.5	0.6‡	1.0	1.0	0.7	1.0	0.8	0.9	1.0	0.8	0.9	0.7	0.8	0.6	0.5	0.5	0.6	0.7	0.5	0.5	0.4	0.3	0.3	0.3	0.2	0.2	0.2	0.0
10th Grade	1.3	1.2‡	1.8	1.7	1.7	1.6	1.7	1.9	1.9	1.8	1.9	1.8	1.5	1.3	1.3	1.4	1.4	1.0	1.1	1.1	0.8	1.0	0.9	0.8	0.5	0.5	0.6	0.0
12th Grade	3.6	3.4‡	3.4	2.9	3.5	3.7	3.9	3.9	3.4	2.9	3.6	3.5	3.2	2.8	3.1	3.0	3.1	2.8	2.5	2.7	2.1	2.5	2.2	1.9	1.9	1.3	1.6	+0.2
Been Drunk Daily [o,aa]																												
8th Grade	0.1	0.1	0.2	0.3	0.2	0.2	0.2	0.3	0.4	0.3	0.2	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0
10th Grade	0.2	0.3	0.4	0.4	0.6	0.4	0.6	0.6	0.7	0.5	0.6	0.5	0.5	0.4	0.4	0.5	0.5	0.3	0.4	0.3	0.2	0.4	0.3	0.3	0.1	0.1	0.2	+0.1
12th Grade	0.9	0.8	0.9	1.2	1.3	1.6	2.0	1.5	1.9	1.7	1.4	1.2	1.6	1.8	1.5	1.6	1.3	1.4	1.1	1.6	1.3	1.5	1.3	1.1	0.8	0.8	1.1	+0.3
5+ Drinks in a Row in Last 2 Weeks																												
8th Grade	10.9	11.3	11.3	12.1	12.3	13.3	12.3	11.5	13.1	11.7	11.0	10.3	9.8	9.4	8.4	8.7	8.3	8.1	7.8	7.2	6.4	5.1	5.1	4.1	4.6	3.4	3.7	+0.3
10th Grade	21.0	19.1	21.0	21.9	22.0	22.8	23.1	22.4	23.5	24.1	22.8	20.3	20.0	19.9	19.0	19.9	19.6	16.0	17.5	16.3	14.7	15.6	13.7	12.6	10.9	9.7	9.8	+0.1
12th Grade	29.8	27.9	27.5	28.2	29.8	30.2	31.3	31.5	30.8	30.0	29.7	28.6	27.9	29.2	27.1	25.4	25.9	24.6	25.2	23.2	21.6	23.7	22.1	19.4	17.2	15.5	16.6	+1.1
Cigarettes																												
Any Daily Use																												
8th Grade	7.2	7.0	8.3	8.8	9.3	10.4	9.0	8.8	8.1	7.4	5.5	5.1	4.5	4.4	4.0	4.0	3.0	3.1	2.7	2.9	2.4	1.9	1.8	1.4	1.3	0.9	0.6	-0.3 s
10th Grade	12.6	12.3	14.2	14.6	16.3	18.3	18.0	15.8	15.9	14.0	12.2	10.1	8.9	8.3	7.5	7.6	7.2	5.9	6.3	6.6	5.5	5.0	4.4	3.2	3.0	1.9	2.2	+0.4
12th Grade	18.5	17.2	19.0	19.4	21.6	22.2	24.6	22.4	23.1	20.6	19.0	16.9	15.8	15.6	13.6	12.2	12.3	11.4	11.2	10.7	10.3	9.3	8.5	6.7	5.5	4.8	4.2	-0.5

(Table continued on next page.)

TABLE 8 (cont.)
Trends in 30-Day Prevalence of Daily Use of Various Drugs in Grades 8, 10, and 12

(Entries are percentages.)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
1/2 Pack+/Day																												
8th Grade	3.1	2.9	3.5	3.6	3.4	4.3	3.5	3.6	3.3	2.8	2.3	2.1	1.8	1.7	1.7	1.5	1.1	1.2	1.0	0.9	0.7	0.6	0.7	0.5	0.4	0.3	0.2	-0.1
10th Grade	6.5	6.0	7.0	7.6	8.3	9.4	8.6	7.9	7.6	6.2	5.5	4.4	4.1	3.3	3.1	3.3	2.7	2.0	2.4	2.4	1.9	1.5	1.5	1.2	1.0	0.6	0.7	0.0
12th Grade	10.7	10.0	10.9	11.2	12.4	13.0	14.3	12.6	13.2	11.3	10.3	9.1	8.4	8.0	6.9	5.9	5.7	5.4	5.0	4.7	4.3	4.0	3.4	2.6	2.1	1.8	1.7	-0.1
Smokeless Tobacco Daily [t]																												
8th Grade	1.6	1.8	1.5	1.9	1.2	1.5	1.0	1.0	0.9	0.9	1.2	0.8	0.8	1.0	0.7	0.7	0.8	0.8	0.8	0.9	0.8	0.5	0.5	0.5	0.8	0.6	0.4	-0.2
10th Grade	3.3	3.0	3.3	3.0	2.7	2.2	2.2	2.2	1.5	1.9	2.2	1.7	1.8	1.6	1.9	1.7	1.6	1.4	1.9	2.5	1.7	2.0	1.9	1.8	1.6	1.0	0.6	-0.4
12th Grade	—	4.3	3.3	3.9	3.6	3.3	4.4	3.2	2.9	3.2	2.8	2.0	2.2	2.8	2.5	2.2	2.8	2.7	2.9	3.1	3.1	3.2	3.0	3.4	2.9	2.7	2.0	-0.7

Source. The Monitoring the Future study, the University of Michigan.

Note. See footnotes following Table 5-5d.

Footnotes for Tables 5 through 8

Approximate Weighted *N*s	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
8th Graders	17,500	18,600	18,300	17,300	17,500	17,800	18,600	18,100	16,700	16,700	16,200	15,100	16,500	17,000
10th Graders	14,800	14,800	15,300	15,800	17,000	15,600	15,500	15,000	13,600	14,300	14,000	14,300	15,800	16,400
12th Graders	15,000	15,800	16,300	15,400	15,400	14,300	15,400	15,200	13,600	12,800	12,800	12,900	14,600	14,600

Approximate Weighted *N*s	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
8th Graders	16,800	16,500	16,100	15,700	15,000	15,300	16,000	15,100	14,600	14,600	14,400	16,900	15,300
10th Graders	16,200	16,200	16,100	15,100	15,900	15,200	14,900	15,000	12,900	13,000	15,600	14,700	13,500
12th Graders	14,700	14,200	14,500	14,000	13,700	14,400	14,100	13,700	12,600	12,400	12,900	11,800	12,600

Notes. Level of significance of difference between the two most recent classes: s = .05, ss = .01, sss = .001. ' — ' indicates data not available. ' ‡ ' indicates that the question changed in the following year. See relevant footnote for that drug. Any apparent inconsistency between the change estimate and the prevalence estimates for the two most recent years is due to rounding.

[a]For 12th graders only: Use of any illicit drug includes any use of marijuana, LSD, other hallucinogens, crack, cocaine other than crack, or heroin; or any use of narcotics other than heroin, amphetamines, sedatives (barbiturates), or tranquilizers not under a doctor's orders. For 8th and 10th graders only: The use of narcotics other than heroin and sedatives (barbiturates) has been excluded because these younger respondents appear to overreport use (perhaps because they include the use of nonprescription drugs in their answers). Due to changes in the amphetamines questions 2013 data for all grades for any illicit drug use, any illicit drug use other than marijuana and 8th and 10th grade any illicit drug use including inhalants are based on one half of the *N* indicated. 12th grade any illicit drug use including inhalants data are based on one form; *N* is one sixth of *N* indicated. 2014 data are based on all forms. See the amphetamine note for details.

[b]In 2001 the question text was changed on half of the questionnaire forms for each age group. Other psychedelics was changed to other hallucinogens and shrooms was added to the list of examples. For the tranquilizer list of examples, Miltown was replaced with Xanax. For 8th, 10th, and 12th graders: The 2001 data presented here are based on the changed forms only; *N* is one half of *N* indicated. In 2002 the remaining forms were changed to the new wording. The data are based on all forms beginning in 2002. Data for any illicit drug other than marijuana and data for hallucinogens are also affected by these changes and have been handled in a parallel manner. Hallucinogens, LSD, and hallucinogens other than LSD are based on five of six forms beginning in 2014; *N* is five sixths of *N* indicated.

[c]For 12th graders only: Data based on five of six forms in 1991–1998; *N* is five sixths of *N* indicated. Data based on three of six forms beginning in 1999; *N* is three sixths of *N* indicated. For 8th and 10th graders only, beginning in 2014 data based on two thirds of *N* indicated.

[d]Inhalants are unadjusted for underreporting of amyl and butyl nitrites.

[e]For 12th graders only: Data based on one of six forms; *N* is one sixth of *N* indicated. In 2011 for flavored alcoholic beverages Skyy Blue and Zima were dropped from the list of examples. An examination of the data did not show any effect from the wording change. In 2014 the PCP use questions were dropped; annual PCP use was moved to another form. In 2016 a question on use of tobacco using a hookah was added to two additional forms; *N* is three sixths of *N* indicated.

[f]Hallucinogens are unadjusted for underreporting of PCP.

[g]For 8th and 10th graders only: Data based on one of two forms in 1996; *N* is one half of *N* indicated. Data based on one third of *N* indicated in 1997–2001 due to changes in the questionnaire forms. Data based on two of four forms beginning in 2002; *N* is one half of *N* indicated. In 2014 a revised question on use of ecstasy (MDMA) including "Molly" was added to one form. The 2013 and 2014 "Original wording" data reported here are for only the questionnaires using the original question wording; *N* is one half of *N* indicated. Beginning in 2014 data

(Footnote continued on next page.)

Footnotes for Tables 5 through 8 (cont.)

reported here for the "Revised wording" are for only the questionnaires which include "Molly;" *N* is two sixths of *N* indicated in 2014 and five sixths of the *N* indicated in 2015. For 12th graders only: Data based on one of six forms in 1996–2001; *N* is one sixth of *N* indicated Data based on two of six forms beginning in 2002; *N* is two sixths of N indicated. In 2014 a revised question on use of ecxtasy (MDMA) including "Molly" was added to one form. The 2013 and 2014 "Original wording" data reported here are for only the questionnaires using the original question wording; *N* is two sixths of *N* indicated. Beginning in 2014 data reported for the "Revised wording" are for only the questionnaires which include "Molly."; *N* is one sixth of the *N* indicated in 2014 and three sixths of the *N* indicated in 2015.

[h]For 12th graders only: Data based on four of six forms; *N* is four sixths of *N* indicated.

[i]In 1995 the heroin question was changed in one of two forms for 8th and 10th graders and in three of six forms for 12th graders. Separate questions were asked for use with and without injection. In 1996, the heroin question was changed in the remaining 8th- and 10th-grade forms. Data presented here represent the combined data from all forms.

[j]For 8th and 10th graders only: Data based on one of two forms in 1995; *N* is one half of *N* indicated. Data based on all forms in 1996 through 2014. In 2015 the question was dropped from 1 form; *N* is four sixths of *N* indicated. For 12th graders only: Data based on three of six forms; *N* is three sixths of N indicated.

[k]Only drug use not under a doctor's orders is included here.

[l]In 2002 the question text was changed in half of the questionnaire forms. The list of examples of narcotics other than heroin was updated: Talwin, laudanum, and paregoric—all of which had negligible rates of use by 2001—were replaced with Vicodin, OxyContin, and Percocet. The 2002 data presented here are based on the changed forms only; *N* is one half of *N* indicated. In 2003, the remaining forms were changed to the new wording. The data are based on all forms beginning in 2003. In 2013 the list of examples was changed on one form: MS Contin, Roxycodone, Hydrocodone (Lortab, Lorcet, Norco), Suboxone, Tylox, and Tramadol were added to the list. An examination of the data did not show any effect from the wording change.

[m]For 8th, 10th, and 12th graders: In 2009, the question text was changed slightly in half of the forms. An examination of the data did not show any effect from the wording change. In 2010 the remaining forms were changed in a like manner. In 2011 the question text was changed slightly in one form; bennies, Benzedrine and Methadrine were dropped from the list of examples. An examination of the data did not show any effect from the wording change. In 2013 the question wording was changed slightly in two of the 8th and 10th grade questionnaires and in three of the 12th grade questionnaires. The new wording in 2013 asked "On how many occasions (if any) have taken amphetamines or other prescription stimulant drugs…" In contrast, the old wording did not include the text highlighted in red. Results in 2013 indicated higher prevalence in questionnaires with the new wording as compared to the old wording; it was proportionally 61% higher in 8th grade, 34% higher in 10th grade, and 21% higher in 12th grade. 2013 data are based on the changed forms only; for 8th, 10th, and 12th graders N is one half of N indicated. Beginning in 2014 all questionnaires included the new, updated wording.

[n]For 8th and 10th graders only: Data based on one of four forms; *N* is one third of *N* indicated. See text for detailed explanation. In 2011 for flavored alcoholic beverages: Skyy Blue and Zima were dropped from the list of examples. An examination of the data did not show any effect from the wording change. Annual synthetic marijuana use questions asked of one third of *N* indicated.

[o]For 12th graders only: Data based on two of six forms; N is two sixths of N indicated. Bidis and kreteks based on one of six forms beginning in 2009; *N* is one sixth *N* indicated.

[p]For 12th graders only: In 2004 the barbiturate question text was changed on half of the questionnaire forms. Barbiturates was changed to sedatives including barbiturates, and "have you taken barbiturates . . . " was changed to "have you taken sedatives . . . " In the list of examples downs, downers, goofballs, yellow, reds, blues, rainbows were changed to downs, or downers, and include Phenobarbital, Tuinal, Nembutal, and Seconal. An examination of the data did not show any effect from the wording change. In 2005 the remaining forms were changed in a like manner. In 2013 the question text was changed in all forms: Tuinal, Nembutal, and Seconal were replaced with Ambien, Lunesta, and Sonata. In one form the list of examples was also changed: Tuinal was dropped from the list and Dalmane, Restoril, Halcion, Intermezzo, and Zolpimist were added. An examination of the data did not show any effect from the wording change.

(Footnote continued on next page.)

Footnotes for Tables 5 through 8 (cont.)

[q]The use of any prescription drug includes use of any of the following: amphetamines, sedatives (barbiturates), narcotics other than heroin, or tranquilizers "…without a doctor telling you to use them."

[r]For 8th and 10th graders only: Data based on one of two forms in 1996; *N* is one half of *N* indicated. Data based on three of four forms in 1997–1998; *N* is two thirds of *N* indicated. Data based on two of four forms in 1999–2001; *N* is one third of *N* indicated. Data based on one of four forms beginning in 2002; *N* is one sixth of *N* indicated. See text for detailed explanation. For 12th graders only: Data based on one of six forms in 1996–2001; *N* is one sixth of *N* indicated. Data based on two of six forms in 2002–2009; *N* is two sixths of *N* indicated. Data for 2001 and 2002 are not comparable due to changes in the questionnaire forms. Data based on one of six forms beginning in 2010; N is one sixth of N indicated.

[s]For 8th, 10th, and 12th graders: In 1993, the question text was changed slightly in half of the forms to indicate that a drink meant more than just a few sips. The 1993 data are based on the changed forms only; *N* is one half of *N* indicated for these groups. In 1994 the remaining forms were changed to the new wording. The data are based on all forms beginning in 1994. In 2004, the question text was changed slightly in half of the forms. An examination of the data did not show any effect from the wording change. The remaining forms were changed in 2005.

[t]For 8th and 10th graders only: Data based on one of two forms for 1991–1996 and on two of four forms beginning in 1997; *N* is one half of *N* indicated. For 12th graders only: Data based on one of six forms; *N* is one sixth of *N* indicated. For all grades in 2011: snus and dissolvable tobacco were added to the list of examples. An examination of the data did not show any effect from the wording change.

[u]For 8th and 10th graders only: In 2006, the question text was changed slightly in half of the questionnaire forms. An examination of the data did not show any effect from the wording change. In 2007 the remaining forms were changed in a like manner. In 2008 the question text was changed slightly in half of the questionnaire forms. An examination of the data did not show any effect from the wording change. In 2009 the remaining forms were changed in a like manner. For 12th graders only: Data based on two of six forms in 1991–2005; N is two sixths of *N* indicated. Data based on three of six forms beginning in 2006; *N* is three sixths of *N* indicated. In 2006 a slightly altered version of the question was added to a third form. An examination of the data did not show any effect from the wording change. In 2007 the remaining forms were changed in a like manner. In 2008 the question text was changed slightly in two of the questionnaire forms. An examination of the data did not show any effect from the wording change. In 2009 the remaining form was changed in a like manner.

[v]For 12th graders only: Data based on two of six forms in 2002–2005; *N* is two sixths of *N* indicated. Data based on three of six forms beginning in 2006; *N* is three sixths of *N* indicated.

[w]For 12th graders only: Data based on two of six forms in 2000; *N* is two sixths of *N* indicated. Data based on three of six forms in 2001; *N* is three sixths of *N* indicated. Data based on one of six forms beginning in 2002; *N* is one sixth of *N* indicated.

[x]For 12th graders only: Data based on two of six forms in 2000; *N* is two sixths of *N* indicated. Data based on three of six forms in 2001–2009; *N* is three sixths of *N* indicated. Data based on two of six forms beginning in 2010; *N* is two sixths of *N* indicated.

[y]The 2003 flavored alcoholic beverage data were created by adjusting the 2004 data to reflect the change in the 2003 and 2004 alcopops data.

[z]For 8th and 10th graders only: Data based on one of four forms; *N* is one third of *N* indicated. See text for detailed explanation. For 12th graders only: Data based on two of six forms; *N* is two sixths of *N* indicated. For all grades: In 2011 the question text was "…had an alcoholic beverage containing caffeine (like Four Loko or Joose)." In 2012 the question text was changed to "…had an alcoholic beverage mixed with an energy drink (like Red Bull)." An examination of the data did not show any effect from the wording changes.

[aa]Daily use is defined as use on 20 or more occasions in the past 30 days except for cigarettes and smokeless tobacco, for which actual daily use is measured, and for 5+ drinks, for which the prevalence of having five or more drinks in a row in the last two weeks is measured.

[bb]8th and 10th grade data based on one third of *N* indicated. 12th grade data based on two of six forms; *N* is two sixths of *N* indicated.

[cc]In 2017, the surveys switched from asking about vaping in general to asking separately about vaping nicotine, marijuana, and just flavoring. Beginning in 2017, data presented for any vaping are based on these new questions.

TABLE 9
Trends in Two Week Prevalence of Extreme Binge Drinking in Grade 12

	Percentage who used in last two weeks														
	1975-2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
Approximate weighted N =	—	*14,700*	*14,200*	*14,500*	*14,000*	*13,700*	*14,400*	*14,100*	*13,700*	*12,600*	*12,400*	*12,900*	*11,800*	*12,600*	
5+ drinks in a row in last 2 weeks	—	27.1	25.4	25.9	24.6	25.2	23.2	21.6	23.7	22.1	19.4	17.2	15.5	16.6	+1.1
10+ drinks in a row in last 2 weeks	—	10.6	12.9	11.1	10.4	10.6	9.9	9.8	10.4	8.1	7.1	6.1	4.4	6.0	+1.6
15+ drinks in a row in last 2 weeks	—	5.7	7.2	5.6	5.6	6.0	6.3	4.6	5.5	4.4	4.1	3.5	2.3	3.1	+0.8

Source. The Monitoring the Future study, the University of Michigan.

Notes. 5+ drinks in a row data are based on all forms. 10+ and 15+ drinks in a row are based on one of six forms; *N* is one sixth of *N* indicated.

TABLE 10
Trends in Harmfulness of Drugs as Perceived by 8th Graders

How much do you think people risk harming themselves (physically or in other ways), if they . . .	Percentage saying great risk [a]														
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Try marijuana once or twice [b]	40.4	39.1	36.2	31.6	28.9	27.9	25.3	28.1	28.0	29.0	27.7	28.2	30.2	31.9	31.4
Smoke marijuana occasionally [b]	57.9	56.3	53.8	48.6	45.9	44.3	43.1	45.0	45.7	47.4	46.3	46.0	48.6	50.5	48.9
Smoke marijuana regularly [b]	83.8	82.0	79.6	74.3	73.0	70.9	72.7	73.0	73.3	74.8	72.2	71.7	74.2	76.2	73.9
Try synthetic marijuana once or twice [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take synthetic marijuana occasionally [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try inhalants once or twice [d]	35.9	37.0	36.5	37.9	36.4	40.8	40.1	38.9	40.8	41.2	45.6	42.8	40.3	38.7	37.5
Take inhalants regularly [d]	65.6	64.4	64.6	65.5	64.8	68.2	68.7	67.2	68.8	69.9	71.6	69.9	67.4	66.4	64.1
Take LSD once or twice [e]	—	—	42.1	38.3	36.7	36.5	37.0	34.9	34.1	34.0	31.6	29.6	27.9	26.8	25.8
Take LSD regularly [e]	—	—	68.3	65.8	64.4	63.6	64.1	59.6	58.8	57.5	52.9	49.3	48.2	45.2	44.0
Try ecstasy (MDMA) once or twice [f]	—	—	—	—	—	—	—	—	—	—	35.8	38.9	41.9	42.5	40.0
Take ecstasy (MDMA) occasionally [f]	—	—	—	—	—	—	—	—	—	—	55.5	61.8	65.8	65.1	60.8
Try salvia once or twice [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take salvia occasionally [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try crack once or twice [d]	62.8	61.2	57.2	54.4	50.8	51.0	49.9	49.3	48.7	48.5	48.6	47.4	48.7	49.0	49.6
Take crack occasionally [d]	82.2	79.6	76.8	74.4	72.1	71.6	71.2	70.6	70.6	70.1	70.0	69.7	70.3	70.4	69.4
Try cocaine powder once or twice [d]	55.5	54.1	50.7	48.4	44.9	45.2	45.0	44.0	43.3	43.3	43.9	43.2	43.7	44.4	44.2
Take cocaine powder occasionally [d]	77.0	74.3	71.8	69.1	66.4	65.7	65.8	65.2	65.4	65.5	65.8	64.9	65.8	66.0	65.3
Try heroin once or twice without using a needle [e]	—	—	—	—	60.1	61.3	63.0	62.8	63.0	62.0	61.1	62.6	62.7	61.6	61.4
Take heroin occasionally without using a needle [e]	—	—	—	—	76.8	76.6	79.2	79.0	78.9	78.6	78.5	78.5	77.8	77.5	76.8
Try OxyContin once or twice [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take OxyContin occasionally [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try Vicodin once or twice [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take Vicodin occasionally [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try Adderall once or twice [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take Adderall occasionally [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try bath salts (synthetic stimulants) once or twice [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take bath salts (synthetic stimulants) occasionally [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try cough/cold medicine once or twice [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take cough/cold medicine occasionally [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try one or two drinks of an alcoholic beverage (beer, wine, liquor) [b]	11.0	12.1	12.4	11.6	11.6	11.8	10.4	12.1	11.6	11.9	12.2	12.5	12.6	13.7	13.9
Take one or two drinks nearly every day [b]	31.8	32.4	32.6	29.9	30.5	28.6	29.1	30.3	29.7	30.4	30.0	29.6	29.9	31.0	31.4
Have five or more drinks once or twice each weekend [b]	59.1	58.0	57.7	54.7	54.1	51.8	55.6	56.0	55.3	55.9	56.1	56.4	56.5	56.9	57.2
Smoke one to five cigarettes per day [c]	—	—	—	—	—	—	—	—	26.9	28.9	30.5	32.8	33.4	37.0	37.5
Smoke one or more packs of cigarettes per day [g]	51.6	50.8	52.7	50.8	49.8	50.4	52.6	54.3	54.8	58.8	57.1	57.5	57.7	62.4	61.5
Use electronic cigarettes (e-cigarettes) regularly [h]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vape an e-liquid with nicotine ocasionally [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vape an e-liquid with nicotine regularly [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Smoke little cigars or cigarillos regularly [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Use smokeless tobacco regularly	35.1	35.1	36.9	35.5	33.5	34.0	35.2	36.5	37.1	39.0	38.2	39.4	39.7	41.3	40.8
Take dissolvable tobacco regularly [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take snus regularly [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take steroids [i]	64.2	69.5	70.2	67.6	—	—	—	—	—	—	—	—	—	—	—
Approximate weighted N =	*17,400*	*18,700*	*18,400*	*17,400*	*17,500*	*17,900*	*18,800*	*18,100*	*16,700*	*16,700*	*16,200*	*15,100*	*16,500*	*17,000*	*16,800*

Table continued on next page.

TABLE 10 (cont.)
Trends in Harmfulness of Drugs as Perceived by 8th Graders

How much do you think people risk harming themselves (physically or in other ways), if they . . .	Percentage saying great risk [a]												2016–2017 change
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	
Try marijuana once or twice [b]	32.2	32.8	31.1	29.5	29.5	28.2	26.0	24.1	23.0	23.0	22.8	22.0	-0.7
Smoke marijuana occasionally [b]	48.9	50.2	48.1	44.8	44.1	43.4	41.7	37.2	36.7	36.8	36.8	34.0	-2.8 ss
Smoke marijuana regularly [b]	73.2	74.3	72.0	69.8	68.0	68.3	66.9	61.0	58.9	58.0	57.5	54.8	-2.7 s
Try synthetic marijuana once or twice [c]	—	—	—	—	—	—	24.4	24.2	23.9	26.0	27.5	23.0	-4.4 sss
Take synthetic marijuana occasionally [c]	—	—	—	—	—	—	36.8	36.2	32.4	33.5	35.4	30.4	-5.0 sss
Try inhalants once or twice [d]	35.8	35.9	33.9	34.1	35.5	34.7	34.2	33.7	34.5	33.7	32.0	31.5	-0.5
Take inhalants regularly [d]	62.1	61.9	59.2	58.1	60.6	59.0	59.0	56.7	55.3	54.1	52.1	50.0	-2.1
Take LSD once or twice [e]	23.8	22.8	21.9	21.4	23.6	21.7	19.9	19.6	20.0	22.2	22.6	23.1	+0.5
Take LSD regularly [e]	40.0	38.5	36.9	37.0	38.6	37.8	35.0	34.5	33.7	37.0	36.8	37.9	+1.1
Try ecstasy (MDMA) once or twice [f]	32.8	30.4	28.6	26.0	27.0	25.4	23.6	24.1‡	46.1	45.5	42.5	43.3	+0.7
Take ecstasy (MDMA) occasionally [f]	52.0	48.6	46.8	43.9	45.0	43.7	41.0	42.1‡	59.7	58.5	54.0	54.6	+0.7
Try salvia once or twice [c]	—	—	—	—	—	—	9.5	8.5	—	—	—	—	—
Take salvia occasionally [c]	—	—	—	—	—	—	16.1	14.6	—	—	—	—	—
Try crack once or twice [d]	47.6	47.3	47.1	46.6	49.6	48.1	47.0	47.1	48.3	49.6	48.9	49.3	+0.4
Take crack occasionally [d]	68.7	68.3	67.9	66.6	68.4	67.7	67.8	66.5	65.5	65.7	65.7	66.9	+1.1
Try cocaine powder once or twice [d]	43.5	43.5	42.7	42.3	45.7	43.3	42.8	43.5	43.9	44.3	44.3	44.5	+0.3
Take cocaine powder occasionally [d]	64.0	64.2	62.7	62.3	64.2	63.5	63.3	62.7	61.8	61.6	62.4	62.7	+0.3
Try heroin once or twice without using a needle [e]	60.4	60.3	60.8	60.0	62.3	61.7	59.1	59.8	60.9	61.4	59.2	62.9	+3.7 ss
Take heroin occasionally without using a needle [e]	75.3	76.4	75.5	74.0	76.7	75.9	75.1	73.4	73.2	72.7	70.3	74.7	+4.4 sss
Try OxyContin once or twice [c]	—	—	—	—	—	—	21.9	19.9	22.1	20.2	21.3	21.0	-0.3
Take OxyContin occasionally [c]	—	—	—	—	—	—	35.3	32.6	34.4	32.5	33.5	32.6	-0.9
Try Vicodin once or twice [c]	—	—	—	—	—	—	17.5	15.0	18.4	16.9	18.3	17.1	-1.2
Take Vicodin occasionally [c]	—	—	—	—	—	—	29.4	26.2	28.2	26.7	28.8	26.7	-2.1
Try Adderall once or twice [c]	—	—	—	—	—	—	17.6	16.5	20.7	19.2	21.4	20.4	-1.0
Take Adderall occasionally [c]	—	—	—	—	—	—	29.9	28.3	32.5	32.0	35.9	33.8	-2.1
Try bath salts (synthetic stimulants) once or twice [c]	—	—	—	—	—	—	24.9	39.3	36.8	33.9	31.8	32.0	+0.1
Take bath salts (synthetic stimulants) occasionally [c]	—	—	—	—	—	—	38.8	51.9	49.1	45.5	42.5	43.1	+0.6
Try cough/cold medicine once or twice [c]	—	—	—	—	—	—	21.2	20.1	22.9	20.9	23.5	21.2	-2.3 s
Take cough/cold medicine occasionally [c]	—	—	—	—	—	—	38.8	37.3	37.9	37.3	38.6	35.2	-3.4 s
Try one or two drinks of an alcoholic beverage (beer, wine, liquor) [b]	14.2	14.9	13.5	14.4	14.9	14.5	13.9	13.7	14.8	15.3	14.7	14.2	-0.5
Take one or two drinks nearly every day [b]	31.3	32.6	31.5	31.5	32.3	31.8	31.4	30.6	31.0	30.9	30.7	30.0	-0.7
Have five or more drinks once or twice each weekend [b]	56.4	57.9	57.0	55.8	57.2	58.4	58.2	55.7	54.3	53.9	53.4	53.7	+0.3
Smoke one to five cigarettes per day [c]	37.0	38.6	38.6	38.6	38.2	37.4	40.4	42.8	41.9	41.7	43.2	41.9	-1.3
Smoke one or more packs of cigarettes per day [g]	59.4	61.1	59.8	59.1	60.9	62.5	62.6	62.4	62.1	63.0	61.2	62.1	+0.9
Use electronic cigarettes (e-cigarettes) regularly [h]	—	—	—	—	—	—	—	—	14.5	18.5	21.3	20.3	-1.0
Vape an e-liquid with nicotine ocasionally [c]	—	—	—	—	—	—	—	—	—	—	—	21.4	—
Vape an e-liquid with nicotine regularly [c]	—	—	—	—	—	—	—	—	—	—	—	38.2	—
Smoke little cigars or cigarillos regularly [c]	—	—	—	—	—	—	—	—	28.8	31.0	32.5	30.8	-1.7
Use smokeless tobacco regularly	39.5	41.8	41.0	40.8	41.8	40.8	37.8	36.2	34.5	36.6	35.1	34.8	-0.3
Take dissolvable tobacco regularly [c]	—	—	—	—	—	—	34.8	32.2	33.5	33.0	34.3	31.9	-2.4
Take snus regularly [c]	—	—	—	—	—	—	42.2	38.9	38.3	37.7	37.9	36.4	-1.5
Take steroids [i]	—	—	—	—	—	—	—	—	—	—	—	—	—
Approximate weighted N =	*16,500*	*16,100*	*15,700*	*15,000*	*15,300*	*16,000*	*15,100*	*14,600*	*14,600*	*14,400*	*16,900*	*15,300*	

Table continued on next page.

TABLE 10 (cont.)
Trends in Harmfulness of Drugs as Perceived by 8th Graders

Source. The Monitoring the Future study, the University of Michigan.
Notes. Level of significance of difference between the two most recent classes: s = .05, ss = .01, sss = .001. ' — ' indicates data not available. Any apparent inconsistency between the change estimate and the prevalence estimates for the two most recent years is due to rounding. "‡' indicates that the question changed the following year.
[a]Answer alternatives were: (1) No risk, (2) Slight risk, (3) Moderate risk, (4) Great risk, and (5) Can't say, drug unfamiliar.
[b]Beginning in 2012 data based on two thirds of *N* indicated.
[c]Data based on one third of *N* indicated.
[d]Beginning in 1997, data based on two thirds of *N* indicated due to changes in questionnaire forms.
[e]Data based on one of two forms in 1993–1996; *N* is one half of *N* indicated. Beginning in 1997, data based on one third of *N* indicated due to changes in questionnaire forms.
[f] Beginning in 2014 data are based on the revised question which included "Molly," *N* is one third of *N* indicated in 2014 and two thirds of *N* indicated in 2015. 2014 and 2015 data are not comparable to earlier years due to the revision of the question text.
[g]Beginning in 1999, data based on two thirds of *N* indicated due to changes in questionnaire forms.
[h]E-cigarette data based on two thirds of *N* indicated. Little cigars or cigarillos data based on one third *N* indicated.
[i] Data based on two forms in 1991 and 1992. Data based on one of two forms in 1993 and 1994; *N* is one half of *N* indicated.

TABLE 11
Trends in Harmfulness of Drugs as Perceived by 10th Graders

How much do you think people risk harming themselves (physically or in other ways), if they . . .	Percentage saying great risk [a]														
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Try marijuana once or twice [b]	30.0	31.9	29.7	24.4	21.5	20.0	18.8	19.6	19.2	18.5	17.9	19.9	21.1	22.0	22.3
Smoke marijuana occasionally [b]	48.6	48.9	46.1	38.9	35.4	32.8	31.9	32.5	33.5	32.4	31.2	32.0	34.9	36.2	36.6
Smoke marijuana regularly [b]	82.1	81.1	78.5	71.3	67.9	65.9	65.9	65.8	65.9	64.7	62.8	60.8	63.9	65.6	65.5
Try synthetic marijuana once or twice [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take synthetic marijuana occasionally [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try inhalants once or twice [d]	37.8	38.7	40.9	42.7	41.6	47.2	47.5	45.8	48.2	46.6	49.9	48.7	47.7	46.7	45.7
Take inhalants regularly [d]	69.8	67.9	69.6	71.5	71.8	75.8	74.5	73.3	76.3	75.0	76.4	73.4	72.2	73.0	71.2
Take LSD once or twice [e]	—	—	48.7	46.5	44.7	45.1	44.5	43.5	45.0	43.0	41.3	40.1	40.8	40.6	40.3
Take LSD regularly [e]	—	—	78.9	75.9	75.5	75.3	73.8	72.3	73.9	72.0	68.8	64.9	63.0	63.1	60.8
Try ecstasy (MDMA) once or twice [f]	—	—	—	—	—	—	—	—	—	—	39.4	43.5	49.7	52.0	51.4
Take ecstasy (MDMA) occasionally [f]	—	—	—	—	—	—	—	—	—	—	64.8	67.3	71.7	74.6	72.8
Try salvia once or twice [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take salvia occasionally [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try crack once or twice [d]	70.4	69.6	66.6	64.7	60.9	60.9	59.2	58.0	57.8	56.1	57.1	57.4	57.6	56.7	57.0
Take crack occasionally [d]	87.4	86.4	84.4	83.1	81.2	80.3	78.7	77.5	79.1	76.9	77.3	75.7	76.4	76.7	76.9
Try cocaine powder once or twice [d]	59.1	59.2	57.5	56.4	53.5	53.6	52.2	50.9	51.6	48.8	50.6	51.3	51.8	50.7	51.3
Take cocaine powder occasionally [d]	82.2	80.1	79.1	77.8	75.6	75.0	73.9	71.8	73.6	70.9	72.3	71.0	71.4	72.2	72.4
Try heroin once or twice without using a needle [e]	—	—	—	—	70.7	72.1	73.1	71.7	73.7	71.7	72.0	72.2	70.6	72.0	72.4
Take heroin occasionally without using a needle [e]	—	—	—	—	85.1	85.8	86.5	84.9	86.5	85.2	85.4	83.4	83.5	85.4	85.2
Try OxyContin once or twice [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take OxyContin occasionally [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try Vicodin once or twice [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take Vicodin occasionally [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try Adderall once or twice [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take Adderall occasionally [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try bath salts (synthetic stimulants) once or twice [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take bath salts (synthetic stimulants) occasionally [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try cough/cold medicine once or twice [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take cough/cold medicine occasionally [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try one or two drinks of an alcoholic beverage (beer, wine, liquor) [b]	9.0	10.1	10.9	9.4	9.3	8.9	9.0	10.1	10.5	9.6	9.8	11.5	11.5	10.8	11.5
Take one or two drinks nearly every day [b]	36.1	36.8	35.9	32.5	31.7	31.2	31.8	31.9	32.9	32.3	31.5	31.0	30.9	31.3	32.6
Have five or more drinks once or twice each weekend [u]	54.7	55.9	54.9	52.9	52.0	50.9	51.8	52.5	51.9	51.0	50.7	51.7	51.6	51.7	53.3
Smoke one to five cigarettes per day [c]	—	—	—	—	—	—	—	—	28.4	30.2	32.4	35.1	38.1	39.7	41.0
Smoke one or more packs of cigarettes per day [g]	60.3	59.3	60.7	59.0	57.0	57.9	59.9	61.9	62.7	65.9	64.7	64.3	65.7	68.4	68.1
Use electronic cigarettes (e-cigarettes) regularly [h]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vape an e-liquid with nicotine ocasionally [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vape an e-liquid with nicotine regularly [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Smoke little cigars or cigarillos regularly [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Use smokeless tobacco regularly	40.3	39.6	44.2	42.2	38.2	41.0	42.2	42.8	44.2	46.7	46.2	46.9	48.0	47.8	46.1
Take dissolvable tobacco regularly [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take snus regularly [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take steroids [i]	67.1	72.7	73.4	72.5	—	—	—	—	—	—	—	—	—	—	—
Approximate weighted N =	*14,700*	*14,800*	*15,300*	*15,900*	*17,000*	*15,700*	*15,600*	*15,000*	*13,600*	*14,300*	*14,000*	*14,300*	*15,800*	*16,400*	*16,200*

Table continued on next page.

TABLE 11 (cont.)
Trends in Harmfulness of Drugs as Perceived by 10th Graders

How much do you think people risk harming themselves (physically or in other ways), if they . . .	Percentage saying great risk [a]												2016–2017 change
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	
Try marijuana once or twice [b]	22.2	22.2	23.1	20.5	19.9	19.3	17.2	15.7	15.2	15.8	16.4	14.8	-1.6
Smoke marijuana occasionally [b]	35.6	36.0	37.0	32.9	30.9	30.1	26.8	25.1	23.9	24.7	24.4	21.9	-2.5 s
Smoke marijuana regularly [b]	64.9	64.5	64.8	59.5	57.2	55.2	50.9	46.5	45.4	43.2	44.0	40.6	-3.4 ss
Try synthetic marijuana once or twice [c]	—	—	—	—	—	—	24.6	24.1	25.0	26.3	26.8	25.1	-1.7
Take synthetic marijuana occasionally [c]	—	—	—	—	—	—	34.9	32.8	30.7	31.7	31.8	29.2	-2.5
Try inhalants once or twice [d]	43.9	43.0	41.2	42.0	42.5	42.4	42.4	43.0	43.1	43.1	40.7	37.9	-2.8 ss
Take inhalants regularly [d]	70.2	68.6	66.8	66.8	67.1	66.2	66.1	65.9	64.7	63.1	59.7	57.7	-2.1
Take LSD once or twice [e]	38.8	35.4	34.6	34.9	33.9	34.2	34.7	34.7	34.5	36.4	34.4	31.6	-2.8 s
Take LSD regularly [e]	60.7	56.8	55.7	56.7	56.1	54.9	56.4	55.9	54.8	58.3	55.2	53.0	-2.2
Try ecstasy (MDMA) once or twice [f]	48.4	45.3	43.2	38.9	36.3	37.2	36.2	36.0‡	53.2	54.8	54.2	55.4	+1.2
Take ecstasy (MDMA) occasionally [f]	71.3	68.2	66.4	62.1	59.2	60.8	59.8	58.6‡	69.0	70.1	69.3	68.6	-0.7
Try salvia once or twice [c]	—	—	—	—	—	—	12.2	10.7	—	—	—	—	—
Take salvia occasionally [c]	—	—	—	—	—	—	20.3	17.1	—	—	—	—	—
Try crack once or twice [d]	56.6	56.4	56.5	57.7	58.1	59.5	59.0	60.2	61.4	62.5	61.3	60.7	-0.7
Take crack occasionally [d]	76.2	76.0	76.5	75.9	76.2	76.5	76.7	77.8	76.4	77.5	75.2	75.1	-0.1
Try cocaine powder once or twice [d]	50.2	49.5	49.8	50.8	52.9	53.0	53.4	54.5	54.1	54.8	54.6	52.5	-2.1 s
Take cocaine powder occasionally [d]	71.3	70.9	71.1	71.0	72.2	72.0	72.6	72.8	71.7	72.6	70.9	70.4	-0.5
Try heroin once or twice without using a needle [e]	70.0	70.5	70.8	72.2	73.0	72.9	72.6	73.2	72.6	74.1	73.3	72.2	-1.0
Take heroin occasionally without using a needle [e]	83.6	84.2	83.1	83.3	84.8	83.4	84.4	84.0	82.5	83.3	82.2	81.4	-0.8
Try OxyContin once or twice [c]	—	—	—	—	—	—	30.9	29.4	29.7	29.9	28.7	27.8	-1.0
Take OxyContin occasionally [c]	—	—	—	—	—	—	48.3	44.7	44.4	43.7	41.4	41.3	-0.1
Try Vicodin once or twice [c]	—	—	—	—	—	—	23.2	21.0	22.5	24.1	21.8	22.1	+0.3
Take Vicodin occasionally [c]	—	—	—	—	—	—	40.3	36.0	36.4	35.4	32.6	32.0	-0.6
Try Adderall once or twice [c]	—	—	—	—	—	—	19.7	17.6	22.2	22.9	22.5	21.6	-0.9
Take Adderall occasionally [c]	—	—	—	—	—	—	34.3	30.5	37.0	37.0	35.8	36.4	+0.6
Try bath salts (synthetic stimulants) once or twice [c]	—	—	—	—	—	—	32.3	50.1	49.6	49.1	42.7	42.5	-0.2
Take bath salts (synthetic stimulants) occasionally [c]	—	—	—	—	—	—	44.9	61.8	61.1	60.4	53.0	51.5	-1.5
Try cough/cold medicine once or twice [c]	—	—	—	—	—	—	23.6	21.6	22.9	24.0	24.0	21.8	-2.3 s
Take cough/cold medicine occasionally [c]	—	—	—	—	—	—	40.4	37.3	38.3	38.2	37.6	36.4	-1.2
Try one or two drinks of an alcoholic beverage (beer, wine, liquor) [b]	11.1	11.6	12.6	11.9	11.9	12.3	11.3	11.3	11.6	12.4	13.3	12.5	-0.8
Take one or two drinks nearly every day [b]	31.7	33.3	35.0	33.8	33.1	32.9	31.8	30.6	31.3	31.2	32.2	30.9	-1.4
Have five or more drinks once or twice each weekend [b]	52.4	54.1	56.6	54.2	54.6	55.5	52.8	52.3	54.0	54.5	54.5	52.0	-2.5 s
Smoke one to five cigarettes per day [c]	41.3	41.7	43.5	42.8	41.4	44.8	49.1	47.7	52.0	52.9	53.0	50.0	-3.0 s
Smoke one or more packs of cigarettes per day [g]	67.7	68.2	69.1	67.3	67.2	69.8	71.6	70.8	72.0	72.9	71.5	69.8	-1.7
Use electronic cigarettes (e-cigarettes) regularly [h]	—	—	—	—	—	—	—	—	14.1	17.0	19.1	19.4	+0.3
Vape an e-liquid with nicotine ocasionally [c]	—	—	—	—	—	—	—	—	—	—	—	18.8	—
Vape an e-liquid with nicotine regularly [c]	—	—	—	—	—	—	—	—	—	—	—	33.3	—
Smoke little cigars or cigarillos regularly [c]	—	—	—	—	—	—	—	—	31.0	34.9	35.3	34.0	-1.3
Use smokeless tobacco regularly	45.9	46.7	48.0	44.7	43.7	45.7	42.9	40.0	39.9	42.5	43.0	40.7	-2.3
Take dissolvable tobacco regularly [c]	—	—	—	—	—	—	33.3	31.3	32.0	35.6	34.2	32.7	-1.6
Take snus regularly [c]	—	—	—	—	—	—	41.0	38.9	38.8	41.8	39.9	38.1	-1.8
Take steroids [i]	—	—	—	—	—	—	—	—	—	—	—	—	—
Approximate weighted N =	*16,200*	*16,100*	*15,100*	*15,900*	*15,200*	*14,900*	*15,000*	*12,900*	*13,000*	*15,600*	*14,700*	*13,500*	

Table continued on next page.

TABLE 11 (cont.)
Trends in Harmfulness of Drugs as Perceived by 10th Graders

Source. The Monitoring the Future study, the University of Michigan.

Notes. Level of significance of difference between the two most recent classes: s = .05, ss = .01, sss = .001. ' — ' indicates data not available. Any apparent inconsistency between the change estimate and the prevalence estimates for the two most recent years is due to rounding. '‡' indicates that the question changed the following year.

[a]Answer alternatives were: (1) No risk, (2) Slight risk, (3) Moderate risk, (4) Great risk, and (5) Can't say, drug unfamiliar

[b]Beginning in 2012 data based on two thirds of *N* indicated.

[c]Data based on one third of *N* indicated.

[d]Beginning in 1997, data based on two thirds of *N* indicated due to changes in questionnaire forms.

[e]Data based on one of two forms in 1993–1996; *N* is one half of *N* indicated. Beginning in 1997, data based on one third of *N* indicated due to changes in questionnaire forms.

[f]Beginning in 2014 data are based on the revised question which included "Molly," *N* is one third of *N* indicated in 2014 and two thirds of *N* indicated in 2015. 2014 and 2015 data are not comparable to earlier years due to the revision of the question text.

[g]Beginning in 1999, data based on two thirds of *N* indicated due to changes in questionnaire forms.

[h]E-cigarette data based on two thirds of *N* indicated. Little cigars or cigarillos data based on one third *N* indicated.

[i]Data based on two forms in 1991 and 1992. Data based on one of two forms in 1993 and 1994; *N* is one half of *N* indicated.

TABLE 12
Trends in Harmfulness of Drugs as Perceived by 12th Graders

How much do you think people risk harming themselves (physically or in other ways), if they . . .	Percentage saying great risk [a]															
	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990
Try marijuana once or twice	15.1	11.4	9.5	8.1	9.4	10.0	13.0	11.5	12.7	14.7	14.8	15.1	18.4	19.0	23.6	23.1
Smoke marijuana occasionally	18.1	15.0	13.4	12.4	13.5	14.7	19.1	18.3	20.6	22.6	24.5	25.0	30.4	31.7	36.5	36.9
Smoke marijuana regularly	43.3	38.6	36.4	34.9	42.0	50.4	57.6	60.4	62.8	66.9	70.4	71.3	73.5	77.0	77.5	77.8
Try synthetic marijuana once or twice	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take synthetic marijuana occasionally	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try LSD once or twice	49.4	45.7	43.2	42.7	41.6	43.9	45.5	44.9	44.7	45.4	43.5	42.0	44.9	45.7	46.0	44.7
Take LSD regularly	81.4	80.8	79.1	81.1	82.4	83.0	83.5	83.5	83.2	83.8	82.9	82.6	83.8	84.2	84.3	84.5
Try PCP once or twice	—	—	—	—	—	—	—	—	—	—	—	—	55.6	58.8	56.6	55.2
Try ecstasy (MDMA) once or twice [b]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try salvia once or twice [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take salvia occasionally	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try cocaine once or twice	42.6	39.1	35.6	33.2	31.5	31.3	32.1	32.8	33.0	35.7	34.0	33.5	47.9	51.2	54.9	59.4
Take cocaine occasionally	—	—	—	—	—	—	—	—	—	—	—	54.2	66.8	69.2	71.8	73.9
Take cocaine regularly	73.1	72.3	68.2	68.2	69.5	69.2	71.2	73.0	74.3	78.8	79.0	82.2	88.5	89.2	90.2	91.1
Try crack once or twice	—	—	—	—	—	—	—	—	—	—	—	—	57.0	62.1	62.9	64.3
Take crack occasionally	—	—	—	—	—	—	—	—	—	—	—	—	70.4	73.2	75.3	80.4
Take crack regularly	—	—	—	—	—	—	—	—	—	—	—	—	84.6	84.8	85.6	91.6
Try cocaine powder once or twice	—	—	—	—	—	—	—	—	—	—	—	—	45.3	51.7	53.8	53.9
Take cocaine powder occasionally	—	—	—	—	—	—	—	—	—	—	—	—	56.8	61.9	65.8	71.1
Take cocaine powder regularly	—	—	—	—	—	—	—	—	—	—	—	—	81.4	82.9	83.9	90.2
Try heroin once or twice	60.1	58.9	55.8	52.9	50.4	52.1	52.9	51.1	50.8	49.8	47.3	45.8	53.6	54.0	53.8	55.4
Take heroin occasionally	75.6	75.6	71.9	71.4	70.9	70.9	72.2	69.8	71.8	70.7	69.8	68.2	74.6	73.8	75.5	76.6
Take heroin regularly	87.2	88.6	86.1	86.6	87.5	86.2	87.5	86.0	86.1	87.2	86.0	87.1	88.7	88.8	89.5	90.2
Try heroin once or twice without using a needle	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take heroin occasionally without using a needle	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try any narcotic other than heroin (codeine, Vicodin, OxyContin, Percocet, etc.) once or twice	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take any narcotic other than heroin occasionally	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take any narcotic other than heroin regularly	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try amphetamines once or twice [d]	35.4	33.4	30.8	29.9	29.7	29.7	26.4	25.3	24.7	25.4	25.2	25.1	29.1	29.6	32.8	32.2
Take amphetamines regularly [d]	69.0	67.3	66.6	67.1	69.9	69.1	66.1	64.7	64.8	67.1	67.2	67.3	69.4	69.8	71.2	71.2
Try Adderall once or twice [e]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try Adderall occasionally [e]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try crystal methamphetamine (ice) once or twice	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try bath salts (synthetic stimulants) once or twice	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take bath salts (synthetic stimulants) occasionally	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try sedatives (barbiturates) once or twice [f]	34.8	32.5	31.2	31.3	30.7	30.9	28.4	27.5	27.0	27.4	26.1	25.4	30.9	29.7	32.2	32.4
Take sedatives (barbiturates) regularly [f]	69.1	67.7	68.6	68.4	71.6	72.2	69.9	67.6	67.7	68.5	68.3	67.2	69.4	69.6	70.5	70.2
Try one or two drinks of an alcoholic beverage (beer, wine, liquor)	5.3	4.8	4.1	3.4	4.1	3.8	4.6	3.5	4.2	4.6	5.0	4.6	6.2	6.0	6.0	8.3
Take one or two drinks nearly every day	21.5	21.2	18.5	19.6	22.6	20.3	21.6	21.6	21.6	23.0	24.4	25.1	26.2	27.3	28.5	31.3
Take four or five drinks nearly every day	63.5	61.0	62.9	63.1	66.2	65.7	64.5	65.5	66.8	68.4	69.8	66.5	69.7	68.5	69.8	70.9
Have five or more drinks once or twice each weekend	37.8	37.0	34.7	34.5	34.9	35.9	36.3	36.0	38.6	41.7	43.0	39.1	41.9	42.6	44.0	47.1
Smoke one or more packs of cigarettes per day	51.3	56.4	58.4	59.0	63.0	63.7	63.3	60.5	61.2	63.8	66.5	66.0	68.6	68.0	67.2	68.2
Use electronic cigarettes (e-cigarettes) regularly [g]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vape an e-liquid with nicotine ocasionally [g]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vape an e-liquid with nicotine regularly [g]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Smoke little cigars or cigarillos regularly	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Use smokeless tobacco regularly	—	—	—	—	—	—	—	—	—	—	—	25.8	30.0	33.2	32.9	34.2
Take steroids	—	—	—	—	—	—	—	—	—	—	—	—	—	—	63.8	69.9
Approximate weighted N =	*2,804*	*2,918*	*3,052*	*3,770*	*3,250*	*3,234*	*3,604*	*3,557*	*3,305*	*3,262*	*3,250*	*3,020*	*3,315*	*3,276*	*2,796*	*2,553*

Table continued on next page.

TABLE 12 (cont.)
Trends in Harmfulness of Drugs as Perceived by 12th Graders

	Percentage saying great risk [a]														
How much do you think people risk harming themselves (physically or in other ways), if they . . .	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Try marijuana once or twice	27.1	24.5	21.9	19.5	16.3	15.6	14.9	16.7	15.7	13.7	15.3	16.1	16.1	15.9	16.1
Smoke marijuana occasionally	40.6	39.6	35.6	30.1	25.6	25.9	24.7	24.4	23.9	23.4	23.5	23.2	26.6	25.4	25.8
Smoke marijuana regularly	78.6	76.5	72.5	65.0	60.8	59.9	58.1	58.5	57.4	58.3	57.4	53.0	54.9	54.6	58.0
Try synthetic marijuana once or twice	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take synthetic marijuana occasionally	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try LSD once or twice	46.6	42.3	39.5	38.8	36.4	36.2	34.7	37.4	34.9	34.3	33.2	36.7	36.2	36.2	36.5
Take LSD regularly	84.3	81.8	79.4	79.1	78.1	77.8	76.6	76.5	76.1	75.9	74.1	73.9	72.3	70.2	69.9
Try PCP once or twice	51.7	54.8	50.8	51.5	49.1	51.0	48.8	46.8	44.8	45.0	46.2	48.3	45.2	47.1	46.6
Try ecstasy (MDMA) once or twice [b]	—	—	—	—	—	—	33.8	34.5	35.0	37.9	45.7	52.2	56.3	57.7	60.1
Try salvia once or twice [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take salvia occasionally	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try cocaine once or twice	59.4	56.8	57.6	57.2	53.7	54.2	53.6	54.6	52.1	51.1	50.7	51.2	51.0	50.7	50.5
Take cocaine occasionally	75.5	75.1	73.3	73.7	70.8	72.1	72.4	70.1	70.1	69.5	69.9	68.3	69.1	67.2	66.7
Take cocaine regularly	90.4	90.2	90.1	89.3	87.9	88.3	87.1	86.3	85.8	86.2	84.1	84.5	83.0	82.2	82.8
Try crack once or twice	60.6	62.4	57.6	58.4	54.6	56.0	54.0	52.2	48.2	48.4	49.4	50.8	47.3	47.8	48.4
Take crack occasionally	76.5	76.3	73.9	73.8	72.8	71.4	70.3	68.7	67.3	65.8	65.4	65.6	64.0	64.5	63.8
Take crack regularly	90.1	89.3	87.5	89.6	88.6	88.0	86.2	85.3	85.4	85.3	85.8	84.1	83.2	83.5	83.3
Try cocaine powder once or twice	53.6	57.1	53.2	55.4	52.0	53.2	51.4	48.5	46.1	47.0	49.0	49.5	46.2	45.4	46.2
Take cocaine powder occasionally	69.8	70.8	68.6	70.6	69.1	68.8	67.7	65.4	64.2	64.7	63.2	64.4	61.4	61.6	60.8
Take cocaine powder regularly	88.9	88.4	87.0	88.6	87.8	86.8	86.0	84.1	84.6	85.5	84.4	84.2	82.3	81.7	82.7
Try heroin once or twice	55.2	50.9	50.7	52.8	50.9	52.5	56.7	57.8	56.0	54.2	55.6	56.0	58.0	56.6	55.2
Take heroin occasionally	74.9	74.2	72.0	72.1	71.0	74.8	76.3	76.9	77.3	74.6	75.9	76.6	78.5	75.7	76.0
Take heroin regularly	89.6	89.2	88.3	88.0	87.2	89.5	88.9	89.1	89.9	89.2	88.3	88.5	89.3	86.8	87.5
Try heroin once or twice without using a needle	—	—	—	—	55.6	58.6	60.5	59.6	58.5	61.6	60.7	60.6	58.9	61.2	60.5
Take heroin occasionally without using a needle	—	—	—	—	71.2	71.0	74.3	73.4	73.6	74.7	74.4	74.7	73.0	76.1	73.3
Try any narcotic other than heroin (codeine, Vicodin, OxyContin, Percocet, etc.) once or twice	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take any narcotic other than heroin occasionally	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take any narcotic other than heroin regularly	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try amphetamines once or twice [d]	36.3	32.6	31.3	31.4	28.8	30.8	31.0	35.3	32.2	32.6	34.7	34.4	36.8	35.7	37.7
Take amphetamines regularly [d]	74.1	72.4	69.9	67.0	65.9	66.8	66.0	67.7	66.4	66.3	67.1	64.8	65.6	63.9	67.1
Try Adderall once or twice [e]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try Adderall occasionally [e]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try crystal methamphetamine (ice) once or twice	61.6	61.9	57.5	58.3	54.4	55.3	54.4	52.7	51.2	51.3	52.7	53.8	51.2	52.4	54.6
Try bath salts (synthetic stimulants) once or twice	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Take bath salts (synthetic stimulants) occasionally	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Try sedatives (barbiturates) once or twice [f]	35.1	32.2	29.2	29.9	26.3	29.1	26.9	29.0	26.1	25.0	25.7	26.2	27.9‡	24.9	24.7
Take sedatives (barbiturates) regularly [f]	70.5	70.2	66.1	63.3	61.6	60.4	56.8	56.3	54.1	52.3	50.3	49.3	49.6‡	54.0	54.1
Try one or two drinks of an alcoholic beverage (beer, wine, liquor)	9.1	8.6	8.2	7.6	5.9	7.3	6.7	8.0	8.3	6.4	8.7	7.6	8.4	8.6	8.5
Take one or two drinks nearly every day	32.7	30.6	28.2	27.0	24.8	25.1	24.8	24.3	21.8	21.7	23.4	21.0	20.1	23.0	23.7
Take four or five drinks nearly every day	69.5	70.5	67.8	66.2	62.8	65.6	63.0	62.1	61.1	59.9	60.7	58.8	57.8	59.2	61.8
Have five or more drinks once or twice each weekend	48.6	49.0	48.3	46.5	45.2	49.5	43.0	42.8	43.1	42.7	43.6	42.2	43.5	43.6	45.0
Smoke one or more packs of cigarettes per day	69.4	69.2	69.5	67.6	65.6	68.2	68.7	70.8	70.8	73.1	73.3	74.2	72.1	74.0	76.5
Use electronic cigarettes (e-cigarettes) regularly [g]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vape an e-liquid with nicotine ocasionally [g]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vape an e-liquid with nicotine regularly [g]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Smoke little cigars or cigarillos regularly	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Use smokeless tobacco regularly	37.4	35.5	38.9	36.6	33.2	37.4	38.6	40.9	41.1	42.2	45.4	42.6	43.3	45.0	43.6
Take steroids	65.6	70.7	69.1	66.1	66.4	67.6	67.2	68.1	62.1	57.9	58.9	57.1	55.0	55.7	56.8
Approximate weighted N =	*2,549*	*2,684*	*2,759*	*2,591*	*2,603*	*2,449*	*2,579*	*2,564*	*2,306*	*2,130*	*2,173*	*2,198*	*2,466*	*2,491*	*2,512*

Table continued on next page.

TABLE 12 (cont.)
Trends in Harmfulness of Drugs as Perceived by 12th Graders

How much do you think people risk harming themselves (physically or in other ways), if they . . .	Percentage saying great risk [a]												2016 – 2017 change
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	
Try marijuana once or twice	17.8	18.6	17.4	18.5	17.1	15.6	14.8	14.5	12.5	12.3	12.9	11.9	-1.1
Smoke marijuana occasionally	25.9	27.1	25.8	27.4	24.5	22.7	20.6	19.5	16.4	15.8	17.1	14.1	-3.0 s
Smoke marijuana regularly	57.9	54.8	51.7	52.4	46.8	45.7	44.1	39.5	36.1	31.9	31.1	29.0	-2.1
Try synthetic marijuana once or twice	—	—	—	—	—	—	23.5	25.9	32.5	33.0	35.6	33.0	-2.6
Take synthetic marijuana occasionally	—	—	—	—	—	—	32.7	36.2	39.4	40.9	43.9	40.0	-3.9
Try LSD once or twice	36.1	37.0	33.9	37.1	35.6	34.7	33.1	34.9	35.5	33.2	31.7	30.0	-1.7
Take LSD regularly	69.3	67.3	63.6	67.8	65.3	65.5	66.8	66.8	62.7	60.7	58.2	56.1	-2.1
Try PCP once or twice	47.0	48.0	47.4	49.7	52.4	53.9	51.6	53.9	53.8	54.4	55.1	53.6	-1.5
Try ecstasy (MDMA) once or twice [b]	59.3	58.1	57.0	53.3	50.6	49.0	49.4	47.5‡	47.8	49.5	48.8	49.1	+0.3
Try salvia once or twice [c]	—	—	—	—	39.8	36.7‡	13.8	12.9	14.1	13.1	13.0	10.2	-2.8
Take salvia occasionally	—	—	—	—	—	—	23.1	21.3	20.0	17.6	16.3	13.8	-2.5
Try cocaine once or twice	52.5	51.3	50.3	53.1	52.8	54.0	51.6	54.4	53.7	51.1	52.7	49.5	-3.2
Take cocaine occasionally	69.8	68.8	67.1	71.4	67.8	69.7	69.0	70.2	68.1	66.3	68.6	64.6	-4.0 s
Take cocaine regularly	84.6	83.3	80.7	84.4	81.7	83.8	82.6	83.3	80.6	79.1	78.3	74.9	-3.5
Try crack once or twice	47.8	47.3	47.5	48.4	50.2	51.7	52.0	55.6	54.5	53.6	53.9	51.6	-2.3
Take crack occasionally	64.8	63.6	65.2	64.7	64.3	66.2	66.5	69.5	68.5	67.8	66.2	65.3	-0.9
Take crack regularly	82.8	82.6	83.4	84.0	83.8	83.9	84.0	85.4	82.0	81.2	81.9	79.8	-2.2
Try cocaine powder once or twice	45.8	45.1	45.1	46.5	48.2	48.0	48.1	49.9	49.9	49.0	49.3	45.1	-4.1 s
Take cocaine powder occasionally	61.9	59.9	61.6	62.6	62.6	64.2	62.6	65.4	64.8	62.8	62.9	60.1	-2.8
Take cocaine powder regularly	82.1	81.5	82.5	83.4	81.8	83.3	83.3	83.9	81.5	80.1	80.7	78.8	-1.9
Try heroin once or twice	59.1	58.4	55.5	59.3	58.3	59.1	59.4	61.7	62.8	64.0	64.5	63.0	-1.5
Take heroin occasionally	79.1	76.2	75.3	79.7	74.8	77.2	78.0	78.2	77.9	78.0	78.7	74.6	-4.1 s
Take heroin regularly	89.7	87.8	86.4	89.9	85.5	87.9	88.6	87.6	85.7	84.8	85.4	83.3	-2.2
Try heroin once or twice without using a needle	62.6	60.2	60.8	61.5	63.8	61.1	63.3	64.5	65.3	62.5	66.1	64.6	-1.5
Take heroin occasionally without using a needle	76.2	73.9	73.2	74.8	76.2	74.7	76.1	76.4	73.6	71.1	74.6	72.7	-1.9
Try any narcotic other than heroin (codeine, Vicodin, OxyContin, Percocet, etc.) once or twice	—	—	—	—	40.4	39.9	38.4	43.1	42.7	44.1	43.6	42.0	-1.6
Take any narcotic other than heroin occasionally	—	—	—	—	54.3	54.8	53.8	57.3	59.0	58.5	55.7	55.5	-0.2
Take any narcotic other than heroin regularly	—	—	—	—	74.9	75.5	73.9	75.8	72.7	73.9	72.4	70.8	-1.6
Try amphetamines once or twice [d]	39.5	41.3	39.2	41.9	40.6‡	34.8	34.3	36.3	34.1	34.0	31.1	31.9	+0.8
Take amphetamines regularly [d]	68.1	68.1	65.4	69.0	63.6‡	58.7	60.0	59.5	55.1	54.3	51.3	50.0	-1.3
Try Adderall once or twice [e]	—	—	—	—	33.3	31.2	27.2	31.8	33.6	34.3	32.5	32.0	-0.5
Try Adderall occasionally [e]	—	—	—	—	41.6	40.8	35.3	38.8	41.5	41.6	40.9	40.6	-0.3
Try crystal methamphetamine (ice) once or twice	59.1	60.2	62.2	63.4	64.9	66.5	67.8	72.2	70.2	70.0	70.0	69.3	-0.6
Try bath salts (synthetic stimulants) once or twice	—	—	—	—	—	—	33.2	59.5	59.2	57.5	54.9	51.3	-3.6
Take bath salts (synthetic stimulants) occasionally	—	—	—	—	—	—	45.0	69.9	68.8	67.4	64.2	61.5	-2.7
Try sedatives (barbiturates) once or twice [f]	28.0	27.9	25.9	29.6	28.0	27.8	27.8	29.4	29.6	28.9	27.4	26.9	-0.5
Take sedatives (barbiturates) regularly [f]	56.8	55.1	50.2	54.7	52.1	52.4	53.9	53.3	50.5	50.6	47.0	44.0	-3.0
Try one or two drinks of an alcoholic beverage (beer, wine, liquor)	9.3	10.5	10.0	9.4	10.8	9.4	8.7	9.9	8.6	10.3	9.5	9.3	-0.2
Take one or two drinks nearly every day	25.3	25.1	24.2	23.7	25.4	24.6	23.7	23.1	21.1	21.5	21.6	21.6	+0.1
Take four or five drinks nearly every day	63.4	61.8	60.8	62.4	61.1	62.3	63.6	62.4	61.2	59.1	59.1	58.7	-0.4
Have five or more drinks once or twice each weekend	47.6	45.8	46.3	48.0	46.3	47.6	48.8	45.8	45.4	46.9	48.4	45.7	-2.7
Smoke one or more packs of cigarettes per day	77.6	77.3	74.0	74.9	75.0	77.7	78.2	78.2	78.0	75.9	76.5	74.9	-1.6
Use electronic cigarettes (e-cigarettes) regularly [g]	—	—	—	—	—	—	—	—	14.2	16.2	18.2	16.1	-2.1
Vape an e-liquid with nicotine ocasionally [g]	—	—	—	—	—	—	—	—	—	—	—	16.4	—
Vape an e-liquid with nicotine regularly [g]	—	—	—	—	—	—	—	—	—	—	—	27.0	—
Smoke little cigars or cigarillos regularly	—	—	—	—	—	—	—	—	38.3	39.7	39.5	38.2	-1.3
Use smokeless tobacco regularly	45.9	44.0	42.9	40.8	41.2	42.6	44.3	41.6	40.7	38.5	38.1	38.4	+0.2
Take steroids	60.2	57.4	60.8	60.2	59.2	61.1	58.6	54.2	54.6	54.4	54.5	49.1	-5.4 ss
Approximate weighted N =	*2,407*	*2,450*	*2,389*	*2,290*	*2,440*	*2,408*	*2,331*	*2,098*	*2,067*	*2,174*	*1,988*	*1,919*	

Table continued on next page.

TABLE 12 (cont.)
Trends in Harmfulness of Drugs as Perceived by 12th Graders

Source. The Monitoring the Future study, the University of Michigan.

Notes. Level of significance of difference between the two most recent classes: s = .05, ss = .01, sss = .001. ' — ' indicates data not available. ' ‡ ' indicates that the question changed the following year. See relevant footnote for that drug. Any apparent inconsistency between the change estimate and the prevalence estimates for the two most recent years is due to rounding.

[a]Answer alternatives were: (1) No risk, (2) Slight risk, (3) Moderate risk, (4) Great risk, and (5) Can't say, drug unfamiliar.

[b] Beginning in 2014 data are based on the revised question which included "Molly." 2014 and 2015 data are not comparable to earlier years due to the revision of the question text.

[c]In 2011 the question on perceived risk of using salvia once or twice appeared at the end of a form. In 2012 the question was moved to an earlier section of the same form. A question on perceived risk of using salvia occasionally was also added following the question on perceived risk of trying salvia once or twice. These changes likely explain the discontinuity in the 2012 results.

[d]In 2011 the list of examples was changed from uppers, pep pills, bennies, speed to uppers, speed, Adderall, Ritalin, etc. These changes likely explain the discontinuity in the 2011 results.

[e]In 2014 "(without a doctor's orders)" added to the questions on perceived risk of using Adderall.

[f]In 2004 the question text was changed from barbiturates to sedatives/barbiturates and the list of examples was changed from downers, goofballs, reds, yellows, etc. to just downers. These changes likely explain the discontinuity in the 2004 results.

[g]Based on two of six forms; N is two times the N indicated.

TABLE 13
Trends in Disapproval of Drug Use in Grade 8

Do you disapprove of people who . . .	Percentage who disapprove or strongly disapprove [a]														
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Try marijuana once or twice [b]	84.6	82.1	79.2	72.9	70.7	67.5	67.6	69.0	70.7	72.5	72.4	73.3	73.8	75.9	75.3
Smoke marijuana occasionally [b]	89.5	88.1	85.7	80.9	79.7	76.5	78.1	78.4	79.3	80.6	80.6	80.9	81.5	83.1	82.4
Smoke marijuana regularly [b]	92.1	90.8	88.9	85.3	85.1	82.8	84.6	84.5	84.5	85.3	84.5	85.3	85.7	86.8	86.3
Try inhalants once or twice [c]	84.9	84.0	82.5	81.6	81.8	82.9	84.1	83.0	85.2	85.4	86.6	86.1	85.1	85.1	84.6
Take inhalants regularly [c]	90.6	90.0	88.9	88.1	88.8	89.3	90.3	89.5	90.3	90.2	90.5	90.4	89.8	90.1	89.8
Take LSD once or twice [d]	—	—	77.1	75.2	71.6	70.9	72.1	69.1	69.4	66.7	64.6	62.6	61.0	58.1	58.5
Take LSD regularly [d]	—	—	79.8	78.4	75.8	75.3	76.3	72.5	72.5	69.3	67.0	65.5	63.5	60.5	60.7
Try ecstasy (MDMA) once or twice [e]	—	—	—	—	—	—	—	—	—	—	69.0	74.3	77.7	76.3	75.0
Take ecstasy (MDMA) occasionally [e]	—	—	—	—	—	—	—	—	—	—	73.6	78.6	81.3	79.4	77.9
Try crack once or twice [c]	91.7	90.7	89.1	86.9	85.9	85.0	85.7	85.4	86.0	85.4	86.0	86.2	86.4	87.4	87.6
Take crack occasionally [c]	93.3	92.5	91.7	89.9	89.8	89.3	90.3	89.5	89.9	88.8	89.8	89.6	89.8	90.3	90.5
Try cocaine powder once or twice [c]	91.2	89.6	88.5	86.1	85.3	83.9	85.1	84.5	85.2	84.8	85.6	85.8	85.6	86.8	87.0
Take cocaine powder occasionally [c]	93.1	92.4	91.6	89.7	89.7	88.7	90.1	89.3	89.9	88.8	89.6	89.9	89.8	90.3	90.7
Try heroin once or twice without using a needle [d]	—	—	—	—	85.8	85.0	87.7	87.3	88.0	87.2	87.2	87.8	86.9	86.6	86.9
Take heroin occasionally without using a needle [d]	—	—	—	—	88.5	87.7	90.1	89.7	90.2	88.9	88.9	89.6	89.0	88.6	88.5
Try one or two drinks of an alcoholic beverage (beer, wine, liquor) [b]	51.7	52.2	50.9	47.8	48.0	45.5	45.7	47.5	48.3	48.7	49.8	51.1	49.7	51.1	51.2
Take one or two drinks nearly every day [b]	82.2	81.0	79.6	76.7	75.9	74.1	76.6	76.9	77.0	77.8	77.4	78.3	77.1	78.6	78.7
Have five or more drinks once or twice each weekend [b]	85.2	83.9	83.3	80.7	80.7	79.1	81.3	81.0	80.3	81.2	81.6	81.9	81.9	82.3	82.9
Smoke one to five cigarettes per day [e]	—	—	—	—	—	—	—	—	75.1	79.1	80.4	81.1	81.4	83.1	82.9
Smoke one or more packs of cigarettes per day [f]	82.8	82.3	80.6	78.4	78.6	77.3	80.3	80.0	81.4	81.9	83.5	84.6	84.6	85.7	85.3
Use electronic cigarettes (e-cigarettes) regularly [e]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vape an e-liquid with nicotine ocasionally [e]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vape an e-liquid with nicotine regularly [e]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Use smokeless tobacco regularly [b]	79.1	77.2	77.1	75.1	74.0	74.1	76.5	76.3	78.0	79.2	79.4	80.6	80.7	81.0	82.0
Take steroids [g]	89.8	90.3	89.9	87.9	—	—	—	—	—	—	—	—	—	—	—
Approximate weighted N =	*17,400*	*18,500*	*18,400*	*17,400*	*17,600*	*18,000*	*18,800*	*18,100*	*16,700*	*16,700*	*16,200*	*15,100*	*16,500*	*17,000*	*16,800*

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TABLE 13 (cont.)
Trends in Disapproval of Drug Use in Grade 8

Do you disapprove of people who . . .	Percentage who disapprove or strongly disapprove [a]												2016–2017 change
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	
Try marijuana once or twice [b]	76.0	78.7	76.6	75.3	73.5	74.4	75.1	72.0	70.5	70.3	70.1	67.3	-2.8 s
Smoke marijuana occasionally [b]	82.2	84.5	82.6	81.9	79.9	81.1	81.6	78.8	77.7	77.5	77.5	75.5	-2.1
Smoke marijuana regularly [b]	86.1	87.7	86.8	85.9	84.3	85.7	85.6	83.8	82.2	82.2	82.3	81.2	-1.1
Try inhalants once or twice [c]	83.4	84.1	82.3	83.1	83.1	82.9	83.1	81.6	80.7	80.6	78.3	77.4	-0.8
Take inhalants regularly [c]	89.0	89.5	88.5	88.4	88.9	88.5	88.6	86.8	85.5	85.4	83.3	82.8	-0.5
Take LSD once or twice [d]	53.9	53.5	52.6	53.2	53.7	55.4	51.8	52.0	52.8	56.0	55.2	56.1	+0.8
Take LSD regularly [d]	55.8	55.6	54.7	55.7	55.8	57.6	54.1	53.6	54.8	58.1	57.6	58.2	+0.6
Try ecstasy (MDMA) once or twice [e]	66.7	65.7	63.5	62.3	62.4	64.2	60.2	60.9	61.0‡	68.2	64.8	63.0	-1.8
Take ecstasy (MDMA) occasionally [e]	69.8	68.3	66.5	65.7	65.9	67.5	63.2	63.4	64.1‡	71.7	67.5	65.8	-1.7
Try crack once or twice [c]	87.2	88.6	87.2	88.4	89.1	88.5	89.0	88.1	88.0	87.5	87.0	87.5	+0.5
Take crack occasionally [c]	90.0	91.2	90.3	91.0	91.5	91.0	91.2	90.3	89.8	89.8	88.8	89.6	+0.8
Try cocaine powder once or twice [c]	86.5	88.2	86.8	88.1	88.4	88.3	88.6	88.0	87.7	87.5	86.8	86.8	0.0
Take cocaine powder occasionally [c]	90.2	91.0	90.1	90.7	91.4	91.3	91.5	90.6	90.1	90.1	89.3	90.0	+0.6
Try heroin once or twice without using a needle [d]	87.2	88.4	86.9	88.6	89.5	87.5	86.8	87.2	87.1	87.1	85.6	87.9	+2.4 s
Take heroin occasionally without using a needle [d]	88.5	89.7	88.2	90.1	90.6	89.0	87.7	88.2	88.1	88.0	86.7	88.7	+2.0
Try one or two drinks of an alcoholic beverage (beer, wine, liquor) [b]	51.3	54.0	52.5	52.7	54.2	54.0	54.1	53.3	53.3	53.7	52.6	51.0	-1.6
Take one or two drinks nearly every day [b]	78.7	80.4	79.2	78.5	79.5	80.7	81.3	80.2	79.6	79.7	79.1	79.5	+0.4
Have five or more drinks once or twice each weekend [b]	82.0	83.8	83.2	83.2	83.6	84.8	86.0	85.0	84.9	85.4	84.9	84.7	-0.2
Smoke one to five cigarettes per day [e]	83.5	85.3	85.0	83.6	84.7	86.8	—	—	—	—	—	—	—
Smoke one or more packs of cigarettes per day [f]	85.6	87.0	86.7	87.1	87.0	88.0	88.8	88.0	87.5	88.8	88.1	88.8	+0.7
Use electronic cigarettes (e-cigarettes) regularly [e]	—	—	—	—	—	—	—	—	58.4	65.0	66.6	—	—
Vape an e-liquid with nicotine ocasionally [e]	—	—	—	—	—	—	—	—	—	—	—	72.0	—
Vape an e-liquid with nicotine regularly [e]	—	—	—	—	—	—	—	—	—	—	—	79.8	—
Use smokeless tobacco regularly [b]	81.0	82.3	82.1	81.5	81.2	82.6	82.7	81.5	80.2	82.5	81.1	81.3	+0.3
Take steroids [g]	—	—	—	—	—	—	—	—	—	—	—	—	—
Approximate weighted N =	*16,500*	*16,100*	*15,700*	*15,000*	*15,300*	*16,000*	*15,100*	*14,600*	*14,600*	*14,400*	*16,900*	*15,300*	

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TABLE 13 (cont.)
Trends in Disapproval of Drug Use in Grade 8

Source. The Monitoring the Future study, the University of Michigan.

Notes. Level of significance of difference between the two most recent classes: s = .05, ss = .01, sss = .001. ' — ' indicates data not available. Any apparent inconsistency between the change estimate and the prevalence estimates for the two most recent years is due to rounding. ' ‡ ' indicates that the question changed the following year.

[a]Answer alternatives were: (1) Don't disapprove, (2) Disapprove, (3) Strongly disapprove, and (4) Can't say, drug unfamiliar. Percentages are shown for categories (2) and (3) combined.

[b]Beginning in 2012, data based on two thirds of *N* indicated.

[c]Beginning in 1997, data based on two thirds of *N* indicated due to changes in questionnaire forms.

[d]Data based on one of two forms in 1993–1996; *N* is one half of *N* indicated. Beginning in 1997, data based on one third of *N* indicated due to changes in questionnaire forms.

[e]Data based on one third of *N* indicated. For MDMA "Molly" was added to the question text in 2015; 2014 and 2015 data are not comparable due to this change.

[f]Beginning in 1999, data based on two thirds of *N* indicated due to changes in questionnaire forms.

[g]Data based on two forms in 1991 and 1992. Data based on one of two forms in 1993 and 1994;*N* is one half of *N* indicated.

TABLE 14
Trends in Disapproval of Drug Use in Grade 10

Do you disapprove of people who . . .	Percentage who disapprove or strongly disapprove[a]														
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Try marijuana once or twice[b]	74.6	74.8	70.3	62.4	59.8	55.5	54.1	56.0	56.2	54.9	54.8	57.8	58.1	60.4	61.3
Smoke marijuana occasionally[b]	83.7	83.6	79.4	72.3	70.0	66.9	66.2	67.3	68.2	67.2	66.2	68.3	68.4	70.8	71.9
Smoke marijuana regularly[b]	90.4	90.0	87.4	82.2	81.1	79.7	79.7	80.1	79.8	79.1	78.0	78.6	78.8	81.3	82.0
Try inhalants once or twice[c]	85.2	85.6	84.8	84.9	84.5	86.0	86.9	85.6	88.4	87.5	87.8	88.6	87.7	88.5	88.1
Take inhalants regularly[c]	91.0	91.5	90.9	91.0	90.9	91.7	91.7	91.1	92.4	91.8	91.3	91.8	91.0	92.3	91.9
Take LSD once or twice[d]	—	—	82.1	79.3	77.9	76.8	76.6	76.7	77.8	77.0	75.4	74.6	74.4	72.4	71.8
Take LSD regularly[d]	—	—	86.8	85.6	84.8	84.5	83.4	82.9	84.3	82.1	80.8	79.4	77.6	75.9	75.0
Try ecstasy (MDMA) once or twice[e]	—	—	—	—	—	—	—	—	—	—	72.6	77.4	81.0	83.7	83.1
Take ecstasy (MDMA) occasionally[e]	—	—	—	—	—	—	—	—	—	—	81.0	84.6	86.3	88.0	87.4
Try crack once or twice[c]	92.5	92.5	91.4	89.9	88.7	88.2	87.4	87.1	87.8	87.1	86.9	88.0	87.6	88.6	88.8
Take crack occasionally[c]	94.3	94.4	93.6	92.5	91.7	91.9	91.0	90.6	91.5	90.9	90.6	91.0	91.0	91.8	91.8
Try cocaine powder once or twice[c]	90.8	91.1	90.0	88.1	86.8	86.1	85.1	84.9	86.0	84.8	85.3	86.4	85.9	86.8	86.9
Take cocaine powder occasionally[c]	94.0	94.0	93.2	92.1	91.4	91.1	90.4	89.7	90.7	89.9	90.2	89.9	90.4	91.2	91.2
Try heroin once or twice without using a needle[d]	—	—	—	—	89.7	89.5	89.1	88.6	90.1	90.1	89.1	89.2	89.3	90.1	90.3
Take heroin occasionally without using a needle[d]	—	—	—	—	91.6	91.7	91.4	90.5	91.8	92.3	90.8	90.7	90.6	91.8	92.0
Try one or two drinks of an alcoholic beverage (beer, wine, liquor)[b]	37.6	39.9	38.5	36.5	36.1	34.2	33.7	34.7	35.1	33.4	34.7	37.7	36.8	37.6	38.5
Take one or two drinks nearly every day[b]	81.7	81.7	78.6	75.2	75.4	73.8	75.4	74.6	75.4	73.8	73.8	74.9	74.2	75.1	76.9
Have five or more drinks once or twice each weekend[b]	76.7	77.6	74.7	72.3	72.2	70.7	70.2	70.5	69.9	68.2	69.2	71.5	71.6	71.8	73.7
Smoke one to five cigarettes per day[e]	—	—	—	—	—	—	—	—	67.8	69.1	71.2	74.3	76.2	77.5	79.3
Smoke one or more packs of cigarettes per day[f]	79.4	77.8	76.5	73.9	73.2	71.6	73.8	75.3	76.1	76.7	78.2	80.6	81.4	82.7	84.3
Use electronic cigarettes (e-cigarettes) regularly[e]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vape an e-liquid with nicotine ocasionally[e]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vape an e-liquid with nicotine regularly[e]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Use smokeless tobacco regularly[b]	75.4	74.6	73.8	71.2	71.0	71.0	72.3	73.2	75.1	75.8	76.1	78.7	79.4	80.2	80.5
Take steroids[g]	90.0	91.0	91.2	90.8	—	—	—	—	—	—	—	—	—	—	—
Approximate weighted N =	*14,800*	*14,800*	*15,300*	*15,900*	*17,000*	*15,700*	*15,600*	*15,000*	*13,600*	*14,300*	*14,000*	*14,300*	*15,800*	*16,400*	*16,200*

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TABLE 14 (cont.)
Trends in Disapproval of Drug Use in Grade 10

Do you disapprove of people who . . .	Percentage who disapprove or strongly disapprove[a]												2016–2017 change
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	
Try marijuana once or twice[b]	62.5	63.9	64.5	60.1	59.2	58.5	56.2	53.2	53.8	52.7	52.6	48.1	-4.6 sss
Smoke marijuana occasionally[b]	72.6	73.3	73.6	69.2	68.0	67.9	65.7	62.1	62.9	62.6	61.9	58.1	-3.8 ss
Smoke marijuana regularly[b]	82.5	82.4	83.0	79.9	78.7	78.8	77.3	73.8	74.6	74.3	73.5	70.2	-3.3 ss
Try inhalants once or twice[c]	88.1	87.6	87.1	87.0	86.5	86.9	85.7	86.1	85.9	84.1	83.3	80.7	-2.6 s
Take inhalants regularly[c]	92.2	91.8	91.6	91.1	90.8	90.9	90.0	89.7	89.7	88.3	87.1	85.4	-1.8
Take LSD once or twice[d]	71.2	67.7	66.3	67.8	68.2	68.5	68.3	69.1	67.8	70.3	69.5	66.9	-2.7
Take LSD regularly[d]	74.9	71.5	69.8	72.2	72.9	72.5	73.0	74.2	73.3	76.5	74.9	74.5	-0.4
Try ecstasy (MDMA) once or twice[e]	81.6	80.0	78.1	76.5	75.5	76.1	75.3	75.4	74.4‡	78.0	76.8	74.7	-2.1
Take ecstasy (MDMA) occasionally[e]	86.0	84.3	83.0	81.3	81.3	82.2	81.2	81.3	80.4‡	84.0	81.7	80.0	-1.7
Try crack once or twice[c]	89.5	89.5	90.8	90.4	90.3	90.9	91.0	90.6	90.6	90.1	89.7	88.4	-1.3
Take crack occasionally[c]	92.0	92.7	92.9	92.8	92.4	93.0	93.0	92.4	92.4	92.1	91.1	90.0	-1.0
Try cocaine powder once or twice[c]	87.3	87.7	88.6	88.4	89.0	89.4	89.3	88.7	88.9	87.9	87.9	86.1	-1.8 s
Take cocaine powder occasionally[c]	91.4	92.0	92.1	92.1	92.2	92.5	92.4	91.8	91.9	91.8	90.8	89.9	-0.9
Try heroin once or twice without using a needle[d]	91.1	90.7	91.4	91.6	91.4	91.6	91.9	91.3	91.9	91.7	90.2	89.7	-0.5
Take heroin occasionally without using a needle[d]	92.5	92.5	92.5	93.0	92.4	92.4	92.9	92.3	92.7	92.7	90.9	90.5	-0.5
Try one or two drinks of an alcoholic beverage (beer, wine, liquor)[b]	37.8	39.5	41.8	39.7	40.3	41.5	39.6	38.5	40.7	40.0	41.8	39.3	-2.5 s
Take one or two drinks nearly every day[b]	76.4	77.1	79.1	77.6	77.6	80.0	78.0	77.1	77.9	78.2	78.6	77.7	-0.9
Have five or more drinks once or twice each weekend[b]	72.9	74.1	77.2	75.1	75.9	77.3	77.5	77.8	79.5	79.6	80.8	80.1	-0.7
Smoke one to five cigarettes per day[e]	80.2	79.7	82.5	80.0	80.6	82.1	—	—	—	—	—	—	—
Smoke one or more packs of cigarettes per day[f]	83.2	84.7	85.2	84.5	83.9	85.8	86.0	86.1	88.0	88.3	88.5	87.8	-0.8
Use electronic cigarettes (e-cigarettes) regularly[e]	—	—	—	—	—	—	—	—	54.6	59.9	65.0	—	—
Vape an e-liquid with nicotine ocasionally[e]	—	—	—	—	—	—	—	—	—	—	—	64.2	—
Vape an e-liquid with nicotine regularly[e]	—	—	—	—	—	—	—	—	—	—	—	73.9	—
Use smokeless tobacco regularly[b]	80.5	80.9	81.8	79.5	78.5	79.5	79.5	77.7	78.7	80.1	81.2	80.7	-0.5
Take steroids[g]	—	—	—	—	—	—	—	—	—	—	—	—	—
Approximate weighted N =	*16,200*	*16,100*	*15,100*	*15,900*	*15,200*	*14,900*	*15,000*	*12,900*	*13,000*	*15,600*	*14,700*	*13,500*	

Table continued on next page.

TABLE 14 (cont.)
Trends in Disapproval of Drug Use in Grade 10

Source. The Monitoring the Future study, the University of Michigan.

Notes. Level of significance of difference between the two most recent classes: s = .05, ss = .01, sss = .001. ' — ' indicates data not available. Any apparent inconsistency between the change estimate and the prevalence estimates for the two most recent years is due to rounding. ' ‡ ' indicates that the question changed the following year.

[a]Answer alternatives were: (1) Don't disapprove, (2) Disapprove, (3) Strongly disapprove, and (4) Can't say, drug unfamiliar. Percentages are shown for categories (2) and (3) combined.

[b]Beginning in 2012, data based on two thirds of *N* indicated.

[c]Beginning in 1997, data based on two thirds of *N* indicated due to changes in questionnaire forms.

[d]Data based on one of two forms in 1993–1996; *N* is one half of *N* indicated. Beginning in 1997, data based on one third of *N* indicated due to changes in questionnaire forms.

[e]Data based on one third of *N* indicated. For MDMA "Molly" was added to the question text in 2015; 2014 and 2015 data are not comparable due to this change.

[f]Beginning in 1999, data based on two thirds of *N* indicated due to changes in questionnaire forms.

[g]Data based on two forms in 1991 and 1992. Data based on one of two forms in 1993 and 1994; *N* is one half of *N* indicated.

TABLE 15
Trends in Disapproval of Drug Use in Grade 12

Do you disapprove of people (who are 18 or older) doing each of the following?[a]	Percentage who disapprove or strongly disapprove[b]															
	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990
Trying marijuana once or twice	47.0	38.4	33.4	33.4	34.2	39.0	40.0	45.5	46.3	49.3	51.4	54.6	56.6	60.8	64.6	67.8
Smoking marijuana occasionally	54.8	47.8	44.3	43.5	45.3	49.7	52.6	59.1	60.7	63.5	65.8	69.0	71.6	74.0	77.2	80.5
Smoking marijuana regularly	71.9	69.5	65.5	67.5	69.2	74.6	77.4	80.6	82.5	84.7	85.5	86.6	89.2	89.3	89.8	91.0
Trying LSD once or twice	82.8	84.6	83.9	85.4	86.6	87.3	86.4	88.8	89.1	88.9	89.5	89.2	91.6	89.8	89.7	89.8
Taking LSD regularly	94.1	95.3	95.8	96.4	96.9	96.7	96.8	96.7	97.0	96.8	97.0	96.6	97.8	96.4	96.4	96.3
Trying ecstasy (MDMA) once or twice[c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Trying cocaine once or twice	81.3	82.4	79.1	77.0	74.7	76.3	74.6	76.6	77.0	79.7	79.3	80.2	87.3	89.1	90.5	91.5
Taking cocaine regularly	93.3	93.9	92.1	91.9	90.8	91.1	90.7	91.5	93.2	94.5	93.8	94.3	96.7	96.2	96.4	96.7
Trying crack once or twice	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	92.3
Taking crack occasionally	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	94.3
Taking crack regularly	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	94.9
Trying cocaine powder once or twice	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	87.9
Taking cocaine powder occasionally	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	92.1
Taking cocaine powder regularly	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	93.7
Trying heroin once or twice	91.5	92.6	92.5	92.0	93.4	93.5	93.5	94.6	94.3	94.0	94.0	93.3	96.2	95.0	95.4	95.1
Taking heroin occasionally	94.8	96.0	96.0	96.4	96.8	96.7	97.2	96.9	96.9	97.1	96.8	96.6	97.9	96.9	97.2	96.7
Taking heroin regularly	96.7	97.5	97.2	97.8	97.9	97.6	97.8	97.5	97.7	98.0	97.6	97.6	98.1	97.2	97.4	97.5
Trying heroin once or twice without using a needle	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Taking heroin occasionally without using a needle	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Trying amphetamines once or twice[d]	74.8	75.1	74.2	74.8	75.1	75.4	71.1	72.6	72.3	72.8	74.9	76.5	80.7	82.5	83.3	85.3
Taking amphetamines regularly[d]	92.1	92.8	92.5	93.5	94.4	93.0	91.7	92.0	92.6	93.6	93.3	93.5	95.4	94.2	94.2	95.5
Trying sedatives (barbiturates) once or twice[e]	77.7	81.3	81.1	82.4	84.0	83.9	82.4	84.4	83.1	84.1	84.9	86.8	89.6	89.4	89.3	90.5
Taking sedatives (barbiturates) regularly[e]	93.3	93.6	93.0	94.3	95.2	95.4	94.2	94.4	95.1	95.1	95.5	94.9	96.4	95.3	95.3	96.4
Trying one or two drinks of an alcoholic beverage (beer, wine, liquor)	21.6	18.2	15.6	15.6	15.8	16.0	17.2	18.2	18.4	17.4	20.3	20.9	21.4	22.6	27.3	29.4
Taking one or two drinks nearly every day	67.6	68.9	66.8	67.7	68.3	69.0	69.1	69.9	68.9	72.9	70.9	72.8	74.2	75.0	76.5	77.9
Taking four or five drinks nearly every day	88.7	90.7	88.4	90.2	91.7	90.8	91.8	90.9	90.0	91.0	92.0	91.4	92.2	92.8	91.6	91.9
Having five or more drinks once or twice each weekend	60.3	58.6	57.4	56.2	56.7	55.6	55.5	58.8	56.6	59.6	60.4	62.4	62.0	65.3	66.5	68.9
Smoking one or more packs of cigarettes per day	67.5	65.9	66.4	67.0	70.3	70.8	69.9	69.4	70.8	73.0	72.3	75.4	74.3	73.1	72.4	72.8
Vape an e-liquid with nicotine ocasionally[f]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vape an e-liquid with nicotine regularly[f]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Taking steroids	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	90.8
Approximate weighted N =	*2,677*	*2,957*	*3,085*	*3,686*	*3,221*	*3,261*	*3,610*	*3,651*	*3,341*	*3,254*	*3,265*	*3,113*	*3,302*	*3,311*	*2,799*	*2,566*

Table continued on next page.

TABLE 15 (cont.)
Trends in Disapproval of Drug Use in Grade 12

Do you disapprove of people (who are 18 or older) doing each of the following?[a]	Percentage who disapprove or strongly disapprove[b]														
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Trying marijuana once or twice	68.7	69.9	63.3	57.6	56.7	52.5	51.0	51.6	48.8	52.5	49.1	51.6	53.4	52.7	55.0
Smoking marijuana occasionally	79.4	79.7	75.5	68.9	66.7	62.9	63.2	64.4	62.5	65.8	63.2	63.4	64.2	65.4	67.8
Smoking marijuana regularly	89.3	90.1	87.6	82.3	81.9	80.0	78.8	81.2	78.6	79.7	79.3	78.3	78.7	80.7	82.0
Trying LSD once or twice	90.1	88.1	85.9	82.5	81.1	79.6	80.5	82.1	83.0	82.4	81.8	84.6	85.5	87.9	87.9
Taking LSD regularly	96.4	95.5	95.8	94.3	92.5	93.2	92.9	93.5	94.3	94.2	94.0	94.0	94.4	94.6	95.6
Trying ecstasy (MDMA) once or twice[c]	—	—	—	—	—	—	82.2	82.5	82.1	81.0	79.5	83.6	84.7	87.7	88.4
Trying cocaine once or twice	93.6	93.0	92.7	91.6	90.3	90.0	88.0	89.5	89.1	88.2	88.1	89.0	89.3	88.6	88.9
Taking cocaine regularly	97.3	96.9	97.5	96.6	96.1	95.6	96.0	95.6	94.9	95.5	94.9	95.0	95.8	95.4	96.0
Trying crack once or twice	92.1	93.1	89.9	89.5	91.4	87.4	87.0	86.7	87.6	87.5	87.0	87.8	86.6	86.9	86.7
Taking crack occasionally	94.2	95.0	92.8	92.8	94.0	91.2	91.3	90.9	92.3	91.9	91.6	91.5	90.8	92.1	91.9
Taking crack regularly	95.0	95.5	93.4	93.1	94.1	93.0	92.3	91.9	93.2	92.8	92.2	92.4	91.2	93.1	92.1
Trying cocaine powder once or twice	88.0	89.4	86.6	87.1	88.3	83.1	83.0	83.1	84.3	84.1	83.3	83.8	83.6	82.2	83.2
Taking cocaine powder occasionally	93.0	93.4	91.2	91.0	92.7	89.7	89.3	88.7	90.0	90.3	89.8	90.2	88.9	90.0	89.4
Taking cocaine powder regularly	94.4	94.3	93.0	92.5	93.8	92.9	91.5	91.1	92.3	92.6	92.5	92.2	90.7	92.6	92.0
Trying heroin once or twice	96.0	94.9	94.4	93.2	92.8	92.1	92.3	93.7	93.5	93.0	93.1	94.1	94.1	94.2	94.3
Taking heroin occasionally	97.3	96.8	97.0	96.2	95.7	95.0	95.4	96.1	95.7	96.0	95.4	95.6	95.9	96.4	96.3
Taking heroin regularly	97.8	97.2	97.5	97.1	96.4	96.3	96.4	96.6	96.4	96.6	96.2	96.2	97.1	97.1	96.7
Trying heroin once or twice without using a needle	—	—	—	—	92.9	90.8	92.3	93.0	92.6	94.0	91.7	93.1	92.2	93.1	93.2
Taking heroin occasionally without using a needle	—	—	—	—	94.7	93.2	94.4	94.3	93.8	95.2	93.5	94.4	93.5	94.4	95.0
Trying amphetamines once or twice[d]	86.5	86.9	84.2	81.3	82.2	79.9	81.3	82.5	81.9	82.1	82.3	83.8	85.8	84.1	86.1
Taking amphetamines regularly[d]	96.0	95.6	96.0	94.1	94.3	93.5	94.3	94.0	93.7	94.1	93.4	93.5	94.0	93.9	94.8
Trying sedatives (barbiturates) once or twice[e]	90.6	90.3	89.7	87.5	87.3	84.9	86.4	86.0	86.6	85.9	85.9	86.6	87.8‡	83.7	85.4
Taking sedatives (barbiturates) regularly[e]	97.1	96.5	97.0	96.1	95.2	94.8	95.3	94.6	94.7	95.2	94.5	94.7	94.4‡	94.2	95.2
Trying one or two drinks of an alcoholic beverage (beer, wine, liquor)	29.8	33.0	30.1	28.4	27.3	26.5	26.1	24.5	24.6	25.2	26.6	26.3	27.2	26.0	26.4
Taking one or two drinks nearly every day	76.5	75.9	77.8	73.1	73.3	70.8	70.0	69.4	67.2	70.0	69.2	69.1	68.9	69.5	70.8
Taking four or five drinks nearly every day	90.6	90.8	90.6	89.8	88.8	89.4	88.6	86.7	86.9	88.4	86.4	87.5	86.3	87.8	89.4
Having five or more drinks once or twice each weekend	67.4	70.7	70.1	65.1	66.7	64.7	65.0	63.8	62.7	65.2	62.9	64.7	64.2	65.7	66.5
Smoking one or more packs of cigarettes per day	71.4	73.5	70.6	69.8	68.2	67.2	67.1	68.8	69.5	70.1	71.6	73.6	74.8	76.2	79.8
Vape an e-liquid with nicotine ocasionally[f]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vape an e-liquid with nicotine regularly[f]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Taking steroids	90.5	92.1	92.1	91.9	91.0	91.7	91.4	90.8	88.9	88.8	86.4	86.8	86.0	87.9	88.8
Approximate weighted N =	*2,547*	*2,645*	*2,723*	*2,588*	*2,603*	*2,399*	*2,601*	*2,545*	*2,310*	*2,150*	*2,144*	*2,160*	*2,442*	*2,455*	*2,460*

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TABLE 15 (cont.)
Trends in Disapproval of Drug Use in Grade 12

Do you disapprove of people (who are 18 or older) doing each of the following?[a]	Percentage who disapprove or strongly disapprove[b]												
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
Trying marijuana once or twice	55.6	58.6	55.5	54.8	51.6	51.3	48.8	49.1	48.0	45.5	43.1	39.0	-4.1 s
Smoking marijuana occasionally	69.3	70.2	67.3	65.6	62.0	60.9	59.1	58.9	56.7	52.9	50.5	46.7	-3.8
Smoking marijuana regularly	82.2	83.3	79.6	80.3	77.7	77.5	77.8	74.5	73.4	70.7	68.5	64.7	-3.9 s
Trying LSD once or twice	88.0	87.8	85.5	88.2	86.5	86.3	87.2	86.6	85.0	81.7	82.4	78.0	-4.4 s
Taking LSD regularly	95.9	94.9	93.5	95.3	94.3	94.9	95.2	95.3	94.7	92.5	92.4	92.7	+0.3
Trying ecstasy (MDMA) once or twice[c]	89.0	87.8	88.2	88.2	86.3	83.9	87.1	84.9‡	83.1	84.5	84.0	85.1	+1.2
Trying cocaine once or twice	89.1	89.6	89.2	90.8	90.5	91.1	91.0	92.3	90.0	89.0	88.4	88.0	-0.4
Taking cocaine regularly	96.1	96.2	94.8	96.5	96.0	96.0	96.8	96.7	96.3	95.2	94.8	94.8	-0.1
Trying crack once or twice	88.8	88.8	89.6	90.9	89.8	91.4	92.8	91.4	89.3	90.2	90.1	89.7	-0.4
Taking crack occasionally	92.9	92.4	93.3	94.0	92.6	93.9	95.0	93.6	91.9	92.5	92.0	91.8	-0.1
Taking crack regularly	93.8	93.6	93.5	94.3	93.1	94.4	95.4	94.1	92.4	92.8	92.6	92.5	0.0
Trying cocaine powder once or twice	84.1	83.5	85.7	87.3	87.0	88.1	88.7	88.2	85.5	86.4	86.6	85.5	-1.2
Taking cocaine powder occasionally	90.4	90.6	91.7	92.3	91.0	92.2	93.0	91.7	90.4	91.3	90.6	90.3	-0.3
Taking cocaine powder regularly	93.2	92.6	92.8	93.9	92.6	93.8	95.0	94.1	91.7	92.4	92.0	92.2	+0.2
Trying heroin once or twice	93.8	94.8	93.3	94.7	93.9	94.3	95.8	95.6	94.7	94.2	94.1	93.7	-0.4
Taking heroin occasionally	96.2	96.8	95.3	96.9	96.2	96.3	97.0	96.9	96.6	95.3	95.5	95.5	0.0
Taking heroin regularly	96.9	97.1	95.9	97.4	96.4	96.7	97.4	97.4	97.1	96.4	95.7	95.9	+0.2
Trying heroin once or twice without using a needle	93.7	93.6	94.2	94.7	93.2	92.6	95.2	93.7	92.5	92.6	93.8	93.3	-0.6
Taking heroin occasionally without using a needle	94.5	94.9	95.3	95.5	94.5	94.1	95.9	94.6	93.5	92.8	94.0	93.8	-0.2
Trying amphetamines once or twice[d]	86.3	87.3	87.2	88.2	88.1‡	84.1	83.9	84.9	83.1	81.4	82.1	81.9	-0.2
Taking amphetamines regularly[d]	95.3	95.4	94.2	95.6	94.9‡	92.9	93.9	93.2	93.0	92.2	92.2	92.0	-0.2
Trying sedatives (barbiturates) once or twice[e]	85.3	86.5	86.1	87.7	87.6	87.3	88.2	88.9	88.5	87.4	86.5	85.9	-0.5
Taking sedatives (barbiturates) regularly[e]	95.1	94.6	94.3	95.8	94.7	95.1	96.1	95.8	95.0	94.7	94.8	94.4	-0.4
Trying one or two drinks of an alcoholic beverage (beer, wine, liquor)	29.0	31.0	29.8	30.6	30.7	28.7	25.4	27.3	29.2	28.9	28.8	27.2	-1.6
Taking one or two drinks nearly every day	72.8	73.3	74.5	70.5	71.5	72.8	70.8	71.9	71.7	71.1	71.8	70.8	-1.1
Taking four or five drinks nearly every day	90.6	90.5	89.8	89.7	88.8	90.8	90.1	90.6	91.9	89.7	91.1	90.7	-0.3
Having five or more drinks once or twice each weekend	68.5	68.8	68.9	67.6	68.8	70.0	70.1	71.6	72.6	71.9	74.2	72.5	-1.7
Smoking one or more packs of cigarettes per day	81.5	80.7	80.5	81.8	81.0	83.0	83.7	82.6	85.0	84.1	85.3	86.6	+1.3
Vape an e-liquid with nicotine ocasionally[f]	—	—	—	—	—	—	—	—	—	—	—	62.0	—
Vape an e-liquid with nicotine regularly[f]	—	—	—	—	—	—	—	—	—	—	—	71.8	—
Taking steroids	89.4	89.2	90.9	90.3	89.8	89.7	90.4	88.2	87.5	87.8	86.7	88.5	+1.8
Approximate weighted N =	*2,377*	*2,450*	*2,314*	*2,233*	*2,449*	*2,384*	*2,301*	*2,147*	*2,078*	*2,193*	*2,000*	*1,870*	

Table continued on next page.

TABLE 15 (cont.)
Trends in Disapproval of Drug Use in Grade 12

Source. The Monitoring the Future study, the University of Michigan.

Notes. Level of significance of difference between the two most recent classes: s = .05, ss = .01, sss = .001. ' —' indicates data not available. ' ‡ ' indicates that the question changed the following year. See relevant footnote for that drug. Any apparent inconsistency between the change estimate and the prevalence estimates for the two most recent years is due to rounding.

[a]The 1975 question asked about people who are 20 or older.

[b]Answer alternatives were: (1) Don't disapprove, (2) Disapprove, and (3) Strongly disapprove. Percentages are shown for categories (2) and (3) combined.

[c]Beginning in 2014 "molly" was added to the question on disapproval of using MDMA once or twice. 2014 and 2015 data are not comparable to earlier years due to this change.

[d]In 2011 the list of examples was changed from upper, pep pill, bennie, speed to upper, speed, Adderall, Ritalin, etc. These changes likely explain the discontinuity in the 2011 results.

[e]In 2004 the question text was changed from barbiturates to sedatives/barbiturates and the list of examples was changed from downers, goofballs, reds, yellows, etc. to just downers. These changes likely explain the discontinuity in the 2004 results.

[f]Based on two of six forms; N is two times the N indicated.

TABLE 16
Trends in Availability of Drugs as Perceived by 8th Graders

How difficult do you think it would be for you to get each of the following types of drugs, if you wanted some?	Percentage saying fairly easy or very easy to get [a]														
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Marijuana	—	42.3	43.8	49.9	52.4	54.8	54.2	50.6	48.4	47.0	48.1	46.6	44.8	41.0	41.1
LSD	—	21.5	21.8	21.8	23.5	23.6	22.7	19.3	18.3	17.0	17.6	15.2	14.0	12.3	11.5
PCP [b]	—	18.0	18.5	17.7	19.0	19.6	19.2	17.5	17.1	16.0	15.4	14.1	13.7	11.4	11.0
MDMA (e.g. ecstasy, "Molly") [b]	—	—	—	—	—	—	—	—	—	—	23.8	22.8	21.6	16.6	15.6
Crack	—	25.6	25.9	26.9	28.7	27.9	27.5	26.5	25.9	24.9	24.4	23.7	22.5	20.6	20.8
Cocaine powder	—	25.7	25.9	26.4	27.8	27.2	26.9	25.7	25.0	23.9	23.9	22.5	21.6	19.4	19.9
Heroin	—	19.7	19.8	19.4	21.1	20.6	19.8	18.0	17.5	16.5	16.9	16.0	15.6	14.1	13.2
Narcotics other than Heroin [b,c]	—	19.8	19.0	18.3	20.3	20.0	20.6	17.1	16.2	15.6	15.0	14.7	15.0	12.4	12.9
Amphetamines [d]	—	32.2	31.4	31.0	33.4	32.6	30.6	27.3	25.9	25.5	26.2	24.4	24.4	21.9	21.0
Crystal methamphetamine (ice) [b]	—	16.0	15.1	14.1	16.0	16.3	15.7	16.0	14.7	14.9	13.9	13.3	14.1	11.9	13.5
Sedatives (barbiturates)	—	27.4	26.1	25.3	26.5	25.6	24.4	21.1	20.8	19.7	20.7	19.4	19.3	18.0	17.6
Tranquilizers	—	22.9	21.4	20.4	21.3	20.4	19.6	18.1	17.3	16.2	17.8	16.9	17.3	15.8	14.8
Alcohol	—	76.2	73.9	74.5	74.9	75.3	74.9	73.1	72.3	70.6	70.6	67.9	67.0	64.9	64.2
Cigarettes	—	77.8	75.5	76.1	76.4	76.9	76.0	73.6	71.5	68.7	67.7	64.3	63.1	60.3	59.1
Vaping device [e]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
E-liquid with nicotine (for vaping) [e]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Steroids	—	24.0	22.7	23.1	23.8	24.1	23.6	22.3	22.6	22.3	23.1	22.0	21.7	19.7	18.1
Approximate weighted N =		*8,355*	*16,775*	*16,119*	*15,496*	*16,318*	*16,482*	*16,208*	*15,397*	*15,180*	*14,804*	*13,972*	*15,583*	*15,944*	*15,730*

Table continued on next page.

TABLE 16 (cont.)
Trends in Availability of Drugs as Perceived by 8th Graders

How difficult do you think it would be for you to get each of the following types of drugs, if you wanted some?	Percentage saying fairly easy or very easy to get [a]												2016–2017 change
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	
Marijuana	39.6	37.4	39.3	39.8	41.4	37.9	36.9	39.1	36.9	37.0	34.6	35.2	+0.6
LSD	10.8	10.5	10.9	10.0	10.0	9.3	7.5	7.4	6.9	6.6	6.9	6.3	-0.6
PCP [b]	10.5	9.5	10.1	9.1	8.0	7.9	6.7	5.8	5.5	5.1	4.8	4.6	-0.1
MDMA (e.g. ecstasy, "Molly") [b]	14.5	13.4	14.1	13.1	12.9	12.0	9.6	9.5	10.1	9.6	8.7	8.0	-0.7
Crack	20.9	19.7	20.2	18.6	17.9	15.7	14.4	13.7	12.0	11.3	11.1	10.2	-0.9
Cocaine powder	20.2	19.0	19.5	17.8	16.6	14.9	14.1	13.5	11.9	11.6	11.0	10.4	-0.6
Heroin	13.0	12.6	13.3	12.0	11.6	9.9	9.4	10.0	8.6	7.8	8.9	8.1	-0.8
Narcotics other than Heroin [b,c]	13.0	11.7	12.1	11.8‡	14.6	12.3	10.6	9.7	9.2	8.8	8.9	8.9	-0.1
Amphetamines [d]	20.7	19.9	21.3	20.2	19.6‡	15.0	13.4	12.8	12.1	11.8	12.1	11.0	-1.1
Crystal methamphetamine (ice) [b]	14.5	12.1	12.8	11.9	10.9	9.6	8.8	8.5	7.7	6.9	6.6	6.6	0.0
Sedatives (barbiturates) [e]	17.3	16.8	17.5	15.9	15.3	12.6	11.1	10.6	10.0	9.0	9.3	9.2	-0.1
Tranquilizers	14.4	14.4	15.4	14.1	13.7	12.0	10.5	10.4	9.8	9.8	11.4	11.8	+0.4
Alcohol	63.0	62.0	64.1	61.8	61.1	59.0	57.5	56.1	54.4	53.6	52.7	53.2	+0.5
Cigarettes	58.0	55.6	57.4	55.3	55.5	51.9	50.7	49.9	47.2	47.0	45.6	46.2	+0.6
Vaping device [e]	—	—	—	—	—	—	—	—	—	—	—	44.1	—
E-liquid with nicotine (for vaping) [e]	—	—	—	—	—	—	—	—	—	—	—	37.2	—
Steroids	17.1	17.0	16.8	15.2	14.2	13.3	12.5	12.9	11.8	11.6	12.6	11.6	-0.9
Approximate weighted N =	*15,502*	*15,043*	*14,482*	*13,989*	*14,485*	*15,233*	*14,235*	*13,605*	*13,208*	*13,494*	*15,628*	*14,042*	

Source. The Monitoring the Future study, the University of Michigan.

Notes. Level of significance of difference between the two most recent classes: s = .05, ss = .01, sss = .001. ' — ' indicates data not available. ' ‡ ' indicates that the question changed the following year. See relevant footnote for that drug. Any apparent inconsistency between the change estimate and the prevalence estimates for the two most recent years is due to rounding.

[a]Answer alternatives were: (1) Probably impossible, (2) Very difficult, (3) Fairly difficult, (4) Fairly easy, (5) Very easy, and (6) Can't say, drug unfamiliar.

[b]Beginning in 1993, data based on one of two of forms; *N* is one half of *N* indicated. Beginning in 2014 data based on one sixth of *N* indicated. For MDMA only: In 2014 the question text was changed in one form to include "Molly." In 2015 a second from was changed to including "Molly;" data based on one sixth of N indicated in 2014 and on one half of N indicated in 2015. An examination of the data did not show any effect from this wording change.

[c]In 2010 the list of examples for narcotics other than heroin was changed from methadone, opium to Vicodin, OxyContin, Percocet, etc. This change likely explains the discontinuity in the 2010 results.

[d]In 2011 the list of examples for amphetamines was changed from uppers, pep pills, bennies, speed to uppers, speed, Adderall, Ritalin, etc. These changes likely explain the discontinuity in the 2012 results.

[e]Beginning in 2017, data based on one half of *N* indicated.

TABLE 17
Trends in Availability of Drugs as Perceived by 10th Graders

How difficult do you think it would be for you to get each of the following types of drugs, if you wanted some?	Percentage saying fairly easy or very easy to get [a]														
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Marijuana	—	65.2	68.4	75.0	78.1	81.1	80.5	77.9	78.2	77.7	77.4	75.9	73.9	73.3	72.6
LSD	—	33.6	35.8	36.1	39.8	41.0	38.3	34.0	34.3	32.9	31.2	26.8	23.1	21.6	20.7
PCP [b]	—	23.7	23.4	23.8	24.7	26.8	24.8	23.9	24.5	25.0	21.6	20.8	19.4	18.0	18.1
MDMA (e.g. ecstasy, "Molly") [c]	—	—	—	—	—	—	—	—	—	—	41.4	41.0	36.3	31.2	30.2
Crack	—	33.7	33.0	34.2	34.6	36.4	36.0	36.3	36.5	34.0	30.6	31.3	29.6	30.6	31.0
Cocaine powder	—	35.0	34.1	34.5	35.3	36.9	37.1	36.8	36.7	34.5	31.0	31.8	29.6	31.2	31.5
Heroin	—	24.3	24.3	24.7	24.6	24.8	24.4	23.0	23.7	22.3	20.1	19.9	18.8	18.7	19.3
Narcotics other than Heroin [b]	—	26.9	24.9	26.9	27.8	29.4	29.0	26.1	26.6	27.2	25.8	25.4	23.5	23.1	23.6
Amphetamines [d]	—	43.4	46.4	46.6	47.7	47.2	44.6	41.0	41.3	40.9	40.6	39.6	36.1	35.7	35.6
Crystal methamphetamine (ice) [b]	—	18.8	16.4	17.8	20.7	22.6	22.9	22.1	21.8	22.8	19.9	20.5	19.0	19.5	21.6
Sedatives (barbiturates)	—	38.0	38.8	38.3	38.8	38.1	35.6	32.7	33.2	32.4	32.8	32.4	28.8	30.0	29.7
Tranquilizers	—	31.6	30.5	29.8	30.6	30.3	28.7	26.5	26.8	27.6	28.5	28.3	25.6	25.6	25.4
Alcohol	—	88.6	88.9	89.8	89.7	90.4	89.0	88.0	88.2	87.7	87.7	84.8	83.4	84.3	83.7
Cigarettes	—	89.1	89.4	90.3	90.7	91.3	89.6	88.1	88.3	86.8	86.3	83.3	80.7	81.4	81.5
Vaping device [e]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
E-liquid with nicotine (for vaping) [e]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Steroids	—	37.6	33.6	33.6	34.8	34.8	34.2	33.0	35.9	35.4	33.1	33.2	30.6	29.6	29.7
Approximate weighted N =		*7,014*	*14,652*	*15,192*	*16,209*	*14,887*	*14,856*	*14,423*	*13,112*	*13,690*	*13,518*	*13,694*	*15,255*	*15,806*	*15,636*

Table continued on next p

TABLE 17 (cont.)
Trends in Availability of Drugs as Perceived by 10th Graders

How difficult do you think it would be for you to get each of the following types of drugs, if you wanted some?	Percentage saying fairly easy or very easy to get [a]												2016–2017 change
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	
Marijuana	70.7	69.0	67.4	69.3	69.4	68.4	68.8	69.7	66.9	65.6	64.0	64.6	+0.6
LSD	19.2	19.0	19.3	17.8	18.3	16.6	14.9	16.3	14.8	15.5	15.2	15.9	+0.7
PCP [b]	15.8	15.4	14.4	13.4	12.6	12.0	10.2	9.4	8.3	9.0	7.6	7.1	-0.4
MDMA (e.g. ecstasy, "Molly") [c]	27.4	27.7	26.7	25.6	25.7	24.8	21.0	20.7	20.4	19.3	16.3	15.0	-1.3
Crack	29.9	29.0	27.2	23.9	22.5	19.7	18.4	17.1	15.1	14.4	13.9	13.8	-0.1
Cocaine powder	30.7	30.0	28.2	24.7	22.6	20.6	19.2	18.3	16.4	16.1	14.9	15.0	+0.1
Heroin	17.4	17.3	17.2	15.0	14.5	13.2	11.9	11.9	10.9	11.0	10.6	10.6	+0.0
Narcotics other than Heroin [b]	22.2	21.5	20.3	18.8‡	28.7	25.0	24.3	22.5	18.8	19.2	16.8	17.7	+1.0
Amphetamines [d]	34.7	33.3	32.0	31.8	32.6‡	28.5	27.3	26.5	25.2	27.3	22.9	24.2	+1.4
Crystal methamphetamine (ice) [b]	20.8	18.8	15.8	14.0	13.3	11.8	10.7	10.0	9.8	8.9	8.2	8.0	-0.2
Sedatives (barbiturates) [e]	29.9	28.2	26.9	25.5	24.9	22.0	20.2	18.3	16.7	16.6	14.2	15.1	+0.9
Tranquilizers	25.1	24.9	24.1	22.3	21.6	20.8	19.7	18.3	17.5	19.4	20.5	23.3	+2.8 s
Alcohol	83.1	82.6	81.1	80.9	80.0	77.9	78.2	77.2	75.3	74.9	71.1	71.5	+0.3
Cigarettes	79.5	78.2	76.5	76.1	75.6	73.6	72.9	71.4	69.0	66.6	62.9	62.5	-0.5
Vaping device [e]	—	—	—	—	—	—	—	—	—	—	—	66.3	—
E-liquid with nicotine (for vaping) [e]	—	—	—	—	—	—	—	—	—	—	—	60.8	—
Steroids	30.2	27.7	24.5	20.8	20.3	18.8	18.0	17.2	16.5	17.0	15.3	15.0	-0.2
Approximate weighted N =	*15,804*	*15,511*	*14,634*	*15,451*	*14,827*	*14,509*	*14,628*	*12,601*	*12,574*	*15,186*	*14,126*	*12,901*	

Source. The Monitoring the Future study, the University of Michigan.

Notes. Level of significance of difference between the two most recent classes: s = .05, ss = .01, sss = .001. ' — ' indicates data not available. ' ‡ ' indicates that the question changed the following year. See relevant footnote for that drug. Any apparent inconsistency between the change estimate and the prevalence estimates for the two most recent years is due to rounding.

[a]Answer alternatives were: (1) Probably impossible, (2) Very difficult, (3) Fairly difficult, (4) Fairly easy, (5) Very easy, and (6) Can't say, drug unfamiliar.

[b]Beginning in 1993, data based on one of two forms; *N* is one half of *N* indicated. Beginning in 2014 data based on one sixth of N indicated.

[c]Beginning in 1993, data based on one of two of forms; *N* is one half of *N* indicated. Beginning in 2014 data based on one sixth of *N* indicated for MDMA only: In 2014 the question text was changed in one form to include "Molly." In 2015 a second from was changed to including "Molly;" data based on one sixth of N indicated in 2014 and on one half of N indicated in 2015. An examination of the data did not show any effect from this wording change.

[d]In 2011 the list of examples for amphetamines was changed from uppers, pep pills, bennies, speed to uppers, speed, Adderall, Ritalin, etc. These changes likely explain the discontinuity in the 2011 results.

[e]Beginning in 2017, data based on one half of *N* indicated.

TABLE 18
Trends in Availability of Drugs as Perceived by 12th Graders

How difficult do you think it would be for you to get each of the following types of drugs, if you wanted some?	Percentage saying fairly easy or very easy to get [a]															
	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990
Marijuana	87.8	87.4	87.9	87.8	90.1	89.0	89.2	88.5	86.2	84.6	85.5	85.2	84.8	85.0	84.3	84.4
Amyl/butyl nitrites	—	—	—	—	—	—	—	—	—	—	—	—	23.9	25.9	26.8	24.4
LSD	46.2	37.4	34.5	32.2	34.2	35.3	35.0	34.2	30.9	30.6	30.5	28.5	31.4	33.3	38.3	40.7
Some other hallucinogen [b]	47.8	35.7	33.8	33.8	34.6	35.0	32.7	30.6	26.6	26.6	26.1	24.9	25.0	26.2	28.2	28.3
PCP	—	—	—	—	—	—	—	—	—	—	—	—	22.8	24.9	28.9	27.7
MDMA (e.g. ecstasy, "molly") [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	21.7	22.0
Cocaine	37.0	34.0	33.0	37.8	45.5	47.9	47.5	47.4	43.1	45.0	48.9	51.5	54.2	55.0	58.7	54.5
Crack	—	—	—	—	—	—	—	—	—	—	—	—	41.1	42.1	47.0	42.4
Cocaine powder	—	—	—	—	—	—	—	—	—	—	—	—	52.9	50.3	53.7	49.0
Heroin	24.2	18.4	17.9	16.4	18.9	21.2	19.2	20.8	19.3	19.9	21.0	22.0	23.7	28.0	31.4	31.9
Some other narcotic (including methadone) [d]	34.5	26.9	27.8	26.1	28.7	29.4	29.6	30.4	30.0	32.1	33.1	32.2	33.0	35.8	38.3	38.1
Amphetamines [e]	67.8	61.8	58.1	58.5	59.9	61.3	69.5	70.8	68.5	68.2	66.4	64.3	64.5	63.9	64.3	59.7
Crystal methamphetamine (ice)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	24.1
Sedatives (barbiturates) [f]	60.0	54.4	52.4	50.6	49.8	49.1	54.9	55.2	52.5	51.9	51.3	48.3	48.2	47.8	48.4	45.9
Tranquilizers	71.8	65.5	64.9	64.3	61.4	59.1	60.8	58.9	55.3	54.5	54.7	51.2	48.6	49.1	45.3	44.7
Alcohol	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cigarettes [g]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vaping device [g]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
E-liquid with nicotine (for vaping) [g]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Steroids	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Approximate weighted N =	*2,627*	*2,865*	*3,065*	*3,598*	*3,172*	*3,240*	*3,578*	*3,602*	*3,385*	*3,269*	*3,274*	*3,077*	*3,271*	*3,231*	*2,806*	*2,549*

Table continued on next p

TABLE 18 (cont.)
Trends in Availability of Drugs as Perceived by 12th Graders

How difficult do you think it would be for you to get each of the following types of drugs, if you wanted some?	Percentage saying fairly easy or very easy to get [a]														
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Marijuana	83.3	82.7	83.0	85.5	88.5	88.7	89.6	90.4	88.9	88.5	88.5	87.2	87.1	85.8	85.6
Amyl/butyl nitrites	22.7	25.9	25.9	26.7	26.0	23.9	23.8	25.1	21.4	23.3	22.5	*22.3*	19.7	20.0	19.7
LSD	39.5	44.5	49.2	50.8	53.8	51.3	50.7	48.8	44.7	46.9	44.7	39.6	33.6	33.1	28.6
Some other hallucinogen [b]	28.0	29.9	33.5	33.8	35.8	33.9	33.9	35.1	29.5	34.5‡	48.5	47.7	47.2	49.4	45.0
PCP	27.6	31.7	31.7	31.4	31.0	30.5	30.0	30.7	26.7	28.8	27.2	25.8	21.9	24.2	23.2
MDMA (e.g. ecstasy, "Molly") [c]	22.1	24.2	28.1	31.2	34.2	36.9	38.8	38.2	40.1	51.4	61.5	59.1	57.5	47.9	40.3
Cocaine	51.0	52.7	48.5	46.6	47.7	48.1	48.5	51.3	47.6	47.8	46.2	44.6	43.3	47.8	44.7
Crack	39.9	43.5	43.6	40.5	41.9	40.7	40.6	43.8	41.1	42.6	40.2	38.5	35.3	39.2	39.3
Cocaine powder	46.0	48.0	45.4	43.7	43.8	44.4	43.3	45.7	43.7	44.6	40.7	40.2	37.4	41.7	41.6
Heroin	30.6	34.9	33.7	34.1	35.1	32.2	33.8	35.6	32.1	33.5	32.3	29.0	27.9	29.6	27.3
Some other narcotic (including methadone) [d]	34.6	37.1	37.5	38.0	39.8	40.0	38.9	42.8	40.8	43.9	40.5	44.0	39.3	40.2	39.2
Amphetamines [e]	57.3	58.8	61.5	62.0	62.8	59.4	59.8	60.8	58.1	57.1	57.1	57.4	55.0	55.4	51.2
Crystal methamphetamine (ice)	24.3	26.0	26.6	25.6	27.0	26.9	27.6	29.8	27.6	27.8	28.3	28.3	26.1	26.7	27.2
Sedatives (barbiturates) [f]	42.4	44.0	44.5	43.3	42.3	41.4	40.0	40.7	37.9	37.4	35.7	36.6	35.3‡	46.3	44.4
Tranquilizers	40.8	40.9	41.1	39.2	37.8	36.0	35.4	36.2	32.7	33.8	33.1	32.9	29.8	30.1	25.7
Alcohol	—	—	—	—	—	—	—	—	95.0	94.8	94.3	94.7	94.2	94.2	93.0
Cigarettes [g]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vaping device [g]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
E-liquid with nicotine (for vaping) [g]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Steroids	46.7	46.8	44.8	42.9	45.5	40.3	41.7	44.5	44.6	44.8	44.4	45.5	40.7	42.6	39.7
Approximate weighted N =	*2,476*	*2,586*	*2,670*	*2,526*	*2,552*	*2,340*	*2,517*	*2,520*	*2,215*	*2,095*	*2,120*	*2,138*	*2,391*	*2,169*	*2,161*

Table continued on next page

TABLE 18 (cont.)
Trends in Availability of Drugs as Perceived by 12th Graders

How difficult do you think it would be for you to get each of the following types of drugs, if you wanted some?	Percentage saying "fairly easy" or "very easy" to get [a]												
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2016–2017 change
Marijuana	84.9	83.9	83.9	81.1	82.1	82.2	81.6	81.4	81.3	79.5	81.0	79.8	-1.1
Amyl/butyl nitrites	18.4	18.1	16.9	15.7	—	—	—	—	—	—	—	—	—
LSD	29.0	28.7	28.5	26.3	25.1	25.1	27.6	24.5	25.9	26.5	28.0	26.3	-1.7
Some other hallucinogen [b]	43.9	43.7	42.8	40.5	39.5	38.3	37.8	36.6	33.6	31.4	32.5	28.4	-4.0
PCP	23.1	21.0	20.6	19.2	18.5	17.2	14.2	15.3	11.1	13.8	12.6	10.6	-2.0
MDMA (e.g. ecstasy, "Molly") [c]	40.3	40.9	41.9	35.1	36.4	37.1	35.9	35.1	36.1	37.1	32.5	29.3	-3.2
Cocaine	46.5	47.1	42.4	39.4	35.5	30.5	29.8	30.5	29.2	29.1	28.6	27.3	-1.3
Crack	38.8	37.5	35.2	31.9	26.1	24.0	22.0	24.6	20.1	22.0	19.8	18.1	-1.7
Cocaine powder	42.5	41.2	38.9	33.9	29.0	26.4	25.1	28.4	22.3	25.8	22.9	21.3	-1.6
Heroin	27.4	29.7	25.4	27.4	24.1	20.8	19.9	22.1	20.2	20.4	20.0	19.1	-0.9
Some other narcotic (including methadone) [d]	39.6	37.3	34.9	36.1‡	54.2	50.7	50.4	46.5	42.2	39.0	39.3	35.8	-3.5
Amphetamines [e]	52.9	49.6	47.9	47.1	44.1‡	47.0	45.4	42.7	44.5	41.9	41.1	38.0	-3.2
Crystal methamphetamine (ice)	26.7	25.1	23.3	22.3	18.3	17.1	14.5	17.2	13.7	15.3	14.5	13.6	-0.9
Sedatives (barbiturates) [f]	43.8	41.7	38.8	37.9	36.8	32.4	28.7	27.9	26.3	25.0	25.7	23.4	-2.3
Tranquilizers	24.4	23.6	22.4	21.2	18.4	16.8	14.9	15.0	14.4	14.9	15.2	14.9	-0.3
Alcohol	92.5	92.2	92.2	92.1	90.4	88.9	90.6	89.7	87.6	86.6	85.4	87.1	+1.7
Cigarettes [g]	—	—	—	—	—	—	—	—	—	—	—	77.9	—
Vaping device [g]	—	—	—	—	—	—	—	—	—	—	—	78.2	—
E-liquid with nicotine (for vaping) [g]	—	—	—	—	—	—	—	—	—	—	—	75.0	—
Steroids	41.1	40.1	35.2	30.3	27.3	26.1	25.0	28.5	22.0	23.7	21.3	20.1	-1.2
Approximate weighted N =	*2,131*	*2,420*	*2,276*	*2,243*	*2,395*	*2,337*	*2,280*	*2,092*	*2,066*	*2,181*	*1,958*	*1,882*	

Source. The Monitoring the Future study, the University of Michigan.

Notes. Level of significance of difference between the two most recent classes: s = .05, ss = .01, sss = .001. ' — ' indicates data not available. ' ‡ ' indicates that the question changed the following year. See relevant footnote for that drug. Any apparent inconsistency between the change estimate and the prevalence estimates for the two most recent years is due to rounding.

[a]Answer alternatives were: (1) Probably impossible, (2) Very difficult, (3) Fairly difficult, (4) Fairly easy, and (5) Very easy.

[b]In 2001 the question text was changed from other psychedelics to other hallucinogens and shrooms was added to the list of examples. These changes likely explain the discontinuity in the 2001 results.

[c]Beginning in 2014 "molly" was added to the question on availability of Ecstasy (MDMA). An examination of the data did not show any effect from this wording change.

[d]In 2010 the list of examples for narcotics other than heroin was changed from methadone, opium to Vicodin, OxyContin, Percocet, etc. This change likely explains the discontinuity in the 2010 results.

[e]In 2011 the list of examples was changed from uppers, pep pills, bennies, speed to uppers, speed, Adderall, Ritalin, etc. These changes likely explain the discontinuity in the 2011 results.

[f]In 2004 the question text was changed from barbiturates to sedatives/barbiturates and the list of examples was changed from downers, goofballs, reds, yellows, etc. to just downers. These changes likely explain the discontinuity in the 2004 results.

[g]Data based on 2 of 6 forms. N is twice the N indicated.

Monitoring the Future website:
http://www.monitoringthefuture.org

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On the Safety of E-cigarettes: “I can resist anything except temptation”1

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Comment

On the Safety of E-cigarettes: "I can resist anything except temptation"[1]

Robert D. Combes and Michael Balls

Strategic policy decisions are being made about e-cigarettes, based on the plausibility of their greater safety, rather than on essential scientific evidence which would permit a proper risk assessment. If e-cigarettes are really 'safer', then their use should be recommended, but only after an intelligent analysis of their risk to human health, based on integrated in silico, in vitro *and clinical studies for both scientific and logistical reasons*

Concern Raised by Public Health England's Proposal for ECs to be Available on the NHS

In a Comment article published in the September 2015 issue of *ATLA*,[2] we expressed our concern that, although we welcomed the prospect of new tobacco-related products aimed at reducing harmful exposures, it appeared that new regulations would require that their relatively greater 'safety' would have to be established via complex testing regimes which would be heavily reliant on traditional animal procedures of doubtful relevance and reliance. We argued that, instead, the focus should be on the intelligent and integrated use of non-animal *in silico*, *in vitro* and clinical studies.

Just before our article went to press for publication, Public Health England (PHE; a UK executive agency, sponsored by the Department of Health) proposed that electronic cigarettes (ECs), a non-tobacco alternative to smoking, should be made available via the NHS (National Health Service),[3] as a means of reducing the general incidence of disease and harm attributable to conventional smoking.

We found that there was an increasingly heated debate about the safety of ECs, between those that want their use encouraged and endorsed with little delay, and others who urge caution. The PHE proposal is a classic example of the temptation of short-term gain irrespective of the possibility of long-term pain.[4] It is dangerous, because the relatively greater safety of ECs has not been scientifically established — and regrettable, because it is likely that other authorities, notably those on the other side of the Atlantic, are likely to insist on the introduction of complex testing regimes which will require animal testing, as is the case for new smoking materials.[2]

Background

PHE's proposal is a matter of concern, mainly because of the lack of safety data and the resulting inability to perform any sort of risk assessment of the type normally undertaken for consumer products, as well as doubts concerning the relevance of the data on the impact of ECs on smoking habits. In addition, our review was not specifically on ECs, as a consequence of which there is other, relevant published information on usage and safety, which needs to be considered. We now take this opportunity to elaborate on our initial response, and on our reasons for urging caution, in the light of recent developments regarding ECs, both at home and in the USA.

This issue needs to be resolved urgently, since the popularity of ECs is rapidly gaining ground, especially with young people, at the expense of tobacco smoking, largely on the assumption that ECs either lack many of the toxic constituents, contaminants and by-products to which conventional smokers are exposed, or that these substances are encountered at sufficiently low concentrations so as to cause no health problems. Moreover, an update on the situation with ECs is timely since: a) the FDA is about to be charged with responsibility for regulating ECs in the USA (http://www.fda.gov/TobaccoProducts/ Labeling/ ucm388395.htm); b) as we write, the *Third Summit on Electronic Cigarettes* has just taken place in London (http://www.e-cigarette-summit.com/); and c) the UK (via the Department of Health and the Medicines and Healthcare Products Regulatory Agency [MHRA]) has a deadline of May 2016 to complete the process of transposing into its national legislation, the EU revised Tobacco Products Directive (http://ec.europa.eu/health/ tobacco/ docs/ dir_201440_en.pdf), which came into force in May 2014.

The situation regarding ECs is also highly relevant to the Three Rs, since we have the prospect of significant levels of safety testing, some of which could involve traditional animal tests, highly invasive procedures and the use of non-human primates, to satisfy new regulatory requirements in Europe and the USA.[2] Although, after careful consideration, we believe that more information is required before ECs become incorporated into strategies for tackling the burden of disease and ill-health due to tobacco smoking, we feel that most, if not all, of the required data could be obtained in a more-timely way by implementing a strategy focused on the coordinated use of chemical, *in vitro* and clinical methods. Moreover, because the information will have largely been obtained by using organotypic tissue culture systems comprised of cells from the target tissues and species, it will be of direct relevance to assessing risk levels arising from the use of ECs.

The Controversy

Understandably, PHE's suggestion has provoked considerable discussion and controversy, while being generally welcomed by those who see ECs as a quick solution to the smoking and health problem. To illustrate the type of approach being taken by some stakeholders to address the EC issue, we quote the opening sentence of what looks like an internal report on the burdens of regulating ECs, but dated September 2013,[5] which states that: *E-cigarettes are very low risk alternatives to cigarettes, used by smokers as a pleasurable way of taking the relatively harmless recreational drug, nicotine*. However, we were unable to find any evidence, or citations to original articles presenting toxicity data, in support of such a potentially far-reaching statement by the authors in their 26-page document, which, essentially, urges the UK Government to resist being overburdened with EU regulations for ECs — requirements which, in the authors' opinion, are unnecessary, because they could delay the take-up of ECs by the public. The authors qualify the risk level, by claiming it is 'very low', again without any reference to quantitative hazard data — most extraordinary!

In direct contradiction, and two years following publication of that statement, our in-depth appraisal[2] of the use, safety assessment and regulatory control of tobacco-related products in general, including ECs, leads us to believe that, whatever the long-term consequences of any such policy, or however worthy the ultimate objective of PHE may be, it is, *in the light of current knowledge*, a reckless and irresponsible suggestion.

Poor Reporting

PHE's justification for its proposal relies heavily on two reports which it commissioned, and which were not peer-reviewed.[6,7] It ignores the possibilities that users might be repeatedly exposed to hitherto undetected contaminants and by-products, as well as to carcinogenic chemicals, or their precursors (which have been detected in solvent extracts and vapours, and which are derived from tobacco during solvent extraction or generated during solvent heating), that can have effects at very low dose levels, following repeat exposures, which can occur without clear threshold doses, thus necessitating zero-dose extrapolation.[8] Also, the PHE report contains information on the likely adoption and use of e-cigarettes by existing and potential smokers that could be of questionable relevance to the UK. This is because this information is derived from experience in other countries, with differing attitudes to smoking, or it applies to other tobacco-related products that are used mainly elsewhere, or it is conflicting, or merely circumstantial.

On comparing our Comment[2] with the PHE document, as well as looking at data that were published before the document was released, we have found that some key references are missing from it, or have been selectively covered, with the omission of some important information. For example, we have previously discussed evidence of the presence in vapours of some tobacco-specific nitrosamines (TSNAs), but the PHE report, which included the same reference,[9] omitted any mention of the analytical data for such chemicals. There are several other reports of the detection of TSNAs in ECs,[10,11] but there is no discussion in the PHE report of the potential role of such contaminants, some of which are highly-potent genotoxins[12] in the aetiology of lung cancer. In fact, cancer is not specifically mentioned anywhere in relation to safety, and there is no record of published reports of exposure to additional substances, such as nanoparticles (NPs) derived from metals[13] (also see Combes and Balls[2]). NPs, together with certain other chemicals, have been linked to respiratory sensitisation and mechanistically-related diseases, such as chronic obstructive pulmonary disease. Sensitisation is another endpoint for which clear thresholds for induction doses are difficult to identify.[14] This might be because they do not exist, as with genotoxins, or because of technical deficiencies, but either way, this complicates risk assessment.

The omission by PHE of several key papers and information from a report that was intended to be used to determine public health policy on the basis of the evidence available, is completely inexcusable. This is especially the case, as the above facts combined suggest that there is a tangible, and, at

present, unquantifiable, risk that repeated and prolonged exposure to even low doses of such chemicals, as would be expected to occur as a result of using ECs, could be sufficient to trigger cellular changes eventually culminating in serious conditions, sometimes not manifested until some considerable time following the onset of exposure.

With regard to the possibility of the presence of undetected chemicals, some of which could be toxic, it is worth noting that very few of the analytical methods in use have been validated for the purpose in question, which could, in part, explain the relatively high levels of variation seen between EC brands, and which also could account for the variation experienced within experiments.

The PHE report also fails to mention one of the main findings of the earlier investigations into the safety of ECs, namely, that different brands can vary substantially in the levels of contaminants, by-products and active components (e.g. nicotine), such that there is an urgent need for more harmonisation of the different products available.[3]

A reminder of how difficult it can be to predict the adverse effects of complex mixtures, such as EC aerosols and liquids, is provided by a recent study[15] on the potential modulating influence of nicotyrine, a product present in tobacco which also arises in EC fluids as a result of slow oxidation of nicotine. This chemical is an inhibitor of cytochrome (CYP) isozymes (CYP P450 mixed function oxidases), which clear nicotine from the body and are active in both hepatic and extrahepatic systems. The authors noted that the metabolism of all of the substrates of the respective isozymes will be affected by nicotyrine. It so happens that one of these substrates is the TSNA, nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK),[12] one of the most potent of the known lung carcinogens in tobacco smoke. This substance is activated in airway cells, both *in vitro* and *in vivo*, by CYP2A13,[12] suggesting a potential anti-carcinogenic effect of nicotyrine, at least for this particular mechanistic pathway.

Neither our Comment,[2] nor the PHE report, referred to a review, published in April 2014, on the toxicity of ECs.[16] The authors of this review concluded that: *The available evidence suggests that these products are by far a less harmful alternative to smoking and significant health benefits are expected in smokers who switch from tobacco to electronic cigarettes.* However, while this seems to be good news, the authors admitted that only very few toxicological studies were available to them. Also missing from the PHE report is reference to an unpublished, but comprehensive 19-page document, available on the Internet,[17] which summarises various aspects of ECs, including safety issues.

The PHE report went considerably further than merely saying that ECs are safer than conventional smoking, by providing a quantitative estimate of the extent of this alleged greater safety. It claimed that ECs are up to 95% safer than conventional smoking, and that: *Best estimates show e-cigarettes are 95% less harmful to your health than normal cigarettes, and when supported by a smoking cessation service, help most smokers to quit tobacco altogether*. Later on, the report states that: *Acknowledging that the evidence base on overall and relative risks of EC in comparison with smoking was still developing, experts recently identified them as having around 4% of the relative harm of cigarettes overall (including social harm) and 5% of the harm to users.*

Misuse of Information

While these two statements are not referenced, it emerges later in the report that they are based on the outcome of a multi-criteria decision analysis (MCDA) study, in which a small group of experts considered the harms to human health and well-being posed by using a wide range of tobacco products.[18] Each product was ranked on a scale which put cigarette smoking top at almost 100% for several properties, including addiction and cancer. The authors stated that: *Within the tobacco products there was a gradual reduction in harm from water pipe, smokeless unrefined, smokeless refined to snus that has 5% of MRH. Among the purer non-tobacco vehicle products ENDS were rated to have only 4% of MRH and for the even purer NRTs the MRH was only rated at about 2%.* [where ENDS = electronic nicotine delivery systems; MRH = maximum relative harm; and NRTs = pharmacological replacement products.]

PHE then used the outcome of this study, as if it were equivalent to experimental data, to derive the 95% figure. Apart from being baffled by how any quantitative risk assessment can be made with the paucity of available hazard data, we are uncertain as to how to interpret the intended meaning of such a statement, other than by concluding that PHE believes that ECs are almost twice as safe as tobacco smoking. The quantification of risk in toxicology, although not a precise process by any means, implies some greater confidence in a particular prediction than is conveyed by a mere qualitative statement, and it has to be derived from detailed quantitative hazard data. However, in this case, the information was merely generated by an *ad hoc* group of experts, and was based on opinions, rather than being grounded in scientific observation.

Moreover, there are many difficulties with the MCDA approach in general, and in particular, with the above application of it.[2,19] This implies that the validity of its outcome is very questionable, being dependent on the amount and rele-

vance of pre-existing information, subject to much value judgement, and difficult to reproduce with a different set of experts, and with the same ill-defined criteria used to assess relative harm. We also noted one inescapable problem, which relates to the large bias in the overwhelming amount of available data on cigarette smoking compared to that on ECs. It is difficult to see how such an imbalance could be compensated for in practice, but it greatly complicates any comparison of the two types of products. The results from an MCDA study should be used only for what they are, that is, *predictions*, rather than as novel experimental data, which they certainly are not. MCDA is part of the analysis of evidence, rather than being an additional source of evidence *per se*.

Another UK study, investigating the perception of relative harm from the use of ECs,[20] involved recording the views of cohorts of smokers and ex-smokers given ECs, and involved standard statistical methods to estimate changes in perception over a three-year period. It was found that the proportion perceiving ECs to be less harmful than cigarettes decreased significantly over the period 2013 to 2014. Unsurprisingly, a major preliminary conclusion of the study was that: *Clear information on the relative harm of cigarettes and e-cigarettes is needed*. Another human study, a randomised controlled trial,[21] found that ECs, with or without nicotine, were only moderately good at assisting smokers to quit. The authors noted that: *Uncertainty exists about the place of e-cigarettes in tobacco control, and more research is urgently needed to clearly establish their overall benefits and harms.*

Like McKee and Capewell,[22] we doubt that the 95% figure can be given any scientific credibility, mainly due to the way in which it was derived. We go further, in saying that the statement is misguided and misleading. It is tempting to even suspect that the latter was used intentionally, as intimated by Kirby,[23] who summed up the situation well, if somewhat rather benevolently, thus: *While the PHE report contains many caveats, albeit subtle and largely missing from the media coverage, it has uniformly adopted the most favourable interpretation of the very limited evidence, rejecting the precautionary principle.*

In response to criticism of the 95% figure,[24] Professor John Britton (chair of the Royal College of Physicians Tobacco Advisory Group and co-chair of the PHE Tobacco Control Implementation Board, and also a co-author of one of the reports on ECs that was commissioned by PHE), suggested that, rather than dwell on an exact percentage figure, the real point is that ECs are substantially safer than tobacco smoking.[25] This begs the following question: If the 95% figure is not meant to be interpreted literally, why include it in the report, unless the aim was to have a headline for gaining publicity, with a view to persuading us all to accept the proposal without further questioning? However, in truth, as we have argued above, there is no *evidence* for the 95% estimate. Moreover, doubts have been expressed about the integrity and objectiveness of the MCDA study, due to the alleged conflicts of interest of some of its authors.[26] Unfortunately, little further information is available, and this fact, together with the other general drawbacks of implementing MCDA, discussed earlier, suggest that extreme caution should be exercised when considering the outcome. A similar issue with conflict of interest was encountered by Pisinger and Døssing,[27] when they found the problem to have arisen in some 34% of the 76 studies relating to EC safety that they reviewed. These authors could draw no firm conclusions from the information, due to high levels of data inconsistency, but they did state that: *Electronic cigarettes can hardly be considered harmless.* This study, incidentally, is yet another key publication missing from the PHE document.

What is Needed is a Role for Alternative Methods

Predictably, few, if any, of the small number of toxicity studies that have been published to date consist of medium-term to long-term investigations. The issue of chronic toxicity due to vaping has been noted by others, including, for example, Rowell and Tarran,[28] who recently discussed the lack of data relating to the ability of chronic exposures to ECs to induce serious lung disease. The need to take into account long-term consequences of EC use also applies to efficacy as well as safety, as Unger notes in a recent editorial: *Longitudinal studies are not yet available to assess the long term effects of e-cigarettes on health or their usefulness as a cessation tool.*[29] Some four years ago, Etter *et al.*[30] stated that ECs had not been adequately tested for safety or efficacy, and the situation has not altered very much since then. Until further studies of high quality and integrity are conducted, the marketing of ECs poses unknown health and safety concerns, particularly because the products available are extremely diverse, many of them on the market are not regulated, and no oversight of quality control is in operation.

While we understand that there is an urgent need to have more safety information, we believe that there is a better way of obtaining it than having several individuals sitting at a table trying to predict the harms of these products, when they have very little reliable information on which to base their decisions. Instead, we suggest the strategy which we have outlined previously,[2] involving an intelligent, integrated testing scheme, comprised mainly of chemical analysis, *in vitro*

methodologies and human/clinical studies. Such an approach would also expedite testing, particularly since traditional *in vivo* methods are often lengthy and their relevance and reliability are highly questionable.

The numbers of publications on *in vitro* studies with EC vapours are increasing (http://www.ashscotland.org.uk/what-we-do/supply-information-about-tobacco-and-health/tobacco-related-research/research-2015/e-cigarettes-2015/). In general, the data are promising, in that, for example, one paper[31] shows that several vapours exhibit substantially less activity in cytotoxicity testing and in a range of genotoxicity assays, compared with that exhibited by cigarette smoke. Other, more-recent studies, one involving the MatTek™ epithelial airway model, confirm the substantially lower cytotoxicity of vapours, and also demonstrate that this applies to airway cells in culture[32] (http://vaperanks.com/big-tobacco-study-claims-e-cigarette-vapor-is-as-harmless-to-human-airway-tissue-as-plain-air/).

However, while all this is encouraging, a glance at the Vape Ranks website (presenting news on ECs, rankings and reviews [www.http://vaperanks.com/]) shows that there is no shortage of other reports which raise legitimate safety concerns relating to ECs, that warrant further investigation. Among such reports are an increasing number of cases where ECs are being used to 'smoke' marijuana, a potentially worrying development (see, for example, Murphy[33]). Some of the investigations conducted *in vitro* also suggest that acute toxic effects could be caused by vaping. For example, a study in which cultures of human gingival fibroblasts were exposed to nicotine-containing or nicotine-free EC fluids, increased the production of reactive oxygen species (ROS) after 24 hours, along with an elevated expression of the *Bax* gene (an early indicator of apoptosis), followed by apoptosis itself, after 48 hours of exposure.[34] The authors concluded that such exposures could lead to periodontitis, but, in addition, the induction of such cellular changes could presage other, more-serious long-term toxicity.

An important part of the integrated testing strategy that we have proposed, involves human clinical studies, which have been undertaken for both efficacy and safety testing (the latter uniquely possible with tobacco and tobacco-related products, at an early stage), rather than following extensive preclinical testing, as with pharmaceuticals (see Combes and Balls[2]). Encouraging results were obtained in some of the first human studies (reviewed in Caponnetto *et al.*[35]), with high levels of tolerance and acceptance of the new products by existing smokers and non-smokers, as well as low incidences of side-effects or of overt signs of toxicity.

However, some subsequent studies have revealed several potential effects which cause concern. One example is an investigation[36] with smokers and non-smokers that involved monitoring changes in plasma nicotine and carbon monoxide (CO) concentration, and heart rate. One brand of ECs increased each of these parameters within the first five minutes of administration, an example of an acute adverse effect caused by vaping. Other evidence that ECs can exert acute effects on users, following brief exposures, was clearly demonstrated in a clinical study,[37] in which: a) non-smokers, using an EC for ten minutes, experienced elevated airway resistance; b) current regular smokers exhibited a significant rise in airway resistance after using an EC for ten minutes; and c) neither COPD nor asthma patients were affected (www.medicalnewstoday.com/articles/ 249784.php). In a blog, Phillips has questioned the relevance of these results.[38] However, although chemicals causing this effect may not elicit an immune response, the changes seen serve as biomarkers of lung exposure and of changes therein that could result in serious health consequences.

Another investigation, still ongoing, involves cohorts of smokers and non-smokers. At the 12-month stage, the results suggest that vaping has little effect on helping smokers to quit.[39] However, the trial is not scheduled to be completed until 2019. It is monitoring self-reported side-effects, and, hopefully, will include an assessment of biomarkers of disease and toxicity.

Nowhere are conflicting views regarding the safety of ECs more sharply delineated than by the different approaches to their use and regulation that are emerging in markets on either side of the Atlantic (reviewed in Combes and Balls[2]). On the one hand, in the UK, some Government agencies appear too ready to approve and promote the use of such products, without going through the necessary standard checks and balances, while, on the other hand, in the USA, the FDA is about to take over the regulation of ECs by subjecting them to a rigorous and formal assessment.

It was on 25 April 2014 that the FDA published a proposed rule, *Deeming Tobacco Products to be Subject to the Federal Food, Drug, and Cosmetic Act*. The period between then and now has been taken up by: a) a 75-day public comment period, which ended on 9 July 2014; b) an extension of the public comment period by 30 days, taking us to 8 August 2014; c) an unknown time delay for consideration and decision by the Agency of additional requests to extend the comment period a second time (which was not granted); and d) the analysis of comments (undisclosed time). Despite these delays, the question concerning the FDA's regulation of ECs is 'when', rather than 'if'. The latest information we can find is an entry in *The Hill* (the website presenting news of US Congress activities) in May 2015, where it is reported that Senator

Richard Blumenthal (D-Conn.) is giving the FDA until the end of the summer 2015 to finalise its deeming regulations for all tobacco products, including ECs and cigars (http://thehill.com/regulation/242125-fda-has-summer-to-finalize-tobacco-deeming-regs-sen-dem-says).

Once the FDA assumes responsibility for ECs for recreational use (it already regulates such products intended for therapeutic purposes), its approach to ECs would appear to be clear from its website (http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm172906.htm). This states that: *E-cigarettes have not been fully studied, so consumers currently don't know: the potential risks of e-cigarettes when used as intended; how much nicotine or other potentially harmful chemicals are being inhaled during use, or whether there are any benefits associated with using these products. Additionally, it is not known whether e-cigarettes may lead young people to try other tobacco products, including conventional cigarettes, which are known to cause disease and lead to premature death.*

This viewpoint is essentially one that we share, and, although we are not in favour of testing just for the sake of it, we fervently believe that it is very simplistic and premature, at this time, to base important public health decisions of the sort currently being proposed by PHE, on inadequate evidence of safety and/or potentially irrelevant and unreliable extrapolation. On the other hand, while we concur with FDA's overall assessment of the situation regarding ECs, we take issue with the way in which the Agency intends to regulate tobacco-related products, especially via the use of the substantial equivalence concept.[2] In addition, our views on the availability of data are shared by other organisations, notably the American Association for Cancer Research and the American Society of Clinical Oncology,[40] and the BMA.[41]

The official EU position on ECs is not clear at this time. The revised EU Directive on the marketing and use of tobacco products merely requires that manufacturers take responsibility for the safety of such products. However, we understand that, in the UK, once the Directive has been transposed into UK legislation, a process that will be facilitated by the Department of Health, the MHRA will become the competent authority (Dr Ian Hudson, personal communication, 2015) for ECs intended for medicinal purposes, which include quitting smoking. Accordingly, the MHRA will regulate such products in the same way that it does medicines. Indeed, the MHRA website has now documented data requirements for ECs (http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con454361.pdf), where it is stated (for preclinical studies) that: *The potential transformation of the formulation on thermal decomposition, and the potential for the heating element and associated components (including adhesives and solder) to shed metallic and other particles on heating, would warrant further investigation by the applicant to assess the inhalation safety risks and to limit exposure where necessary. In addition, the applicant should provide a detailed safety review of all the components in the formulation from the available literature; in particular a review of the safety following inhalation exposure (including long-term exposure) would be relevant. A comprehensive evaluation of the potential extractables and leachables originating from all components of the electronic cigarette should also be provided, with associated toxicological review.* For clinical studies, for some unaccountable reason, the focus is on the levels of nicotine in the body and its pharmacodynamics, to ensure that endogenous levels do not exceed maximum safe levels. We feel that this represents a missed great opportunity for undertaking biomarker and biomonitoring safety studies on vapours in the clinical setting, as we have explained in more detail elsewhere.[2]

How these regulations are going to be applied in practice after the various stakeholders and pressure groups, including the tobacco industry, have argued their various standpoints remains to be seen. However, if the MHRA sticks to its procedures and requirements for new medicines, it should be the case that: a) if the supporting toxicological data are deemed relevant and suitable, there will be no need for further testing and/or review; and b) where this is not so, or where data are missing, such information would have to be obtained by toxicity testing, according to International Conference on Harmonisation (ICH)-approved regulatory test methods for new medicinal products. Whether any products currently on the market will receive exemption is a matter of conjecture at this time. Therefore, we are now confronted by a ludicrous situation, whereby two UK Government authorities, the MHRA and PHE, both with the responsibility for safeguarding public health, are giving out different messages — the former has the remit of controlling the sale of the ECs according to international regulatory requirements, while the latter endorses the use of ECs now. Furthermore, the PHE report and its associated documents can be downloaded from the MHRA website — no wonder there is so much confusion!

Some notes on the presentations given at the Third E-Cigarette Summit, have been posted on the web (http://www.ecigarettedirect.co.uk/ashtray-blog/wp-content/uploads/2015/11/E-Cig-Summit-3-PDF.pdf). The notes provide a preliminary impression that the debate shows no signs of letting up, although it would appear that there is a growing admission among the protagonists that ECs are not harmless, and, among those looking at health

effects, that they are probably safer than smoking, but by how much it is difficult to tell. Perhaps we could be heading in the right direction, after all. We should get a better idea once the presentations have been uploaded to the resources section of the summit's website.

Concluding Comments

We are puzzled by: a) why there is such a gulf between the UK and the USA in approaches to regulating ECs; and, more importantly, b) why the fundamentals of toxicology, underpinning public health and safety, involving hazard identification and risk assessment,[42] seem to have been ignored by PHE, and are being overlooked in the ongoing debate by a growing number of stakeholders and so-called experts, when the same are usually so rigorously applied to other consumer products.

Calls endorsing the wider usage of ECs are being driven by two main factors, both of which cannot be supported on scientific grounds: a) an understandable, but misguided, wish for having a quick fix for the major health problems associated with smoking; and b) a mistaken belief that there is no need to test complex mixtures, such as EC liquids and vapours, when the levels of ingredients, whose presence and contribution to toxicity are known, are at very low concentrations. If this were possible, most of toxicology would now merely consist of chemical analysis of test samples, except in rare cases where the threshold of regulation concept[43] can legitimately be applied — for example, when synergistic or antagonistic effects between constituents can be accommodated.

One way in which risk assessment can be approached is to derive likely exposure levels from analytical data on the constituents of vapours and compare them with recommended maximum allowable daily intake figures for humans, obtained from safety tests. However, since most of the information relates to data obtained under laboratory conditions, mainly with rodents, sometimes involving different routes of exposure, it has to be extrapolated and scaled up to be relevant to human populations, and adjusted to provide for an extra margin of safety. Moreover, predicting exposure levels is confounded by individual differences in the way in which ECs are used, the extent to which they are used, the differences in design and composition of ECs, the degree of vapour inhalation, and variation in the biotransformation of inhaled constituents, and also by the possible endogenous generation of more TSNAs from vaped nicotine.[44]

It has been noted elsewhere (http://www.tobacco.ucsf.edu/9-chemicals-identified-so-far-e-cig-vapor-are-california-prop-65-list-carcinogens-and-reproductive-t) that nine constituents variously found in EC fluids and/or aerosols, are listed by the Environmental Protection Agency (EPA) of the US State of California as being of concern with regard to human safety, as part of the Agency's drive to improve and simplify the regulation of environmental chemicals. These chemicals are: acetaldehyde, cadmium, formaldehyde, isoprene, lead, nickel, nicotine, N-nitrosonornicotine (NNN) and toluene. NNN is widely considered to be a carcinogen in tobacco smoke. As a worse-case scenario, we have taken the threshold value of concern for this chemical (which the EPA has identified from rodent carcinogenicity studies, after adjustments for species and test system extrapolation), to have a NSRL (non-significant risk level) of 0.5μg/day (NSRL is the level of exposure that would result in no more than one excess case of cancer in 100,000 individuals exposed to the chemical). We have compared this figure with the amount of NNN that different ECs users might be expected to be exposed to, based on the maximum levels of chemical reported in Gureckis and Love,[4] which is 4.3μg/150 puffs (equivalent to 14.3μg/day for a user taking 500 puffs/day). As the respective NSRL value is 0.5μg/day, the expected exposure under these conditions exceeds the level of concern by almost 30-fold. Presumably, such a result would raise the possibility that ECs with similar constituent profiles could prompt the EPA in California to require appropriate product labelling as a precondition for marketing approval. We stress, however, that these are preliminary data, subject to several uncertainties, not the least of which are vaping behaviour and individual susceptibility, and we plan to investigate risk assessment in more detail for more ECs, and also for other risk assessment methods, such as the Margin of Exposure (see Hahn *et al.*[45]).

The more and more we read, the more convinced we are that the whole debate about ECs is premature, and would not be happening with other, equally dangerous consumer products, in the absence of powerful lobbying on behalf of industry. The title of the PHE report includes the phrase *...foundation for evidence-based policy and practice.* This sounds great, until one realises that the foundation is very weak indeed, having been built on sand, in the words of McKee and Capewell,[22] and that the evidence used was incomplete, conflicting, and used selectively. It is crucial that these new types of products are labelled appropriately and accurately, not only with regard to their benefits, but also with appropriate and proportionate warnings of any hazards to which users may be exposed. This will only be possible after there has been a full and scientifically-sound investigation of the toxicity of these products.

We seem to be living in a world now where the term *evidence-based* increasingly seems to be being used to imply some new revelatory approach to

scientific activity that guarantees high quality. We have 'evidence-based medicine' and, more-recently, 'evidence-based toxicology', and now: 'evidence-based public health' and 'evidence-based regulation'. But, in truth, of course, *evidence-based* is not a new concept, nor is it a panacea for quality — any thorough scientific piece of work is only as good as the evidence on which it is based. What does appear to be new is the attempt to use the phrase as a smokescreen for sub-standard scientific investigation, otherwise there would be no need to use it at all!

We leave the last word to the British Heart Foundation (BHF), by quoting from a booklet entitled *10 Minutes to Change Your Life — Time to Quit*, which is available in its high-street charity shops or from its website (https://www.bhf.org.uk/~/media/files/publications/smoking/g925_time_to_quit_01_14_booklet_chart.pdf). This states that: *E-cigarettes allow you to breathe in nicotine vapour. Unlike tobacco smoke, this nicotine [vapour] doesn't contain many of the chemicals that cause cancer and heart disease. But scientists don't know yet if e-cigarettes can help you quit or if they cause any long-term damage to your health.*

Simple, clear, informative and correct — this is where the debate needs to start and it is why the temptation for a quick fix to the smoking issue must be resisted!

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ANALYSIS

Evidence about electronic cigarettes: a foundation built on rock or sand?

Public Health England recently endorsed the use of e-cigarettes as an aid to quitting smoking. **Martin McKee** and **Simon Capewell** question the evidence on safety and efficacy underpinning the recommendations

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Those responsible for safeguarding the health of the public must often tackle complex and controversial issues. Public Health England (PHE) has been courageous in entering the debate on the role of electronic cigarettes in tobacco control. In a new report it concludes that e-cigarettes are much safer than conventional cigarettes,[1] and one of its author is quoted as describing them as a potential "game changer" in tobacco control.[2] Media coverage suggests that the debate is now over, with a BBC correspondent describing the evidence as "unequivocal."[2] However, although British organisations such as the Royal College of Physicians of London[3] and ASH UK,[4] have endorsed some of the report's conclusions, albeit with caveats, many others have come to the opposite opinion. These include the British Medical Association, the UK Faculty of Public Health, the US Centers for Disease Control and Prevention, the American Lung Association, the World Health Organization,[5] the European Commission,[6] and other leading international health bodies.[7] The available evidence about e-cigarettes suggests that the debate is far from over and questions remain about their benefits and harms.

Defining the role of e-cigarettes

Fundamental divisions seem to exist between those engaged in this debate. Supporters of e-cigarettes focus narrowly on existing smokers, comparing the devices' effects with those of smoking conventional cigarettes. As well as being an aid to quitting, e-cigarettes are seen as having a role for people who do not want to quit, offering a safer substitute for some of the cigarettes they would otherwise smoke.

Meanwhile, those on the other side of the debate express concern about uptake of e-cigarettes among people, especially children and adolescents, who would not otherwise smoke and about their long term health effects. They argue that although e-cigarettes do not contain some of the most harmful substances found in conventional cigarettes, such as tar, they do contain other substances such as formaldehyde (a carcinogen) and diverse flavourings. Thus, it is equally important to include non-smoking as a comparator. They also draw attention to important epidemiological evidence that contrary to what is widely believed, reduced smoking (as opposed to quitting) may not reduce overall risk of death.[8] The expression "dual use," which acknowledges that two thirds of e-cigarette users also smoke, rarely occurs in the PHE report. Although some dual use is inevitable during the quitting process, if this persists long term health concerns remain. A recent cohort study by McNeill and colleagues showed that dual use among daily "vapers" apparently remained above 80% after 12 months follow-up, which is worrying.[9]

Quality of the evidence

A fundamental principle of public health is that policies should be based on evidence of effectiveness. So does the available evidence show clearly that e-cigarettes are as effective as established quitting aids? Unfortunately not. The recent Cochrane review is widely cited,[10] but it included only two randomised controlled trials, both with important limitations, and concluded that the evidence was of "low or very low quality by GRADE standards." The PHE report authors concede the weakness of the evidence, noting how a single observational study with substantial limitations offers "some of the best evidence to date on the effectiveness of e-cigarettes for use in quit attempts."

Where there is uncertainty about risks, the precautionary principle should apply. Thus, in the absence of scientific consensus that the substance is not harmful to the public, the burden of proof that it is not harmful falls on those taking an action. The quality of the evidence cited by PHE therefore becomes crucial. The headline message from the PHE report, widely quoted in the media, is that "best estimates show

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e-cigarettes are 95% less harmful to your health than normal cigarettes," seemingly leaving little room for uncertainty about long term risks. Yet a recent systematic review,[11] which the PHE report surprisingly fails to cite, came to a different conclusion. It found serious methodological problems in many of the 76 studies it reviewed, and one third of the studies (34%) were published by authors with conflicts of interest. The systematic review also expressed concern about the effects of various substances in e-cigarettes, some but not all of which are also found in conventional cigarettes. It concluded that "due to many methodological problems, severe conflicts of interest, the relatively few and often small studies, the inconsistencies and contradictions in results, and the lack of long-term follow-up no firm conclusions can be drawn on the safety of e-cigarettes. However, they can hardly be considered harmless."

We might also expect that the prominently featured "95% less harmful" figure was based on a detailed review of evidence, supplemented by modelling. In fact, it comes from a single meeting of 12 people convened to develop a multicriteria decision analysis (MCDA) model to synthesise their opinions on the harms associated with different nicotine containing products; the results of the meeting were summarised in a research paper.[12] The authors state: "The sponsor of the study had no role in any stage of the MCDA process or in the writing of this article, and was not present at the workshop." However, given the importance of complete transparency in an area as controversial as this, it is legitimate to ask about the sponsors. One is a company called EuroSwiss Health.[13] An internet search reveals little about its activities other than that it funded the meeting, but it is one of several companies registered at the same address in a village outside Geneva with the same chief executive. He is reported to have previously received funding from British American Tobacco (BAT)[14] for writing a book on nicotine as a means of harm reduction,[15] although the book states that "the statements, findings, conclusions and recommendations contained in the book were developed independently of BAT." He also endorsed BAT's public health credentials in its 2013 sustainability report.[16]

The paper also acknowledges support from Lega Italiana Anti Fumo (Italian Anti-Smoking League), whose chief scientific adviser was one of the 12 people attending the meeting. He declares funding from an e-cigarette manufacturer but not the funding he is reported elsewhere to have received previously from tobacco company Philip Morris International.[17] The rationale for selecting the members of the panel is not provided, but they include several known e-cigarette champions, some of whom also declare industry funding in the paper.[12] Some others present at the meeting are not known for their expertise in tobacco control. The meeting was also attended by the tobacco lead at PHE. Furthermore, their paper tellingly concedes that "A limitation of this study is the lack of hard evidence for the harms of most products on most of the criteria." However, none of these links or limitations are discussed in the PHE report.

Uncertainty around harms

The PHE report asserts that the available evidence suggests that e-cigarettes are not currently re-normalising smoking among children and young people in the UK. However, this remains a major concern for health professionals and parents. In England, experimentation with e-cigarettes among young people is worrying high, with over one fifth of 11-15 year olds having ever used e-cigarettes[18]; 73% of the young people surveyed who had tried e-cigarettes were non-smokers. Uptake of e-cigarettes among young non-smokers is a particular concern, given that nicotine use in young people may disrupt brain development with long term, irreversible consequences for brain function.[19] The authors categorically dismiss the possibility that e-cigarettes may be a gateway to smoking, arguing that even the concept of a children's gateway should be rejected. This view seems premature, particularly given recently emerging evidence[20] such as an American study, published after the PHE report, which concluded that "those who had ever used e-cigarettes at baseline compared with nonusers were more likely to report initiation of combustible tobacco use over the next year."[21] Furthermore, none of the research so far can be considered conclusive, and longer term studies are needed.

Evidence on the risk of e-cigarette aerosol to bystanders in enclosed public spaces is sparse. However, the PHE report seems to equate lack of evidence with evidence of lack of effect. It claims that there is "no identified risk to bystanders," a view that may be premature.

The report has many other omissions, such as concerns about product safety, including forged safety certificates reported by a BBC *Fake Britain* documentary in December 2014, and the lack of evidence of risks from long term dual use with conventional cigarettes.[22] Yet perhaps its most striking feature is its consistent adoption of the most optimistic position on the limited evidence available. To take one example, the report offers reassurance that e-cigarettes when "used as intended pose no risk of nicotine poisoning to users." This is true, but it is equally true of all poisons. The report rightly calls for nicotine to be in child-proof containers given the attraction of colourful packaging. However, it quotes a report of over 2400 poisoning cases in the United States up to February 2014[23] as saying "none resulted in any serious harm," although the US report included reference to a death attributed to suicide. Nor does it cite the report's conclusion that "the public should be aware that e-cigarettes have the potential to cause acute adverse health effects and represent an emerging public health concern."

The PHE authors also fail to consider the practical consequences of their recommendations. If e-cigarettes are so safe, presumably there will be no restriction on using them in cars. This will make the forthcoming ban on smoking in cars with children virtually unenforceable because it will be extremely difficult to determine what is causing a cloud of smoke or vapour in a moving car.

Finally, the PHE summary states, "The accuracy of nicotine content labelling currently raises no major concerns." Surely, England's leading public health agency cannot be indifferent to a situation where consumer product information is known to be wildly inaccurate?[6 24]

Where next for policy on e-cigarettes?

In 2016, the European Union Tobacco Products Directive[25] will come into force despite some of the most intensive tobacco industry lobbying ever seen.[26] Most of the lobbying effort concerned packaging of conventional cigarettes. However, there was also a powerful attack on the directive's substantial restrictions on e-cigarettes. These restrictions will hopefully limit the negative effect of this flawed PHE report. Meanwhile, directors of public health and the wider community desperately need advice on e-cigarettes that is evidence based and free from any suspicion of influence by vested interests.

Happily, a consensus may be emerging. The English chief medical officer (CMO) recently said that, if e-cigarettes have a role in smoking cessation that should be as "licensed medicines. This would provide assurance on the safety, quality, and efficacy to consumers who want to use these products as quitting aids."[27] That would, of course, require data to show that they were both

safe and effective because, as the CMO also notes, "there continues to be a lack of evidence on the long-term use of e-cigarettes." We agree with this view.

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Key messages

- Public Health England's endorsement of the safety and efficacy of e-cigarettes is based on uncertain evidence
- The quality of evidence that e-cigarettes help smokers to quit is weak
- Recent evidence questions the conclusion that e-cigarettes are not a gateway to smoking
- Until better evidence is available public health strategies should follow the precautionary principle

American Heart Association | American Stroke Association

Impact of Electronic Cigarettes on the Cardiovascular System

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Tobacco smoking is a major public health threat for both smokers and nonsmokers. There is accumulating evidence demonstrating that smoking causes several human diseases, including those affecting the cardiovascular system. Indeed, tobacco smoking is responsible for up to 30% of heart disease–related deaths in the United States each year.[1] This is the single most preventable risk factor related to the development of cardiovascular disease, bringing about a trend toward tobacco harm reduction that started years ago.[2] As tobacco usage declined over time in the United States, industries introduced an alternative known as electronic cigarettes (e-cigarettes) claiming they were a healthier alternative to tobacco smoking.[3]

Since then, the number of e-cigarette users has increased significantly because of the perception that they serve as a healthy substitute to tobacco consumption with minimal or no harm, a lack of usage regulations (although that has now changed), and the appealing nature of these devices, among other reasons.[4] Consequently, e-cigarettes became the most commonly used smoking products, especially among youth, with more than a 9-fold increase in usage from 2011 to 2015.[5] Based on these considerations, it is clear that there are many unanswered questions regarding the overall safety, efficacy of harm reduction, and the long-term health impact of these devices.

Besides their potential negative health effects on users, there is increasing evidence that e-cigarettes emit considerable levels of toxicants, such as nicotine, volatile organic compounds, and carbonyls, in addition to releasing particulate matter (PM).[6,7] Thus, they possess a potential harm to nonusers either through secondhand or thirdhand exposure. This is especially the case in vulnerable populations, such as children, elderly, pregnant females, and those with a history of cardiovascular disease.[8] Thus, it is critical to establish e-cigarettes' short- and long-term health effects on both users and nonusers. In this review, we will discuss the current state of literature regarding the potential negative cardiovascular effects of direct/active and passive e-cigarette exposure. Furthermore, we will review the possible impact of the individual constituents of the e-cigarette on hemodynamics and their contribution to the development of cardiovascular disease. The notion that e-cigarettes may negatively impact the cardiovascular system should uncover new avenues of research focused on establishing and understanding the safety of e-cigarette usage on human health.

E-Cigarettes

E-cigarettes, also known as vape pens, e-cigars, or vaping devices, are electronic nicotine delivering systems, which generate an aerosolized mixture containing flavored liquids and nicotine that is inhaled by the user.[9] The extensive diversity of e-cigarettes arises from the various nicotine concentrations present in e-liquids, miscellaneous volumes of e-liquids per product, different carrier compounds, additives, flavors, and battery voltage.[9] Regardless of the exact design, each e-cigarette device has a common functioning system, which is composed of a rechargeable lithium battery, vaporization chamber, and a cartridge (Figure 1). The lithium battery functions as the powerhouse; it is connected to the vaporization chamber that contains the atomizer[9] (Figure 1). In order to deliver nicotine to the lungs, the user inhales through a mouthpiece, and the airflow triggers a sensor that then switches on the atomizer.[9–11] Finally, the atomizer vaporizes liquid nicotine in a small cartridge (Figure 1) and delivers it to the lungs.[9]

With regard to their design, there are 4 generations of devices currently on the market.[4] The first-generation e-cigarettes are the "ciga-like" devices, which are utilized mainly by new e-cigarette users; they are constructed of a cartomizer (cartridge and an atomizer) with a low-voltage battery (3.7 V).[4,12–14] Second-generation e-cigarettes are primarily used by more-experienced users and are bigger in size with a refillable tank (unlike first-generation devices).[4,13,14] Their battery voltage is adjustable, allowing users to use low or high voltage (3–6 V) during vaping.[4,13,14] The third-generation

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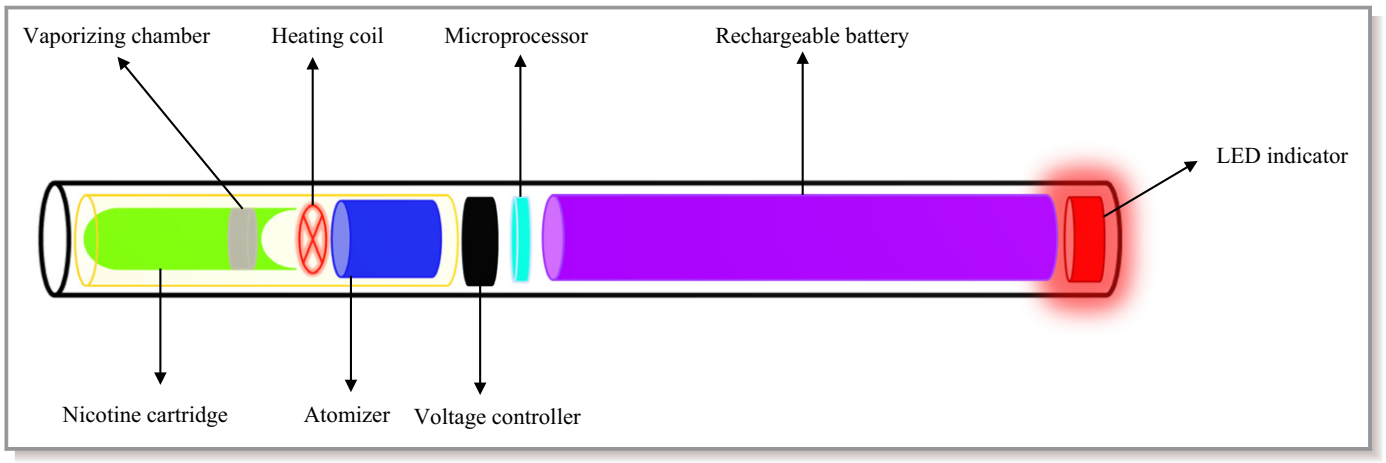

Figure 1. Typical e-cigarette design. E-cigarettes are usually composed of nicotine cartridge (e-liquid container), vaporizing chamber, a heating coil (heats e-liquid) followed by an atomizer (e-vapor generator), rechargeable battery and voltage controller (which will adjust the amount of nicotine delivered during vaping), microcompressor, and LED indicator—not present in all types—to activate the battery and visually mimic the conventional cigarette, respectively. LED indicates light-emitting diode.

devices are also known as mods and have the largest size batteries, with voltages up to 8 V.[13] Finally, the fourth and most recent generation includes Sub ohm tanks (devices whose atomizer coils have a resistance of less than 1 ohm) and temperature control devices, which allow for temperature modulation during vaping. With these devices, the "vaper" can inhale huge puff volumes, leading to extremely high e-liquid consumption per puff.[4]

Taken together, there is diversity in e-cigarette designs, which has an effect on the levels of ingredients being delivered to the user and the environment (including nonusers). This variability also complicates our ability to assess the health consequences of e-cigarettes.

Prevalence of e-Cigarette Usage

Since their introduction in 2007, e-cigarettes have experienced widespread success among smokers, nonsmokers, pregnant females, and even youth. Their sales increased by 14-fold since 2008,[15] contributing to scientists' desire/necessity to evaluate their safety, population patterns, and usage reasons.[16] Usage patterns vary depending on consumers' age group.[4] In adults, usage increased over the past decade to include 3.8% of US adults, of which almost 16% are current cigarette smokers, whereas 22% are former smokers.[17] Importantly, almost 3.2% of individuals who never smoked before/naïve have tried e-cigarettes, reflecting exposure to harmful chemicals for "neoteric" purposes.[17,18] In fact, adults primarily use e-cigarettes to discontinue smoking because they perceive them to be: (1) a healthier choice, which can reduce nicotine cravings, and (2) less harmful to nonusers in their proximity.[4,19] As for seniors, it appears that e-cigarettes are used to stop smoking or to bypass smoke-free policies.[20,21]

Usage of e-cigarettes among the youth is mainly linked to their curiosity and the "appealing" flavored nature of e-liquids.[19] It is alarming that this group has the highest increase in usage[18]; 5.3% of all users are middle school students, and 16% are high school students. This is a 9- and 10-fold increase, respectively, since 2011.[18] Because the brain is only fully developed by the age of mid-twenties, youths' exposure to nicotine may disrupt their brain development, and hinder attention and learning, while elevating susceptibility for addiction to nicotine or other drugs such as cocaine.[22]

Despite the known negative consequences of tobacco smoking, many pregnant females continue to use e-cigarettes based on their safety perception as compared with tobacco.[23] Ironically, given that nicotine contributes to the negative health consequences of smoking on newborns, e-cigarette use will likely expose the fetus to nicotine, leading to adverse effects, such as reduced cognitive deficits and perhaps even sudden infant death syndrome.[22,24,25]

It is to be noted that aggressive marketing provoked a false perception, albeit has yet to be confirmed, about the effectiveness and safety of these devices, which further emboldened their use.[20] In light of the aggressive marketing and the fact that e-cigarettes use is growing among all populations, it is paramount to establish their safety profiles, especially in vulnerable populations, and take measures to ensure their protection.

Public Health and e-Cigarettes

The long-term health effects of e-cigarettes have not yet been documented in humans; however, the short-term negative effects have been suggested by several studies.[8,9,26,27] These studies focused mainly on the cytotoxic profile of e-cigarettes

Table 1. Potential Effects of e-Cigarettes on Biological Systems

System	Effects of e-Cigarettes
Pulmonary system	Upper and lower respiratory tract irritation[9,26,27] Bronchitis, cough, and emphysema[9,26,27]
Immune system	Inflammation induction[28] Reduce immune efficiency[29]
Central nervous system	Behavioral changes[9] Memory impairment (animal models)[9,10] Tremor and muscle spasms[10]
Miscellaneous	Ocular irritation[9] Contact dermatitis and burns[9,31] Nausea and vomiting[9,31] Throat and mouth irritation[30,31]

and their effects on the respiratory tract,[9,26,27] central nervous system,[9,10] immune system,[28,29] and a few others[9,30,31] (Table 1).

As the primary system exposed to vapors from e-cigarettes, most reported health effects have centered on the pulmonary tract. Recent clinical and animal studies showed that (active or passive) e-vapors/e-cigarettes may cause irritation of both the upper and lower respiratory tract, in addition to inducing bronchospasm and cough[9,32–34]; the latter effects may be attributed to a chain of inflammatory reactions through oxidative stress.[28]

As for effects on other systems, e-cigarettes also reduce, in mice, the efficiency of the immune system, as reflected by the increased susceptibility to infection with influenza A and Streptococcus pneumonia.[29] As for the central nervous system, e-cigarettes may alter brain functions, which affects the mood, learning abilities, memory, and could even induce drug dependence in both humans and animals.[35–37] E-cigarettes may also directly damage neurons and cause tremor and muscle spasms.[9]

Carcinogenicity, mostly manifested in the lungs, mouth, and throat,[30] is another important aspect of the e-cigarette's negative health profile; this may be linked to nitrosamines, propylene-glycol (the major carrier in e-liquids), and even some flavoring agents.[9,31] In fact, one study indicated that after being heated and vaporized, propylene glycol may transform into propylene oxide, which is a class 2B carcinogen. Moreover, e-liquid exposure was found to exert a direct cytotoxic effect on human embryonic stem cells and mouse neural stem cells, highlighting a potential harm for pregnant females.[15,32] Other adverse effects include nausea, vomiting, and contact dermatitis, as well as eye, mouth, and throat irritation.[9,31] It is noteworthy that the harm related to e-cigarette usage reaches further beyond "beings" to include fire hazards and explosions; issues the public tends to underestimate.[38,39]

In summary, there is increasing evidence that short term e-cigarette exposure exerts deleterious effects on multiple biological systems, but the mechanism by which these effects occur is presently unknown. While the long-term effects have not yet been studied, one can predict that e-cigarettes will likely cause more harm if used for extended periods, a notion that also warrants investigation.

The Impact of e-Cigarettes on the Cardiovascular System

Cardiovascular disease is the major cause of death among smokers[1] and is responsible for as much as 30% of heart disease–related deaths in the United States each year.[1] As smokers considered safer alternatives to help them quit, they started using e-cigarettes, in part, because they have "lower" levels of harmful constituents.[19] Nevertheless, this notion should be reconciled in light of the high "sensitivity" of the cardiovascular system and evidence of a nonlinear dose-response relationship between tobacco exposure and development of cardiovascular disease. Thus, even exposure to low levels of harmful constituents could have a pronounced effect, and, consequently, the reduction of such materials in e-cigarettes does not assure a proportional harm reduction.[40] Conversely, exposure to toxicants may not necessarily translate into a negative health effect.

It is therefore paramount to evaluate e-cigarette's short- and long-term safety on the cardiovascular system, especially given the limited studies in this area and/or their controversial findings.[28] Several studies suggest that e-cigarette use acutely and negatively (increased) impacted vital signs, such as heart rate[41,42] and blood pressure.[43,44] In this regard, Andrea et al showed that heart rate acutely increased after e-cigarettes use by smokers,[41] which was also observed in a separate study.[42] Additionally, Yan et al found that e-cigarettes elevated both diastolic blood pressure and heart rate in smokers, but to a lesser extent when compared with tobacco cigarettes.[43]

It was also found that endothelial cell dysfunction and oxidative stress, which play important roles in the pathogenesis of cardiovascular disease,[45] are associated with e-cigarettes, even a single use, but the effect was less pronounced compared with cigarette smoking.[46] On the other hand, relative to cigarette smoking, e-cigarette use caused a comparable and rapid increase in the number of circulating endothelial progenitor cells, which could be attributed to acute endothelial dysfunction and/or vascular injury.[47] Given that platelets are key players in the development of cardiovascular disease—especially thrombosis and atherosclerosis—a recent in vitro study evaluated the effects of e-cigarettes on these cells.[48]

Consequently, e-cigarette vapor extracts were found to enhance activation (aggregation and adhesion) of platelets from healthy human volunteers.[48]

Alternatively, some studies have shown that short-term exposure to e-cigarettes has no cardiovascular harm.[49–51] These studies found that acute exposure to e-cigarettes had no immediate effects on the coronary circulation, myocardial function, and arterial stiffness.[10,49,50] Another study revealed no significant changes in smokers' heart rate after acute use of e-cigarettes.[52] However, the discrepancy in findings should be examined in the context of evidence indicating that vaping topography (e-cigarette usage patterns such as inhalation duration and the magnitude of inhaled volume) and user's experience are critical factors in determining the health effects of e-cigarettes.[39,53] The discrepancy in the results, aside from the user's experience and vaping topography, which could be attributed to differences in sample size, study groups (former smokers' versus nonsmokers), exposure's nature (acute versus pro-longed), and wide variety of e-cigarette products, makes it difficult to draw conclusions regarding the cardiovascular health consequences of e-cigarettes. Of note, the long-term effects of e-cigarettes have not been studied, nor has the mechanism(s) by which they exert their effects on the cardiovascular system.

Although some studies support and promote the idea that e-cigarettes could be a safer alternative to tobacco, it is important to consider (and address) the public safety of these devices to nonusers who are in proximity and would be subject to secondhand vaping/exposure.[54] Furthermore, a new threat, thirdhand vaping/exposure, has been discovered; it arises from exposure to e-cigarette residues remaining on surfaces in areas where vaping took place.[55] Given that secondhand and even thirdhand exposure to tobacco smoke exerts toxicity, including the cardiovascular system,[56] whether e-cigarettes are a source of secondhand or thirdhand vapors was investigated. Subsequent studies provided substantial evidence that e-cigarettes are not an emission-free device; instead, they negatively affect indoor air quality. Specifically, e-cigarette vaping was found to release various potentially noxious constituents.[57,58]

Although the indoor use of e-cigarettes was found to result in lower levels of "secondhand and thirdhand" residues, compared with tobacco smoke,[59] these hazards are still a health threat to those who are involuntarily exposed (nonusers). The latter notion should be considered with survey findings that e-cigarette users (unfortunately) do not consider laws that prohibit tobacco smoking to apply to them and hence vape in smoke-free areas.[60] This is consistent with another survey that showed a large proportion of middle and high school students have been exposed to secondhand vapes.[61] Thus, research should be initiated to evaluate health effects of secondhand and thirdhand vaping, which would, in turn, inform (stricter) e-cigarette regulations.

The Impact of e-Cigarette Toxicants/Constituents on the Cardiovascular System

There are limited studies on the health effects of e-cigarettes, particularly on the cardiovascular system. Therefore, to gain a better understanding of their possible/potential harm, we sought to review the effects of constituents/toxicants known to exist in e-cigarettes. In this regard, e-liquids and e-vapors are a source of a large number of these chemicals,[7,10,53,57,62–66] affecting several biological systems[37,43,67–88] (Table 2). The levels of some of these toxicants in e-cigarette aerosols are claimed to be lower than in tobacco smoke. For instance, several studies have shown that e-cigarette usage results in lower volatile organic compounds levels compared with the combustible cigarette.[64,89,90] Notably, the levels of e-cigarette chemicals appear to vary between studies, attributed to the wide range of products on the market, different nicotine concentrations, study designs, vaping techniques (puffing topography), and users' experiences.[91] Nevertheless, most studies do support the presence of carbonyl compounds, nicotine, and particulate matter in e-cigarette liquids and/or vapors,[8,9] and those will be the focus of the discussion in the following sections.

The Impact of Nicotine on the Cardiovascular System

Nicotine, which is the major constituent in most smoking products, is considered a strong alkaloid that can be absorbed by various routes: oral mucosa, lungs, skin, or gut.[93] After absorption, nicotine is metabolized by the liver into cotinine as one of the metabolites.[94] Most e-liquids contain nicotine at concentrations that vary between 0 and 36.6 mg/mL.[95] Interestingly, it has been reported that several e-cigarette brands inaccurately labeled nicotine concentration,[96] and, in fact, some of the "nicotine free" brands apparently contain some.[8] As expected, e-liquids with higher nicotine concentrations deliver more nicotine than those with lower concentrations.[43,97]

Nicotine delivery to the human body is affected by other factors, such as the type of device used.[39] Thus, studies on first-generation e-cigarettes reported delivery of low concentrations of nicotine to the bloodstream,[98] unlike newer-generation devices (equipped with a high-capacity battery).[13] To this end, Farsalinos et al showed a 35% to 72% increase in nicotine delivery with newer generations of e-cigarettes, relative to first-generation devices.[13] Furthermore, although studies have shown that conventional cigarettes result in

Table 2. Chemicals Emitted in e-Cigarette Vapors and Their Potential Health Effects

	Chemical	Detected Concentration Range	Biological System Affected
	Nicotine	ND to 36.6 mg/mL[10,62,63]	Lung tumor promoter[67] Addiction[67] Gastrointestinal carcinogen[67] Raises blood pressure and heart rate[68] Reduce brain development in adolescents[37]
	Cotinine	ND*	Reduce fertility and reproduction[69]
Aldehydes	Acetaldehyde	0.11 to 2.94 μg/15 puffs[53,64,65]	Carcinogen[70] Aggravation of alcohol-induced liver damage[71]
	Acrolein	0.044 to 6.74 μg/15 puffs[53,64,65]	Ocular irritation[72] Respiratory irritation[72] Gastrointestinal irritation[72]
	Formaldehyde	0.2 to 27.1 μg/15 puffs[53,64,65]	Carcinogen[68] Bronchitis, pneumonia, and increase asthma risk in children[73,74] Ocular, nasal, and throat irritant[74]
	o-Methyl benzaldehyde	ND to 7.1 μg/15 puffs[7]	Unknown
	Acetone	ND to 91.2[7]	Gastric distress[75] Weakness of extremities and headache[75] Ocular irritation[75]
Volatile organic compounds	Propylene glycol	0 to 82.875 mg/15 puffs[7]	Throat and airways irritation.[76] Carcinogen[68] Gastric distress[68] Increase asthma risk in children[68] Ocular irritation[68]
	Glycerin	75 to 225 μg/15 puffs[57]	Lipoid pneumonia[77] Ocular, dermal, and pulmonary irritant[78]
	3-Methylbutyl-3-methylbutanoate	1.5 to 16.5 μg/15 puffs[57]	Unknown
	Toluene	<0.63 μg/15 puffs[64]	CNS damage[79] Renal damage[80]
Nitrosamines	NNN	0.8 to 4.3 ng/e-cigarette[64]	Carcinogen[87]
	NNK	1.1 to 28.3 ng/e-cigarette[64]	Carcinogen[87]
Metals	Chromium	ND to 0.0105 μg/15 puffs[7,66]	Pulmonary irritation and inflammation, nasal mucosa atrophy and ulcerations[81] Nasal mucosa atrophy, reduce fertility and reproduction[82]
	Cadmium	ND to 0.022 μg/15 puffs[64,66]	Increase risk of lung cancer[83] Pulmonary and nasal irritation[83]
	Lead	0.025 to 0.57 μg/15 puffs[64,66]	Hypertension induction[83,84,88] Renal damage[88] CNS damage[84,88]
	Nickel	0.0075 to 0.29 μg/15 puffs[64,66]	Carcinogen[43] CNS and pulmonary damage[85] Renal and hepatic toxicity[85]

ND indicates not detected; CNS, central nervous system; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N-nitrosamines.
*Variable concentrations found in plasma after using e-cigarettes.[92]

quicker and 60% to 80% higher plasma nicotine levels,[45,98,99] e-cigarettes vaping still could result in comparable levels,[92] especially with experienced smokers who can adjust the topography of vaping.[53,62,100,101] However, e-cigarette users take a longer time to reach such levels.[53,92] Consistent with its systemic uptake, comparable saliva and plasma levels were reported for cotinine, which is considered one of the major metabolites and a marker of nicotine, in both e-cigarette users and conventional smokers.[92,102,103] Collectively, these studies support the notion that e-cigarette usage results in increased nicotine delivery to the human body.

Studies with conventional cigarettes showed that nicotine increased the risk of cardiovascular disease in smokers, including the development of acute coronary disease,[46] elevated blood pressure,[104] and heart failure.[105] As for nicotine effects on thrombogenesis, it seems to be controversial, with studies suggesting it to be elevated,[106,107] reduced,[108] or not affected[109]; but this discrepancy could be attributed to the dose of nicotine used,[110] route of administration,[111] and the method used to measure platelet function. Additionally, it was established that nicotine induces endothelial dysfunction,[112] angiogenesis,[113] inflammation,[114] and lipogenesis, which may increase thrombosis risk. Conversely and interestingly, nicotine delivered from nicotine replacement therapy was not found to be associated with increased cardiovascular diseases risk.[104] This finding could be attributed to the standardized dose-delivery system of nicotine replacement therapy, in which the nicotine dose is reduced over a short period of time.[104] Thus, it seems that the cardiovascular effects of nicotine depend on the dose delivered and its distribution kinetics.[115–117] Given that the pharmacokinetics of nicotine delivery to human body by e-vaping seems to be different from tobacco smoking, both in the magnitude and the speed by which peak levels are reached,[118] it is essential to evaluate whether "e-vaped" nicotine has an effect on cardiovascular system.

Unfortunately, studies on e-cigarette nicotine effects have been limited, and controversial. A study by D'Ruiz et al indicated an elevation in heart rate after using (different brands of) e-cigarettes, which correlated with elevation in plasma nicotine levels. This is consistent with findings that both heart rate and plasma nicotine were elevated after 5 minutes of the first puff, and throughout 1 hour of the ad-lib period in e-cigarette users.[43] A separate study found no changes in heart rate in e-cigarette users, and no increase in nicotine plasma levels were observed.[52] However, these "guilt by association" studies do not provide a direct cause-and-effect relationship between nicotine concentration and human hemodynamics. This notion seems to be consistent with a recent in vitro study by Rubenstein et al, which indicated that the enhanced activity of human platelets upon exposure to e-vapor extracts was independent of nicotine.[48] It is clear that further investigation is warranted to address and better understand the short- and long-term effects of nicotine delivered by e-cigarettes on the cardiovascular system.

Additional concerns related to e-cigarettes include nicotine dependence and toxicity, given that the nicotine concentrations found in plasma of e-cigarette smokers are high enough to produce and maintain nicotine dependence, especially in youth. This may explain why many adolescents shift to tobacco smoking in their adulthood or cannot abandon vaping easily.[22] E-cigarettes may also present higher risks of nicotine toxicity, especially for children, because some incidents of ingesting e-liquids were reported.[9,119] In fact, the number of calls to poison centers for ingestion of e-liquids increased from "one per month in September 2010 to 215 per month in February 2014".[120] Thus, the Child Nicotine Poisoning Prevention Act was initiated in January 2016; this required e-cigarettes manufacturers to use child-resistant e-liquid packaging.

Concerns also exist for passive exposure to nicotine (nonusers); there is considerable evidence that e-vapors are a source of nicotine contamination.[103] Indeed, examination of indoor air quality revealed a significant elevation of air nicotine concentrations, which was commensurate with an increase in nicotine levels in plasma and saliva of nonusers.[90] In agreement with these results, salivary concentrations of cotinine were found to be elevated in nonusers living with e-cigarette users.[103,121] In addition to this, a detectable amount of nicotine was found on the surfaces of e-cigarette users' homes, suggesting a potential risk for thirdhand exposure.[55,59] Taken together, these data advocate that e-cigarettes are a source of secondhand and thirdhand exposure to nicotine, especially in sensitive or vulnerable populations, regardless of whether its levels from passive exposure to e-vapors are similar or lower than those from tobacco smoke.

The Impact of Carbonyl Compounds on the Cardiovascular System

In addition to nicotine, e-cigarettes emit other potentially harmful constituents like carbonyls; this includes aldehydes, such as formaldehyde, acetaldehyde, and acrolein,[64,122] which result from thermal degradation of propylene glycol and glycerol (most commonly used solvents in e-liquids[123]). As was the case with nicotine, newer generations of e-cigarettes reportedly result in comparable carbonyls levels relative to cigarettes (voltage dependent).[122,124] In this regard, whereas some studies showed that levels of aldehydes increased significantly under high voltage, or "dry-puff" conditions,[122,125] recent studies confirmed their presence even under normal puffing conditions.[126] Interestingly, levels of the acrolein metabolite, 3-HPMA, were found to be elevated in urine samples obtained from e-cigarette smokers when compared with nonsmokers, confirming its systemic delivery to the human body.[127] On the other hand, levels of 3-HPMA were reduced by 83% when tobacco smokers switched to e-cigarettes and were similar to levels observed in those who quit smoking.[128] The presence of the aforementioned aldehydes represents a major health concern; in fact, formaldehyde was classified as a carcinogen and acetaldehyde as a potential carcinogen by the International Agency for Research on Cancer.[129]

Aside from their cytotoxic effects, animal studies suggest that aldehydes exert various negative cardiovascular

effects.[130–132] Given the limited clinical studies evaluating the effects of e-cigarette aldehydes on the human cardiovascular system, we will rely on and extrapolate evidence from non-e-cigarette sources. In this regard, animal studies revealed that formaldehyde exposure altered the heart rate,[132] by a sympathetic nerve activity,[132] and it also altered blood pressure[133] and cardiac contractility.[131] Additionally, subacute and chronic inhalation of formaldehyde was associated with cardiac oxidative stress and, consequently, cardiac cell damage.[134] With regard to platelets, it was shown that total platelet count significantly increased in mice exposed to formaldehyde gas[130]; this effect should be considered in the context of the importance of platelets in hemostasis and their role in thrombotic disorders. As for acetaldehyde, elevated blood pressure and heart rate were reported in animals following inhalation of variable doses, which could be attributed to its sympathomimetic effect.[135,136] It is noteworthy that formaldehyde and acetaldehyde concentrations used in these studies are comparable to the levels generated by e-cigarettes. Collectively, studies clearly suggest potential harm from exposure to aldehydes, which could serve as a basis for future and further studies focusing on the cardiovascular consequences of their chronic exposure in real-life e-cigarette settings.

Exposure from smoking and other sources to acrolein, the other carbonyl, is associated with a wide range of cardiovascular toxicity.[137] Thus, inhalation of only 3 ppm of acrolein caused an increase in systolic, diastolic, and mean arterial blood pressure in an animal model.[138] Furthermore, acrolein-mediated autonomic imbalance caused an increase in the risk of developing arrhythmia in rats.[139] Additionally, it has been suggested that acrolein can directly induce myocardial dysfunction and cardiomyopathy.[140] As for the mechanisms of acrolein-induced cardiotoxicity, the following is some of what has been proposed thus far: the formation of myocardial protein-acrolein adduct, induction of oxidative stress signaling, upregulation of proinflammatory cytokines, and inhibition of cardioprotective signaling.[140,141]

In line with the negative effects on the vasculature, acrolein can result in vascular injury by impairing vascular repair capacity, as well as increasing the risk of thrombosis and atherosclerosis, a possible result of endothelial dysfunction, dyslipidemia, and platelet activation, among others.[142–144] Moreover, Sithu et al found that inhalation of acrolein vapor, generated from either acrolein liquid or tobacco smoke, results in a prothrombotic phenotype in mice.[145] Acute (5 ppm for 6 hours) or subchronic (1 ppm for 6 hours/day for 4 days) exposure to acrolein, regardless of its source, induced platelet activation and aggregation.[145] Additionally, an increase in acrolein-protein adduct in platelets was observed, which suggests its systemic delivery and that it exerts a direct effect on platelets.[145] In support of this notion, a human study revealed a correlation between levels of acrolein metabolite (ie, 3-HPMA) and platelet-leukocyte aggregates, in addition to increased risk of cardiovascular diseases.[146] The effects of acrolein on the cardiovascular system are summarized in Figure 2.

Although acrolein sources were different in these studies, to gain insight regarding their relevance and applicability to e-cigarettes, we converted the concentrations emitted from e-cigarettes to ppm, as reported by several studies, taking into account puff volumes[64,147–149] (Table 3). Thus, based on the average of 120 puffs/day reported in the literature,[101] our calculated levels of acrolein emitted by e-cigarette users per day were found to vary between 0.00792 and 8.94 ppm/day (Table 3). Because its harmful cardiovascular levels fall within this range, acrolein emitted from e-cigarettes may produce similar harm, which warrants investigation.

As mentioned before, an additional concern, that is often forgotten or ignored, is that e-cigarettes can be a source of secondhand or thirdhand exposure to aldehydes (and other toxicants) for nonusers.[150,151] Indeed, under human puffing conditions, indoor air quality was found to be reduced, attributed to aldehydes emission in e-cigarette vapors.[57] Even though detected levels were low, they may still pose a health concern, especially in people with a history of cardiovascular disease, as well as in children, casino/housekeeping workers, and in pregnant women. Hence, the safety of exposure to low levels of aldehydes for extended periods of time needs to be examined in nonusers who live with e-cigarette users or work in places where their use is allowed.

The Impact of PM on the Cardiovascular System

Another health concern related to e-cigarette usage is the generation of fine and ultrafine particles, known as PM, which represents the solid and liquid particles suspended in the air. PM2.5, which includes particles with a diameter of 2.5 μm or less, will be the focus of this section because of their small size; this enables them to easily penetrate airways and reach circulation, thereby causing a potential hazard to the respiratory and cardiovascular systems.[152] Several studies evaluated their presence in e-cigarette vapors and concluded that significant levels of PM2.5 are indeed exhaled by e-cigarette users.[58] The number of particles and size distribution in emitted PM in e-vapors were found to vary depending on the e-liquid, nicotine concentration, and puffing topography[12,101,153] and seem to be comparable to those generated from tobacco smoke.[153,154]

Several studies, conducted under controlled conditions that almost resemble real-life settings, revealed a significant increase in PM2.5 concentrations in rooms and/or experimental chambers in which e-cigarettes were consumed by

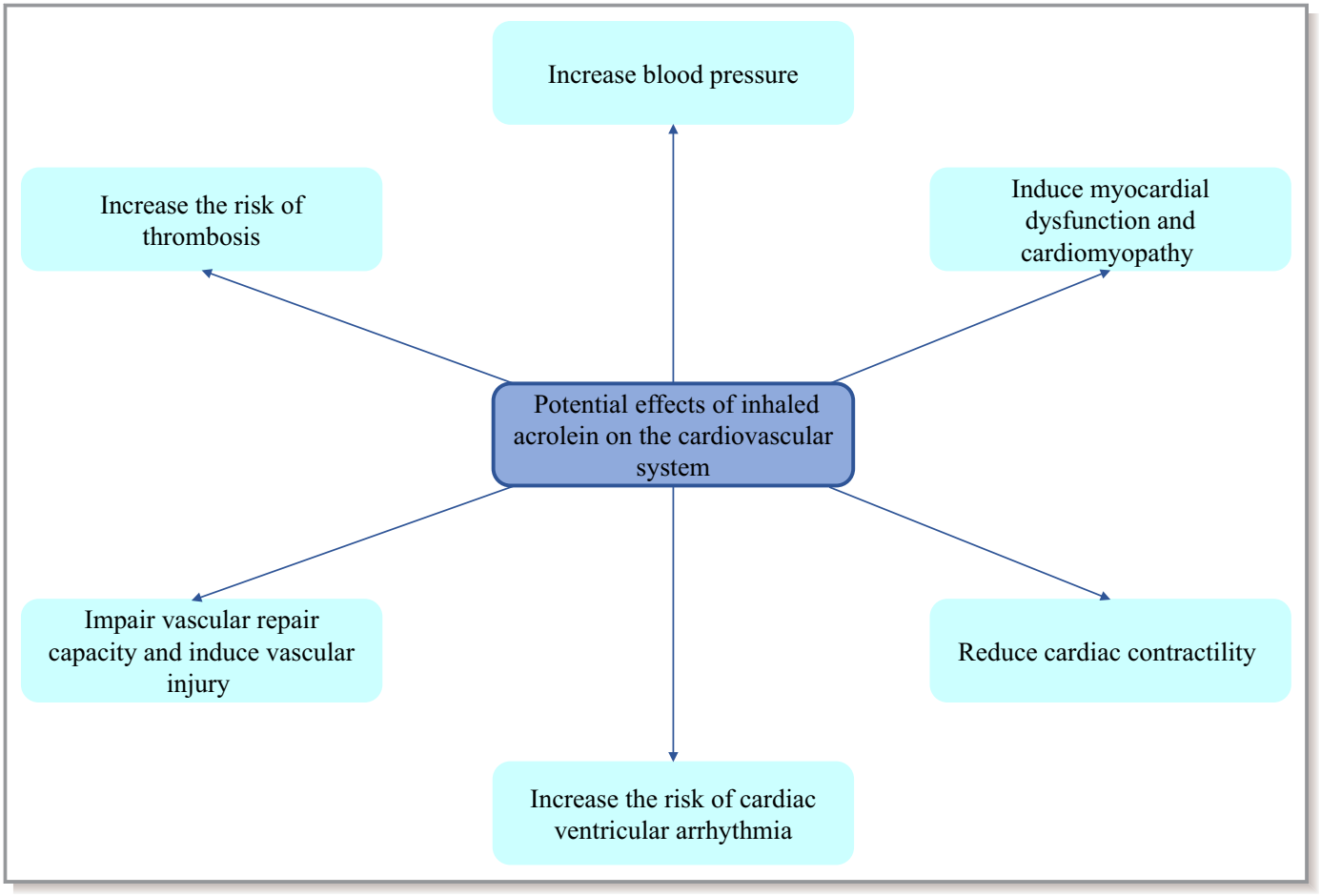

Figure 2. Effects of acrolein on the cardiovascular system. Wide ranges of cardiovascular effects of acrolein inhalation from smoking and ambient air pollution are reported in animal studies.[138,139,142,146]

human subjects.[57,65,90] This highlights e-cigarettes as a source of PM2.5 secondhand exposures.[57,65,90] In fact, PM2.5 concentrations increased dramatically (125–330-folds) in hotel rooms where e-cigarette use was allowed for 2 days, compared with the same rooms before active vaping occurred.[155] Surprisingly, these concentrations of PM2.5 are higher than the reported values from tobacco smoking in Hookah cafes and indoor bars.[155] On the other hand, it has been shown that the level of PM2.5 in houses of e-cigarette users was 95% lower than those from homes of conventional cigarette users.[58] Collectively, these studies provide evidence that e-cigarette users do indeed exhale PM2.5, thus putting themselves as well as nonusers under health risks.

Table 3. Acrolein Concentrations Emitted in e-Cigarette Vapors

Reference	Puff Volume	Acrolein Concentration/15 puffs*	Acrolein Concentration/d (120 puffs)	Acrolein Concentration ppm†	Acrolein Concentration ppm/d (120 puffs)
Goniewicz et al[64]	70 mL	0.07 to 4.19 μg	0.564 to 33.516 μg	6.6×10^{-5} to 0.0039	0.00792 to 0.468
Uchiyama et al[147]	55 mL	3.15 to 24 μg	25.2 to 192 μg	0.0038 to 0.029	0.456 to 3.48
Gillman et al[148]	55 mL	0.3 to 82.5 μg	2.4 to 660 μg	0.00036 to 0.1	0.0432 to 12
Flora et al[149]	55 mL	61.5 μg	492 μg	0.0745	8.94

*15 puffs=1 conventional cigarette.

†ppm=μg/mL, to convert μg/puff to ppm, we divided the concentration (μg) by the volume of each puff (mL).

$$\text{ppm} = \frac{\text{concentration (μg)}}{\text{volume (mL)}}$$

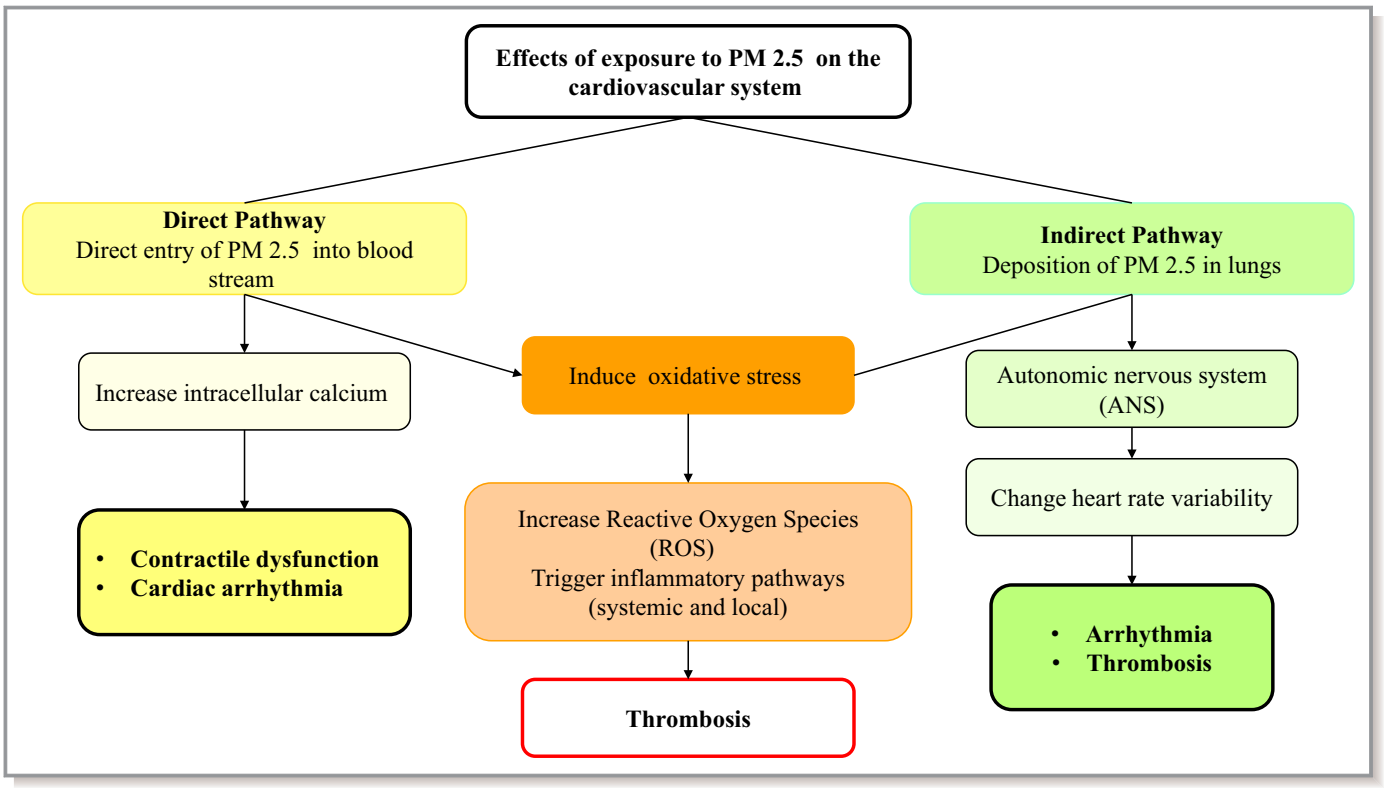

Figure 3. Effects of particulate matter (PM2.5) on the cardiovascular system. PM2.5 exposure from tobacco and environment/ambient negatively affects the cardiovascular system either directly or indirectly. The direct pathway is mediated by the delivery of PM2.5 into the bloodstream. The indirect pathway is attributed to deposition of PM2.5 in lungs and a modulation of autonomic nervous system. Oxidative stress is triggered by both pathways and induces local and systemic inflammatory processes. PM2.5 indicates particulate matter less than 2.5 microns in diameter.

Epidemiological and clinical studies suggest a strong association between human exposure to PM2.5 and the risk of cardiovascular disease development. Specifically, these studies showed that exposure to PM2.5 from ambient air pollution and/or tobacco smoking is linked to hypertension,[156] coronary artery disease,[157] myocardial infarction,[158,159] atherosclerosis,[156] arrhythmia,[160] as well as mortality relative risk.[161,162] Interestingly, risk of atherosclerosis was reported to increase with long-term exposure to ambient air PM2.5, and to be higher in elderly, female, and nonsmoker participants,[163] underscoring the sensitivity of special populations. This notion is consistent with reports that exposure of the elderly population with a history of cardiovascular disease to PM2.5 for only 28 days was accompanied with higher resting cerebrovascular resistance and increased mean arterial blood pressure.[164]

The physiomolecular mechanisms underlying the aforementioned effects are divided into a direct and indirect pathway, as summarized in Figure 3.[156] The direct pathway is mediated by the delivery of PM2.5 into the bloodstream, thereby targeting multiple organs.[165,166] Thus, if ion channels and calcium regulation are affected by PM2.5, it could lead to contractile dysfunction and arrhythmia,[165,167] whereas vascular dysfunction and thrombus formation can result from producing local oxidative stress and inflammation.[168–170] Regarding the indirect pathway, PM2.5-induced cardiovascular toxicity is associated with the development of inflammatory responses and modulation of the autonomic nervous system.[167] Thus, deposition of PM2.5 on alveoli was found to trigger the release of a host of proinflammatory mediators, vasoactive molecules, and reactive oxygen species into the circulation. These will subsequently affect vascular integrity and induce thrombogenesis.[168,170] As for PM2.5 modulation of the autonomic nervous system, it results in increased vasoconstriction and change in heart rate variability, which will potentially enhance the risk of developing arrhythmias and thrombosis.[171]

Importantly, it has been found that the dose-response relationship between PM exposure and cardiovascular mortality is also nonlinear,[172] and that a consequential adverse cardiovascular outcome can happen as a result of exposure to low levels.[172] Interestingly, it was suggested that PM2.5 is responsible for more than 90% of the predicted harm caused by thirdhand smoke pollutants.[173] Although, clearly, PM2.5 from ambient air pollution and smoking exerts harmful effects on the cardiovascular system, its mere presence—as a result of e-cigarette use—does not mean that it will have an effect; this issue should be investigated.

Studies have shown that e-cigarette PM2.5, even from a single puff, undergoes cardiopulmonary delivery into the systemic circulation,[174] resulting in a significant amount of deposition in the respiratory tree.[175] Furthermore, in vitro experiments documented a venous absorption between 7% and 18% of the total e-aerosol and arterial absorption through the alveoli between 8% and 19%.[174] Finally, a recent in vitro study concluded that PM2.5 may be the primary constituent that mediates e-cigarette-induced platelet activation and aggregation.[48] Based on these considerations, it is important to examine the negative health effects of short- and long-term (active and passive) exposure to e-cigarettes PM2.5.

Recent Regulatory Updates

Because of the growing evidence that e-cigarettes' present potential harm to public health, and the "skyrocketing" usage among youth, the US Food and Drug Administration issued new legislation (on August 8, 2016) that extended their regulations to e-cigarettes. This is expected to protect public health, minimize the risks associated with e-cigarettes and reduce youth's exposure to these devices. Under this expansion, manufacturers will be required to report all ingredients and undergo a premarket review to obtain permission to market their products.[176] Furthermore, selling of e-cigarettes to those aged <18 years is now prohibited, as is selling any tobacco products in vending machines (unless in an adult-only facility).[176] Of note, the tobacco 21 movement, a regulation that advocates for raising the minimum legal sale age for tobacco products to 21, was followed during 2016 only in 2 states (California and Hawaii). However, as of March 2017, the pattern is expanding to include at least 220 localities across the United States.[177] Nonetheless, and unfortunately, e-cigarettes are still available for purchase from online vendors, which would be the first alternative for youth. Thus, this aspect/"loophole" should be covered/closed by state legislation or by stricter rules from the US Food and Drug Administration.

The Public Health and Tobacco Policy Center report revealed that even though 31 states have (state) restrictions and laws addressing where e-cigarettes usage is allowed, only 10 of 31 prohibited their use wherever tobacco is prohibited effective January 2017. The majority of the remaining states prohibit vaping in schools, day care facilities, and a few on campuses.[178] However, concerns remain regarding the use of e-cigarettes at work and public places across the country, which results in exposing nonusers to potentially harmful vapors.

Conclusion

Although much is known about smoking-induced cardiovascular toxicity, little is known about that of e-cigarettes. This is an issue that continues to be a subject of debate. Nevertheless, based on the current body of evidence, e-cigarettes are not emission free (as some believe) and, in fact, they emit various potentially harmful and toxic chemicals. Whether or not the levels of these toxicants are lower than traditional smoking remains controversial. In this connection, recent studies showed that e-cigarettes-emitted chemicals reach levels comparable to tobacco smoke, and those levels vary depending on multiple factors, including types of devices, e-liquid, vaping topography, and vaping experience.[179] Given the sensitivity of the cardiovascular system and its "smoke" nonlinear dose-response/toxicity relationship, it is important to evaluate the cardiovascular safety of e-cigarettes.

Although it was originally argued that e-cigarettes are "harm free," the present prevailing belief is that they are "reduced harm" alternatives to conventional cigarettes. This latter notion is still debatable and not supported by conclusive evidence, especially considering the wide variation between e-cigarette products. Even if that were the case, their harm can still extend to innocent/bystander nonsmokers through secondhand and thirdhand vaping, including children, pregnant women, casino/housekeeping workers, and people with preexisting cardiovascular and other diseases.

The widespread and increasing usage of e-cigarettes in the United States is concerning because of the lack of studies on the long-term health effects of these devices on biological systems. Therefore, future research should establish, under real-life conditions, not only the long-term, but also the short-term negative effects of e-cigarette usage, on both users (active) and nonusers (passive), and provide mechanistic insights regarding these effects. These should, in turn, guide and shape policy for further evidence-based vaping control. Ultimately, we hope to underscore the need for prevention of exposure to various forms of vaping, especially in vulnerable populations like children and youth.

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Disclosures

None.

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Key Words: cardiovascular disease • electronic cigarettes • safety • smoke • tobacco use

Impact of Electronic Cigarettes on the Cardiovascular System

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Particulate Matter from Electronic Cigarettes and Conventional Cigarettes: a Systematic Review and Observational Study.

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OBJECTIVES:

The aim of this study is to review the literature on the composition of aerosols from electronic cigarettes (e-cigarettes) originated by human vaping and to describe the emission of particulate matter ≤ 2.5 μm in diameter (PM(2.5)) from conventional and e-cigarettes at home in real-use conditions.

METHODS:

We conducted a systematic literature search in PubMed and Web of Science. We measured PM(2.5) in four different homes: one from a conventional cigarette smoker, one from an e-cigarette user, and two from non-smokers.

RESULTS:

The review identified eight previous investigations on the composition of aerosols from e-cigarettes originated by human vaping and indicated that emissions from e-cigarettes can contain potential toxic compounds such as nicotine, carbonyls, metals, and organic volatile compounds, besides particulate matter. In the observational study, the PM(2.5) median concentration was 9.88 μg/m³ in the e-cigarette user home and 9.53 and 9.36 μg/m³ in the smoke-free homes, with PM(2.5) peaks concurrent with the e-cigarette puffs.

CONCLUSION:

Both the literature review and the observational study indicate that e-cigarettes used under real-conditions emit toxicants, including PM(2.5). Further research is needed to characterize the chemicals emitted by different types of e-cigarettes and to assess secondhand exposure to e-cigarette aerosol using biological markers.

KEYWORDS:

E-cigarette; Electronic cigarette; Electronic nicotine delivery system; Particulate matter; Tobacco smoke pollution

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Particulate Matter from Electronic Cigarettes and Conventional Cigarettes: a Systematic Review and Observational Study

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Abstract
Objectives The aim of this study is to review the literature on the composition of aerosols from electronic cigarettes (e-cigarettes) originated by human vaping and to describe the emission of particulate matter ≤2.5 μm in diameter ($PM_{2.5}$) from conventional and e-cigarettes at home in real-use conditions.
Methods We conducted a systematic literature search in PubMed and Web of Science. We measured $PM_{2.5}$ in four different homes: one from a conventional cigarette smoker, one from an e-cigarette user, and two from non-smokers.
Results The review identified eight previous investigations on the composition of aerosols from e-cigarettes originated by human vaping and indicated that emissions from e-cigarettes can contain potential toxic compounds such as nicotine, carbonyls, metals, and organic volatile compounds, besides particulate matter. In the observational study, the $PM_{2.5}$ median concentration was 9.88 μg/m^3 in the e-cigarette user home and 9.53 and 9.36 μg/m^3 in the smoke-free homes, with $PM_{2.5}$ peaks concurrent with the e-cigarette puffs.
Conclusion Both the literature review and the observational study indicate that e-cigarettes used under real-conditions emit toxicants, including $PM_{2.5}$. Further research is needed to characterize the chemicals emitted by different types of e-cigarettes and to assess secondhand exposure to e-cigarette aerosol using biological markers.

Keywords Tobacco smoke pollution · Particulate matter · Electronic cigarette · E-cigarette · Electronic nicotine delivery system

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Introduction

Electronic cigarettes, also called "e-cigarettes" or "e-cigs," are the most known electronic nicotine delivery system. An e-cigarette is an electronic device commonly shaped like a cigarette and designed to vaporize a mixture of nicotine, propylene glycol, and other chemicals. The e-cigarette heats the mixture via a battery activated by puffing. Interest in e-cigarettes has been recently growing among smokers, manufacturers, including leading cigarette companies, and also among tobacco control health professionals, researchers, and advocates who are concerned with their potential risks at the individual and public health level.

Concern exists regarding the potential passive exposure to the aerosol exhaled by e-cigarette users, as their use has increased in indoor places, including those with tobacco smoke-free bans [1]. Some studies show that the aerosol generated from e-cigarettes contains toxic compounds (such as volatile organic compounds, aldehydes, nitrosamines, polyaromatic hydrocarbons, glycols, and nicotine), although in lower amounts than conventional cigarettes [2••, 3, 4, 5•]. Some of them have analyzed e-cigarette emissions, mainly in controlled conditions [1, 5•, 6], and have found that e-cigarettes emit fine and ultrafine particles (also known as particulate matter). The objective of this manuscript is to systematically review the existing literature on secondhand exposure from e-cigarette aerosol in humans under real-life or mimicked real-life conditions and to describe the emission of particulate matter of less than 2.5 μm in diameter ($PM_{2.5}$) from e-cigarettes at home in real-life use conditions and compare it that of conventional cigarettes.

Methods

Literature Review

We performed systematic literature search in PubMed (US National Library of Medicine; http://www.pubmed.org) and in the Web of Science (using the Web of Science® Core Collection WoS, Thomson Reuters; http://webofscience.com) in order to identify relevant literature. Three search topics were combined: (1) "electronic nicotine delivery systems/electronic cigarettes," combined the search terms ("electronic cigarette*" OR e-cigarette* OR e-cig* OR ecig* OR "electronic nicotine delivery system*" OR "electronic nicotine delivery device*"); (2) "vapour", combined the search terms (vapor* OR vapour* OR aerosol* OR emission*); and (3) secondhand exposure, combined the search terms (secondhand OR second-hand OR passive OR involuntar* OR expos* OR environmental OR pollution).

The last updated literature search was performed in January 27, 2015. We identified 90 different articles for screening (33 duplicated in both databases). After reviewing the titles and abstracts, we find eligible 31 (see Fig. 1 for details) and reviewed their full text. We finally included eight studies focused on the composition of aerosol from e-cigarettes originated by human vaping. The other 23 articles excluded focused on health effects of vaping (n=2) or in the composition of the aerosol of e-cigarettes originated by "smoking machines" (n=21), which were not the focus of this paper (Fig. 1).

Observational Study

We measured $PM_{2.5}$ in real conditions in the homes of one conventional cigarette smoker, one e-cigarette user, and two non-smokers (smoke-free homes), who voluntarily agreed to participate in the study and signed an informed consent form. The research and ethics committee of the Bellvitge University Hospital provided ethical approval for the study protocol. The e-cigarette user and the non-smokers lived in totally smoke-free homes with no known infiltration of tobacco smoke into them from outdoors from other apartments in the same block. The measurement was taken for 1 h while the users of e-cigarette or conventional cigarette were smoking 2 m away from the monitor. During that time, the conventional smokers smoked three cigarettes, and the e-cigarette user made 42 puffs (ad libitum use) using an e-liquid containing 18 mg of nicotine (the e-cigarette device was Tornado™ model, one of the first medium-sized vaporizers launched in 2010, and the e-cigarette liquid brand was Totally Wicked™). We registered the time when conventional cigarettes were lighted and the every puff was done (both for conventional and e-cigarettes). The measurements of $PM_{2.5}$ were performed with a TSI SidePak Personal Aerosol Monitor model AM510 (TSI Inc. Minnesota, USA), which uses a built-in sampling pump to draw air through the device where the particulate matter in the air scatters the light from a laser determining the amount of light scattering. The monitor was zero-calibrated prior to each use with a HEPA filter, according to the manufacturer's specifications, and was set to a 1-s sampling interval, and a K factor of 0.52 was applied to data [7]. We plotted the 60-s averaged concentrations of $PM_{2.5}$ during the 1-h measurements. We computed the median (and interquartile range (IQR)) $PM_{2.5}$ concentrations by type of home.

Results

Literature Search

Most studies tried to replicate the human vaping in enclosed settings (rooms between 8 and 60 m^3) under controlled conditions, except a typical observational study conducted in Spain [8••]. The main methodological characteristics and

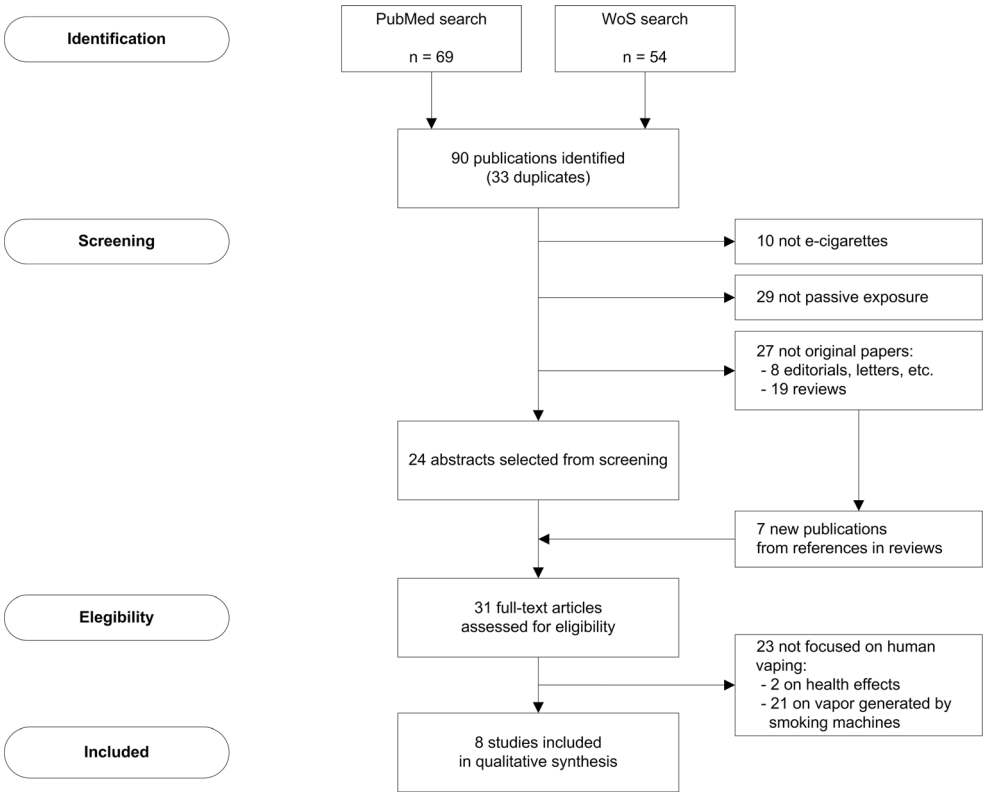

Fig. 1 Flow diagram of information through the different phases of the systematic review. *WoS* Web of Science

results are shown in Table 1. A study of the release of VOCs and fine and ultrafine particles from e-cigarettes under near-to-real-use conditions conducted in an experimental chamber with vapor produced by a volunteer who took six deep-lung puffs found an increase in fine particles, ultrafine particles, and VOCs after the use of an e-cigarette [2••]. The concentration of some aldehydes and other compounds were detected over the limit of determination as well as a high amount of 1,2-propanediol and nicotine in the exhaled air. In an experimental study of secondhand aerosol exhaled by three volunteers, the median of the droplet size exhaled by the e-cigarette users were 0.34 μm in e-cigarettes with nicotine and 0.29 μm in the e-cigarettes without nicotine [9], indicating no difference in the particle diameter of the e-cigarettes with or without nicotine. In the investigation of emissions of particulate matter and ultrafine particles generated by e-cigarettes under mimicking real-life conditions in a 50-m^3 room furnished as an office where a volunteer used an e-cigarette with and without nicotine [6], total suspended particles emissions were systematically higher in vapor from e-cigarettes without nicotine (11.6 μg/m^3) than from e-cigarettes with nicotine (1.2 μg/m^3), but ultrafine particle concentrations were similar (641 particles/cm^3 among e-cigarettes without nicotine and 566 particles/cm^3 among e-cigarettes with nicotine). Two studies were performed to evaluate "the secondhand exposure to nicotine and other tobacco-related toxicants from e-cigarettes": the authors used five male volunteers (dual users of e-cigarettes and conventional tobacco cigarettes) to generate the vapor and found that e-cigarettes were a source of secondhand exposure to nicotine and $PM_{2.5}$ but not to CO or VOCs, as compared to baseline (no emissions). An experimental study simulating a real-world scenario (café-like setting) [10•] assessed indoor concentrations of e-cigarette aerosol in terms of particulate matter and other compounds. During the vaping sessions, substantial amounts of 1,2-propanediol, glycerine, and nicotine were found in the gas phase, as well as high concentrations of $PM_{2.5}$ (mean 197 μg/m^3). In another experiment [11], the authors analyzed the particles and inorganic and organic compounds generated by the consumption of e-cigarettes. The room mimicked a real-life setting under controlled conditions (a 48-m^3 room where one volunteer used e-cigarettes ad libitum). Organic and inorganic elements and metals were detected in the aerosol of e-cigarettes, including toxic metals (Ni, Zn, and Ag). The mass balance and distribution of water, glycerin, nicotine, phenolics, and carbonyls in exhaled e-cigarette aerosol was described in an experimental study with two disposable electronic cigarettes [12]. Total phenolics and carbonyls in exhaled e-cigarette aerosol were not significantly different than the amounts observed in exhaled breaths or air room samples. The only observational study available [8••] considered the exposure to e-cigarette aerosol during a week in the homes of a sample of five non-smokers non-exposed to secondhand smoke who lived with an e-cigarette user and 24 similar non-

Table 1 Published papers on the composition of aerosols of electronic cigarettes originated by human vaping

Author, publication year (reference)	Design of study	Setting	How emissions were generated	Main finding(s)
Schripp et al. 2013 [2••]	Five controlled experiments	Room (48 m^3)	A volunteering smoker (experiment 1) and an e-cigarette user exhaling one e-cigarette puff (experiment 2)	An increase in fine particles, ultrafine particles, and volatile organic compounds were observed after the use of the e-cigarette. The concentration of some aldehydes and other compounds were detected over the limit of determination. The experiment revealed a high amount of 1,2-propanediol in the exhaled air. Other main components were the carrier substance 1,2,3-propanetriol, the flavoring source diacetin, as well as traces of apple oil (3-methylbutyl-3-methylbutanoate) and nicotine.
Bertholon et al. 2013 [9]	Experiment (six experiments, three with nicotine and three without nicotine) simulated a real-world scenario (café-like setting)	Conference room (40 m^3)	Three volunteers	The median of the droplet size exhaled by the e-cigarette users were 0.34 μm in electronic cigarettes with nicotine and 0.29 μm in the e-cigarette without nicotine.
Ruprecht et al. 2014 [6]	Experiment simulating real-life conditions	Homes	Three volunteer smokers	PM and TSP emissions were systematically higher in electronic cigarettes without nicotine. PM emitted by electronic cigarettes without nicotine were between 3.5 and 9.9 μg/m^3, depending on the size of the particles.
Czogala et al. 2014 [5•]	Experimental study with two disposable electronic cigarettes		Five volunteers (dual e-cigarette/tobacco smokers)	Electronic cigarettes are a source of secondhand exposure to nicotine and $PM_{2.5}$ but not to CO or volatile organic compounds (toluene), as compared to baseline (no emissions). Conventional cigarettes originated higher concentrations of nicotine, $PM_{2.5}$, CO, and volatile organic compounds (toluene, ethylbenzene, m,p-xylene, and o-xylene), as compared to electronic cigarettes.
Schober et al. 2014 [10•]	Cross-sectional, observational		Nine volunteer occasional smokers	During the vaping sessions substantial amounts of 1,2-propanediol, glycerine, and nicotine were found in the gas-phase, as well as high concentrations of $PM_{2.5}$ (mean 197 μg/m^3). The concentration of putative carcinogenic PAH in indoor air increased by 20 % to 147 ng/m^3, and aluminum showed a 2.4-fold increase. PNC ranged from 48,620 to 88,386 particles/cm^3, with peaks at diameters 24–36 nm.
Saffari et al. 2014 [11]	Five controlled experiments		Three volunteer smokers and a total of six e-cigarette samples (three with nicotine and three without nicotine)	Black carbon and particle-phase PAHs were not detected in e-cigarette's aerosol. Emission rates of organic compounds as well as total emission of inorganic elements and metals were detected in electronic cigarettes. There were also toxic metals (such as Ni, Zn, and Ag) in e-cigarette's aerosol. Secondhand particle-phase nicotine accounted for about 0.02 % of the total nicotine generation and emission during e-cigarette vaping.
Long 2014 [12]	Experiment (six experiments, three with nicotine and three without nicotine) simulated a real-world scenario (café-like setting)		Twenty electronic cigarettes user (maximum of 99 puffs)	Distribution of exhaled e-cigarette aerosol showed the composition was greater than 99.9 % water and glycerin, a small amount of nicotine (<0.06 %). Total phenolics and carbonyls in exhaled e-cigarette aerosol were not significantly different than the amounts observed in exhaled breaths.
Ballbè et al. 2014 [8••]	Experiment simulating real-life conditions		Real use of electronic cigarettes during 1 week	Airborne nicotine in e-cigarette users' homes was higher than in control homes (smoke-free homes).

Adapted from Fernández E, Fu M, Martínez-Sánchez JM. Exposure to secondhand aerosol from electronic nicotine delivery systems: a systematic review. Barcelona: Institut Català d'Oncologia, WHO Collaborating Center for Tobacco Control; 2015 [18]

smokers in smoke-free and e-cigarette free homes. The median airborne nicotine concentrations in the homes of non-smokers exposed to e-cigarettes was 10-fold (0.11 μg/m^3) higher than the nicotine concentration (0.01 μg/m^3) in the control (smoke-free and e-cigarette free) homes.

Observational Study

Figure 2 presents the real-time plots (moving average of 60 s) of $PM_{2.5}$ concentrations for 1 h in the four homes. The $PM_{2.5}$ median concentration was 572.52 μg/m^3 in the conventional cigarettes smoker's home (interquartile range (IQR) 431.08–747.24). This concentration was significantly higher than the concentrations in the home of the e-cigarette user and the non-smoker homes. The concentration in the home of the e-cigarette user (9.88 μg/m^3, IQR 8.84–11.96) was similar to those in the non-smokers homes (9.53 μg/m^3, IQR 8.32–10.50, and 9.36 μg/m^3, IQR 8.84–10.40). While the $PM_{2.5}$ medians in the e-cigarette user home and non-smokers smoke-free homes were similar, we noticed $PM_{2.5}$ peaks concurrent with the e-cigarette puffs, as also shown in Fig. 2.

Discussion

The systematic review provides an overview of the few "real-life" studies on the seconhand exposureto aerosol of e-cigarettes. These studies indicate that emissions from e-cigarettes do contain potential toxic compounds such as nicotine, carbonyls, metals, and organic volatile compounds, besides particulate matter. While usually these compounds are generally at lower concentrations than those found in secondhand tobacco smoke, these findings made false the popular statement that e-cigarette emissions are "only water vapor," or that they only include glycerin and propylene glycol beyond nicotine. The number of studies available and the types of e-cigarettes assessed is relatively small, and it is thus unknown if the chemicals and their concentrations vary markedly or not across different e-cigarette types. Moreover, whether secondhand exposure from e-cigarettes poses health risks at short- and long-term is still unknown, and needs further investigation.

Few studies have attempted to investigate e-cigarette aerosols in real-life conditions [8••]. In most of the papers [2••, 5•, 6, 9, 10•, 11, 12], "real-life conditions" refer to simulation of active vaping in a controlled room or chamber, by means of human volunteers actively vaping. Although this approach could serve to control for a number of variables by design, the conditions are so specific that generalization of results are far from satisfactory. Well conducted observational studies in true real conditions, in which the behavior of active vapers and bystanders is registered, together with a valid measurement of environmental markers and personal biomarkers of exposure, should offer new clues about the exposure to e-cigarette emissions.

We have found similar concentrations of $PM_{2.5}$ in the smoke-free homes and in the e-cigarette user homes, both under 10 μg/m^3, which is the threshold concentration for long-term exposures established in the Air Quality Guidelines of the World Health Organization [13]. This is in contrast to the $PM_{2.5}$ concentrations in the conventional cigarette user's home, which were 58 times higher than in the e-cigarette user home. The air nicotine concentrations in the homes of smokers of conventional cigarettes were similar to the concentrations that have been observed in hospitality venues when smoking was allowed [14].

In our observational study, the particulate matter emissions from e-cigarette study were similar to those found in the smoke-free homes. We however observed $PM_{2.5}$ peaks (over the 10 μg/m^3 limit) concurrent with the e-cigarette puffs. This supports past observations that e-cigarettes emit particulate matter [2••, 5•, 6, 10•, 11]. E-cigarettes produce an aerosol with fewer chemical components than those in conventional cigarettes because they do not require combustion, and hence, the temperature reached is lower than that in the conventional cigarettes, as shown in other studies [3, 15].

Some caution in the interpretation of the results of our observational study is needed, because they are based in the homes of four volunteers and only one vaper, using a specific

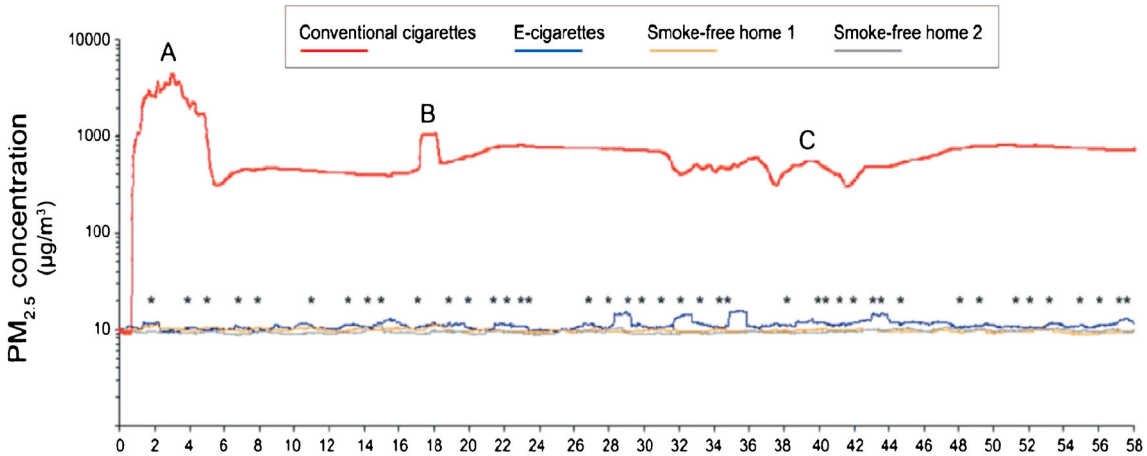

Fig. 2 Real-time $PM_{2.5}$ concentrations (moving average of 60 s) in the e-cigarettes user's home, in a conventional cigarettes user's home, and in two smoke-free homes. Sixty-minute sampling while smoking or using e-cigarette. **a** One cigarette smoked for 6 min. **b** One cigarette smoked for 7 min. **c** One cigarette smoked for 5 min. *E-cigarette puff (42 puffs during the sampling period)

type of vaporizer. Another potential limitation could be related to the possible differences (size and distribution) of the particulate matter from e-cigarettes and conventional cigarettes. An experimental study with aerosol from three e-cigarettes produced by a standard smoking machine [16] showed that the average particle number concentration and particle size of the aerosol from the e-cigarettes is comparable to that of the fresh mainstream tobacco burning cigarette smoke. However, differences among e-cigarette aerosols, due to differences in the type of devices (i.e., cig a likes, medium-sized vaporizers, and tank vaporizers or "mods") that operate at different voltages and temperatures are possible. Despite the potential limitations, our observational study is the first attempting to assess the emission of $PM_{2.5}$ from e-cigarette vapor in real-life use conditions at home, with real e-cigarette and cigarette users and not smoking machines in a laboratory or controlled room, and a long time analyzed (60 min). As shown by the literature review, few studies have attempted to investigate e-cigarette aerosols in real-life or quasi-real-file conditions. In most of the papers, "real-life conditions" refer to simulation of active vaping in a controlled room or chamber, by means of human volunteers actively "vaping". Although this approach could serve to control for a number of variables by design, the conditions are so specific that generalization of results are far from satisfactory. In addition to further controlled experiments mimicking real-life conditions with using e-cigarette users to produce the aerosols, well designed and conducted observational studies in *true* real conditions, in which the behavior of not only active vapers but also bystanders is registered, together with a valid measurement of environmental markers and personal biomarkers of exposure, should offer complementary clues about the exposure to e-cigarette aerosols.

Conclusions

In addition to the literature results, our empirical results support that e-cigarette use in real conditions emit $PM_{2.5}$, although these are notably lower than those from conventional cigarettes as also shown in previous studies. These results add new information to characterize secondhand exposure to e-cigarette emissions and warrant further research using sensitive particle monitors to assess longer period of time [17]. Additional research is needed assessing these relevant chemicals and potential new ones across a variety of e-cigarette devices as well as measuring personal biological markers among exposed people [8••].

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Contributors EF, MB, XS, MF, ES, and JMMS conceived the study. MB and JMMS conducted the fieldwork. EF, MF, and JMMS performed the literature search. EF, MB, MF, and JMMS analyzed the data. All authors contributed to data interpretation. EF drafted the manuscript, which was revised with substantial contributions from all the authors, who approved the final version. EF is the guarantor.

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Compliance with Ethics Guidelines

Conflict of Interest Esteve Fernández, Montse Ballbè, Xisca Sureda, Marcela Fu, Esteve Saltó, and Jose M. Martínez-Sánchez declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent Ethical approval for systematic reviews is not necessary and hence was requested. The ethics committee of the Bellvitge University Hospital provided ethical approval for the study protocol of the observational study including the information and written informed consent forms.

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Format: Abstract

Int J Hyg Environ Health. 2014 Jul;217(6):628-37. doi: 10.1016/j.ijheh.2013.11.003. Epub 2013 Dec 6.

Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers.

Author information

Abstract

Despite the recent popularity of e-cigarettes, to date only limited data is available on their safety for both users and secondhand smokers. The present study reports a comprehensive inner and outer exposure assessment of e-cigarette emissions in terms of particulate matter (PM), particle number concentrations (PNC), volatile organic compounds (VOC), polycyclic aromatic hydrocarbons (PAH), carbonyls, and metals. In six vaping sessions nine volunteers consumed e-cigarettes with and without nicotine in a thoroughly ventilated room for two hours. We analyzed the levels of e-cigarette pollutants in indoor air and monitored effects on FeNO release and urinary metabolite profile of the subjects. For comparison, the components of the e-cigarette solutions (liquids) were additionally analyzed. During the vaping sessions substantial amounts of 1,2-propanediol, glycerine and nicotine were found in the gas-phase, as well as high concentrations of PM2.5 (mean 197 μg/m(3)). The concentration of putative carcinogenic PAH in indoor air increased by 20% to 147 ng/m(3), and aluminum showed a 2.4-fold increase. PNC ranged from 48,620 to 88,386 particles/cm(3) (median), with peaks at diameters 24-36 nm. FeNO increased in 7 of 9 individuals. The nicotine content of the liquids varied and was 1.2-fold higher than claimed by the manufacturer. Our data confirm that e-cigarettes are not emission-free and their pollutants could be of health concern for users and secondhand smokers. In particular, ultrafine particles formed from supersaturated 1,2-propanediol vapor can be deposited in the lung, and aerosolized nicotine seems capable of increasing the release of the inflammatory signaling molecule NO upon inhalation. In view of consumer safety, e-cigarettes and nicotine liquids should be officially regulated and labeled with appropriate warnings of potential health effects, particularly of toxicity risk in children.

KEYWORDS:

Electronic cigarette; FeNO; Health effects; Indoor air quality; Nicotine; Polycyclic aromatic hydrocarbons; Secondhand smoking; Vaping; Volatile organic compounds; e-Cigarette

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Twelve myths about e-cigarettes that failed to impress the TGA

theconversation.com/twelve-myths-about-e-cigarettes-that-failed-to-impress-the-tga-72408

Simon Chapman

Australia's Therapeutic Goods Administration (TGA) last week rejected an application to liberalise the scheduling of nicotine (see from page 71).

This prompted the predictable round of protests from proponents of e-cigarettes who have long touted them as the next public health wonder of the world, even as important as antibiotics.

But unlike antibiotics, which are heavily regulated, require a prescription, and must demonstrate both safety and efficacy to regulatory bodies, e-cigarettes and the liquids used in them are virtually unregulated.

Tobacco harm reduction has had a history of monumental failures. It started with the global multi-million dollar promotion of filters. One of these was the infamous asbestos-filtered "micronite filters" in Kent cigarettes. More recently, we saw the now outlawed consumer deceptions of the light and mild cigarette fiasco. And on the way we even had "reduced carcinogen" brands.

These were designed to keep people smoking and slow the mass exodus that began in the early 1960s. Millions did just that. Only quitting and the decreasing incidence of smoking (ie. never starting) have dramatically decreased the tobacco disease epidemic.

It would be wonderful if e-cigarettes were finally a harm reduction holy grail. But there are many reasons to remain cautious.

Here I look at 12 mantras about e-cigarettes that seem to have failed to impress the TGA.

1. Vaping is '95% less harmful than smoking'

A hand-picked group of 12 produced this magic number when asked to rank the health risks of 12 nicotine delivery products, including cigarettes. Several of the group had no research record or expertise in tobacco control; some had histories of financial connections with manufacturers of e-cigarettes and tobacco companies. There were no toxicologists, cancer or cardiovascular specialists among the authors.

The "95%" number was uncritically repeated in a Public Health England report, which even described e-cigarettes as "around 95% *safer* [not *less dangerous*] than smoking" (my emphasis). Incredulous toxicologists have since pointed out "there is no evidence for the 95% estimate".

The extreme pro e-cigarette activist Carl Phillips, who has a long history of support from tobacco manufacturers, summed it up beautifully:

> This specific point estimate (synonymous with "5% as bad for you as smoking") has rapidly evolved into "fact" (in the political sense of that term). It is repeated in a large fraction of popular press reports and widely used in arguments, snipes, and broadsides from vaping advocates. It seems to have emerged from nowhere when the Public Health England report asserted the figure. That traced to what was actually a huge misinterpretation of what was only a made-up number, from one junk-science journal article.

Phillips may be unique in believing the number is closer to 1%. His supporters in the tobacco and vaping industries are probably very happy with the PR potential of that estimate.

2. Vaping is orders of magnitude less harmful than smoking

Because vapers don't inhale smoke, with its toxic cocktail of carcinogens, irritants and carbon monoxide, this is almost certainly going to be the consensus when sufficient longitudinal data emerge, particularly when it comes to cancer. However, the already mentioned "group of 12" has claimed that "The paucity of evidence for serious harm to users of e-cigarettes over the years since they were first marketed in 2006, with millions purchased, in itself is evidence" of vaping being all but benign.

Even perceptive vapers have seen through this nonsense. It took several decades for the full effects of smoking tobacco to emerge. Worrying evidence about cardio-respiratory effects is already mounting. These highly respected researchers estimated the long-term effects of vaping may equate to 50% of the risk of cardio-respiratory harm that tobacco causes, what they call a "substantial" exposure.

Tobacco-caused cancers may well reduce in people who only vape. But cancer deaths represent only 37% of all tobacco deaths: cardio-respiratory deaths make up most of the rest.

3. Nicotine in vaping is benign

While some make facile comparisons of the risks of nicotine with drinking coffee, the International Agency for Research on Cancer recently noted "evidence has indicated the potential for nicotine to cause DNA damage" and "inhibit apoptosis, and stimulate cell proliferation and angiogenesis …", declaring that evaluation of electronic cigarettes and nicotine is a "high priority".

The recent US Surgeon General Report highlighted the adverse effects of nicotine on brain development in young people and in pregnancy. A recent study has further revealed previously unrecognised negative effects of nicotine, and vaping, on the heart.

4. Vaping has caused 6.1 million European smokers to quit

This factoid was megaphoned from a paper authored by a researcher with a history of funding from e-cigarette manufacturers. It was a secondary analysis of a cross-sectional survey since pilloried in the journal Addiction, where it was published. As any epidemiology

student knows, causality can never be claimed from cross sectional studies. Among other criticisms, the critics asked:

> How many of those who claim that they have stopped with the aid of e-cigarettes would have stopped anyway, and how many of those who used an e-cigarette but failed to stop would have stopped had they used another method.

They also noted the questions asked would have allowed those who quit for only a short period to say they had “stopped”.

Longitudinal studies with a minimum of 12 months follow-up of randomly selected cohorts have shown sobering results, a long way from the hype of vaping having the equivalent efficacy of antibiotics. One such follow-up reported:

> Daily use of e-cigarettes while smoking appears to be associated with subsequent increases in rates of attempting to stop smoking and reducing smoking, but not with smoking cessation.

A companion paper reported daily use of tank-system (refillable) e-cigarettes were the only type of e-cigarette to show a significant improvement in smoking cessation. The very latest data from England show about half of daily e-cigarette users are also smoking (slide 9) and the rate at which English smokers have tried to stop is the lowest in 2016 (30.9%) than it has been since 2007 (42.5%) when the study began (slide 22).

This raises important questions about whether e-cigarettes may be keeping many smokers smoking, while helping others to quit.

5. Just cutting back smoking (rather than quitting) significantly reduces risk

It’s obvious, surely, if you don’t quit but only cut down the amount you smoke, the reduced smoking is going to reduce the harm you are doing? Obvious that is, until you actually look at very large studies that have looked at the death rates down the track in those who reduce but don’t quit.

First, two examples followed 479,156 men for 11 years and found no association between smoking reduction and all cancer risk but a significant decrease in risk of lung cancer, with the size of risk reduction “disproportionately smaller than expected”. Second, a study of 51,210 people followed from the 1970s until 2003 found no evidence smokers who cut down their daily cigarette consumption by more than 50% reduced their risk of premature death significantly.

Vaping advocate and Addiction editor Professor Robert West puts it succinctly:

> I think as far as using an e-cigarette to reduce your harm while continuing to smoke is concerned there really isn’t good evidence that it has any benefit.

And as we saw earlier, a large proportion of people who vape, continue to smoke.

6. Vape is just like water vapour and (often) nicotine

But let's not forget some 8,000 beguiling often kiddie-friendly flavours in e-juice that help the nicotine go down (with apologies to Mary Poppins) have mostly been approved as food additives but have never been approved for inhalation. Here's what the US flavouring industry said:

> The manufacturers and marketers of ENDS [electronic nicotine delivery systems], and all other flavored tobacco products, and flavor manufacturers and marketers, should not represent or suggest that the flavor ingredients used in these products are safe because they have … status for use in food because such statements are false and misleading.

And then there's the liquid propylene glycol in which the nicotine and flavour chemicals are vapourised. Dow Chemical, which manufactures it, says unambiguously, reflecting human data:

> … breathing spray mists of these materials should be avoided. In general, Dow does not support or recommend the use of Dow's glycols in applications where breathing or human eye contact with the spray mists of these materials is likely …

Vapers average about 200 inhalations a day, with this study finding a range of 6 to 611 puffs. That's an average 73,050 deep lung bastings a year, and right up to 223,168. Like cigarette smoke, vape mist contains fine, ultra-fine and nanoparticles, including metals and silicate. It is anything but just like inhaling steam in a shower.

Put simply, we have no data on what happens to people's long-term respiratory or cardiovascular health when they pull these nanoparticles deep into their lungs daily, over many years, at the above rates.

7. Nicotine-free cigarettes contain no nicotine

E-cigarette advocates were excited about a recent study reporting many US teens did not vape for nicotine, but for the flavours. In NSW, it is illegal to sell vape liquid containing nicotine. But a NSW Health random check found many samples contained it. Other examples in the US, and elsewhere, of alleged "non-nicotine" refills turning out to contain nicotine exist, hence the headline "'Nicotine-Free' E-Cigs Still Deliver the Juice".

The US Food and Drug Administration (FDA) summed up:

> Testing also suggested that quality control processes used to manufacture these products are inconsistent or non-existent.

8. Second-hand vape is harmless, so it should not be restricted

I'd rather sit next to a vaper than a smoker. But those vape clouds we see and then don't see don't just vanish. They can be measured. This study of a vapers' meeting where 59-86 people were vaping found counts of PM2.5 airborne particles (fine particulate matter, 2.5 micrometers or less in diameter) 125-330 times higher than in the same room when empty. This is higher than particle concentrations recorded in bars where cigarette or waterpipe smoking are allowed. That will likely explain the other real-world experiences reported by

vapers like this.

If vaping were allowed in bars, restaurants and planes, we all would face behaviour likethis scene. Try imagining workable regulatory wording that would allow “discreet” vaping by a few, but prohibited exuberant “clouding” by a group of vapers drinking in a bar.

If vaping emissions were really benign, indoor vaping advocates should take courage and call for it to be allowed in classrooms, crèches, hospitals and neonatal wards. The fact they don’t rather suggests they know well such a position would be irresponsible.

9. There’s no good evidence for e-cigarettes being a gateway to smoking in young people

In England, this appears to be the case. But in the USA, there’s a rapidly growingbody of evidence suggesting a possible effect. Centers for Disease Controldata from 2015 demonstrate a concerning sudden cessation and plateau in the previous decline of US high school students smoking tobacco, while e-cigarette use is skyrocketing.

Smoking was plummeting in young people in the USA and UK long before e-cigarettes appeared. Today, more young people in the US are using nicotine than ever, which may signal health and brain developmental problems down the track.

10. E-cigarette explosions are overrated

E-cigarette advocates point out other lithium battery-powered items like mobile phones and laptops have exploded, so we should all calm down about dramatic explosions.

However, vapers have noted explosions tend to take place, not just during re-charging, but during use, leading to mounting reports from hospitals of terrible burns and injuries.

When mobile phones explode, we see global recalls as happened with the Samsung Galaxy Note 7. The lack of regulatory standards for e-cigarettes and their components stands in stark contrast to these other products. I’m very pleased e-cigarettes are banned on airlines, but wonder about what would happen if one exploded in stowed luggage.

11. Big Tobacco really wants its smoking customers to switch to e-cigarettes

If this was true, how do we then explain the companies continue to do all they can to wreck effective tobacco control policies like plain packaging, graphic health warnings and significant tobacco tax hikes?

In Hong Kong in December 2016 British American Tobacco was still lobbying against graphic health warnings. And Philip Morris was threatening Uruguay over its advanced tobacco control policies, until it lost its case at the World Bank’s International Centre for Settlement of Investment Disputes in 2016.

Surely, if they were sincere here, they should be pleased governments are trying to get smokers to quit? Philip Morris has been running targeted advertising campaigns with major

youth appeal. And new evidence collated from its own documents demonstrates its interest in e-cigarettes, as long ago as 1990, was only ever for them to be used as a complement to cigarettes.

Big Tobacco has heavily invested in e-cigarettes, with all major tobacco companies now having them in their portfolios. The big picture here is that Big Tobacco wants people to smoke *and* vape, not vape *instead of* smoking.

12. Leading public health agencies encourage 'light touch' regulation

This is mostly the case in England, but very much not the case in many other nations. Advocates constantly point to two e-cigarette "friendly" reports from the UK Royal College of Physicians and Public Health England, which had several common authors.

But 18 nations ban e-cigarettes outright, with more having various degrees of restrictions. Among leading agencies with strong concerns about e-cigarettes are the US Surgeon General, the World Health Organization, the FDA, 31 mostly major health agencies that petitioned the FDA to regulate e-cigarettes, Australia's National Health and Medical Research Council and now the TGA.

E-cigarettes have been generating a huge wave of research interest over the past few years. The next decade promises to throw the light of much needed evidence on many of the issues above. In the meantime, the Australian TGA's caution should be respected.

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OBSERVATIONS

YANKEE DOODLING

Start-up e-cigarette brand aims to "improve smokers' lives"

But the Juul "epidemic" in schools is very worrisome

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Great news: the prevalence of cigarette smoking continues to decline in the US, now down to about 14% of the population.[1] Quite a change from 42% in the early 1960s. Furthermore, high school students' cigarette smoking rate has declined to a new low of 9%.[1]

These decreases may be, in part, because of the increased use of electronic nicotine delivery systems (ENDS), or e-cigarettes. And that, on the other hand, may not be good news, because e-cigarettes have become wildly popular with teenagers. As *Time* magazine recently said, "Vaping is the new smoking. Is that a good thing?"[2]

The most popular US e-cigarette is now a relatively new one called Juul. It has come out of nowhere to become the leading e-cigarette in the US by far. Nielsen surveys show that Juul's market share in convenience store sales exceeded 50% in March this year.[3]

Unlike the other leading e-cigarettes in the US (Vuse, MarkTen, Blu), Juul is not owned by a major tobacco company. Founded by two engineers who were former smokers, Juul has been run like a Silicon Valley start-up company, with offices in a renovated warehouse in San Francisco. Cleverly named to evoke precious jewels and energy promoting joules, Juul was designed to be an un-cigarette. As opposed to the industry standard "cigalikes" that are cigarette shaped tubes, Juul looks like a sleek, black USB drive. Rechargeable in your laptop, Juuls use small, colorful pods to supply nicotine "e-juice," which comes in a choice of eight flavors. All this is packaged in beautifully spare, white boxes more befitting an iPhone than a lowly cigarette.

[Image: Richard B Levine/SIPA USA/PA Images]

Juul's success is not just because of great design and packaging, however. Its "biggest breakthrough was chemical."[4] It is the first e-cigarette to use nicotine salts, which better mimic the rapid "hit" of a combustible cigarette when the vapor reaches the back of the throat.[4] This may help explain its popularity and phenomenal growth rate.

Juul denies marketing to teenagers and says its mission is "to improve the lives of the world's one billion adult smokers."[5] It has pledged $30m (£23m; €26m) over the next three years to prevent youth accessing its products, and the Juul website sales platform has a state of the art ID matching algorithm to prevent minors from purchasing them.[5]

But Juuls are wildly popular in US high schools, where "juuling" has become a verb and the latest cool thing. US newspapers have sounded the alarm: "The Juul is too cool,"[3] "Schools and parents fight a Juul e-cigarette epidemic,"[6] "'I can't stop': schools struggle with vaping explosion."[7] These articles are full of

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personal testimonies from teenagers who cannot stop juuling. The concern is that Juul is producing a new generation of nicotine addicts.

The US Food and Drug Administration, which regulates tobacco products, is clamping down on illegal sales of e-cigarettes to minors, but kids are easily finding ways to circumvent the law, obtaining Juuls from dealers in their schools.[4]

I would take the company's declarations that Juuls are an adult product aimed at improving lives more seriously if it didn't offer flavors called mango, cool cucumber, fruit medley, and crème brûlée. How about just tobacco and maybe menthol flavors, like cigarettes? And if it really wanted to help smokers quit, maybe it should sell pods with decreasing concentrations of nicotine. Of course, that would eventually put it out of business, but with a billion smokers to reach, it would take a while.

Watch out, world. Juul is on the way.

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The irresponsible promotion of e-cigarettes and Swaptober

The House of Commons Science and Technology Select Committee have launched an inquiry into e-cigarette impact, implications, and regulation.[1] National guidance for improving health should be evidence based, with a complete understanding of what is disseminated and encouraged. However, despite substantial gaps in research, e-cigarettes are promoted as part of smoking cessation efforts, including in the Public Health England (PHE) campaign, One You. Should the suggestion of e-cigarettes as a lesser evil be promoted when evidence of their long-term effect is insufficient?

Stoptober is a 28-day PHE initiative that occurs annually in October, with the aim of supporting smokers to quit the habit. In 2017, the campaign began promoting e-cigarettes, which, as stated by the National Institute of Clinical Excellence (NICE), are devices that are not understood in terms of the long-term health benefits or harms.[2] The promotion of e-cigarettes also features in the One You campaign. However, the addition of e-cigarettes to the 2017 mass-media promotion of Stoptober is even more surprising given that the evidence that e-cigarettes aid smoking cessation or reduction is of very low quality,[3] and data are insufficient for a confident estimation of their effectiveness.[4] Hence, the presentation of e-cigarettes alongside evidence-based medicinal products (licensed nicotine-replacement therapy) seems premature, and their portrayal as quitting aids under the Stoptober message of "if you can stop smoking for 28-days, you are five times more likely to quit" is misleading.[5] The Independent British Vape Trade Association sponsors Stoptober, which, among other activities, promotes the vape industry and thus presents a potential conflict of interest. A further concern is the evidence of e-cigarette use by UK children.[6] Preliminary evidence also suggests that e-cigarette use could have deleterious effects in relevant patient groups (eg, those with chronic obstructive pulmonary disease). Given that further understanding of the health implications of e-cigarettes is needed, promotion to the public, including young people and vulnerable populations at risk of shorter-term effects, is not an appropriate implementation strategy.

An emerging concern is Swaptober, another annual October initiative. Launched in 2016, Swaptober aims to convert smokers from traditional cigarettes to e-cigarettes, and is promoted in support of Stoptober. E-cigarettes are promoted as a healthier alternative to smoking, particularly as a first step towards smoking cessation for those finding it difficult to stop. However, e-cigarette companies do not encourage smoking cessation, but rather encourage a long-term swap. Thus, Swaptober, which occurs at the same time as Stoptober, could overshadow and reduce the effectiveness of Stoptober. In line with NICE guidance,[2] smoking cessation should be encouraged, not the swapping to an alternative that is not fully understood. PHE have reported and subsequently been key in publicising the expert opinion that e-cigarettes are 95% safer than tobacco.[7] The credibility of this estimate has been questioned, and has been referred to as a premature conclusion about devices that warrant rigorous safety assessment.[8]

NICE called for caution regarding recommendations for e-cigarettes as a suitable alternative because of the paucity of evidence regarding the long-term health effects.[2] This stance contradicts the views of PHE and the Royal College of Physicians,[7,9] both of whom advocate the wide promotion of e-cigarettes as a substitute for smoking. The contradictory stance of the UK's expert health organisations is likely to confuse public understanding. The inclusion of e-cigarettes in mass-media campaigns to help quit smoking is an example of short-term gain irrespective of the possible long-term consequences. Despite the divide in e-cigarette opinion, all health organisations should accept the need for a balanced approach to e-cigarette regulation. The House of Commons Science and Technology Select Committee inquiry[1] will probably highlight key gaps in the evidence regarding the health benefits or harms of e-cigarettes, which need to be addressed before any further public promotion of e-cigarettes. Until substantial evidence has been gathered on the health implications of e-cigarettes, the promotion of e-cigarettes by health organisations is irresponsible, unethical, and potentially harmful.

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Submission to The Standing Committee on Health, Aged Care and Sport on Electronic Cigarettes and Vapourisers.

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Professor Simon Chapman AO PhD FASSA Hon FFPH (UK) is an Emeritus Professor in Public Health at the University of Sydney, from which he retired in February 2016. He has authored 515 articles, editorials and letters published in peer reviewed journals and 20 books and major reports. His work has been cited over 12,000 times. In 1997 he won the World Health Organisation's World No Tobacco Day Medal and in 2003 he was awarded the American Cancer Society's Luther Terry Award for outstanding individual leadership in tobacco control. In 2008 he won the NSW Premier's Cancer Researcher of the Year award and the Public Health Association of Australia's Sidney Sax medal. He was inaugural deputy editor (1992-1997) then editor (1998-2008) of the BMJ's specialist journal *Tobacco Control.* He is now its editor emeritus. In 2013, he was made Australian Skeptic of the Year and an Officer in the Order of Australia for his contributions to public health.

Professor Mike Daube AO has been Professor of Health Policy at Curtin University since 2005. Before this he was Director General of Health for Western Australia. His roles have included President of the Public Health Association of Australia, President of the Australian Council on Smoking and Health, Deputy Chair of the National Preventative Health Taskforce (and chair of the tobacco committee), Vice-Chair of the WHO FCTC Review Group, and chair, member and patron of many further government and non-government committees in Australia and elsewhere. He has worked on tobacco issues nationally and internationally for more than forty years, and has published widely on this and related issues. He is an Officer in the Order of Australia, and has received further awards from the World Health Organization, the American Cancer Society's Luther Terry Distinguished Career Award, the Australian Medical Association, the National Heart Foundation of Australia, the Public Health Association of Australia, the Thoracic Society of Australia and New Zealand, Environmental Health Australia, the World Federation of Public Health Associations and many other organisations.

David Bareham MSc has been working as a Specialist Respiratory Physiotherapist at Lincolnshire Community Health Services UK NHS Trust for ten years. He currently has two peer reviewed articles related to electronic cigarettes, including one with *Lancet Respiratory Medicine*. He has another review article on e-cigarettes which has just been accepted for publication in the U.S. Last October, in collaboration with Professor Martin McKee and Professor Simon Capewell, he presented Expert Testimony to the English National Institute for Health and Care Excellence Public Health Advisory Committee on the Role of E-cigarettes in Smoking Cessation. His opinions here are his own, and not necessarily those of his employer.

Associate Professor Matthew Peters MD FRACP FThorSoc is a Respiratory Physician and Head of Respiratory Medicine at Concord Hospital. He has academic appointments at Macquarie University and Sydney University. Although a full-time clinician, he has authored over 100 peer-reviewed publications and he has supervised 10 successful PhD students. For more than a decade he was Chair of Action on Smoking and Health, Australia. In 2017 his work in preventing and improving the treatment and care of patients with lung cancer was acknowledged when he received a lifetime achievement award from Lung Foundation Australia.

Summary

The Therapeutic Goods Administration is in every sense Australia's national "umpire" on claims about therapeutic product safety and efficacy. Its decisions over decades have given Australia one of the world's best and most envied therapeutic regulatory systems. Those who have been working to have the TGA circumvented as this umpire are challenging its authority on the flimsiest of pretexts. They have refused to accept the TGA umpire's decision, a course of action which brings them great discredit.

Given current knowledge of risk and uncertainty of benefit for ENDS, unregulated availability should not be an option. The purported benefits are small, uncertain and certainly unexceptional. However, evidence of harms are emerging.

As a core part of the case being put forward for the benefits of ENDS is based on a therapeutic claim (efficacy in smoking cessation), the TGA remains the appropriate regulator for nicotine-containing products. The TGA is also vastly experienced in assessing therapeutic product safety. For these two reasons ENDS must remain under TGA regulation.

To date, there is poor evidence of cessation superiority compared to best practice. Where an effect has been shown it has been small in magnitude. As concluded by the Cochrane Collaboration, the available data on ENDS' efficacy in smoking cessation are low to very low in quality. The clearest conclusion is that there is no exceptional scientifically identified effect that would justify any exceptionalist departure from normal TGA regulatory processes. In addition, the available data apply to only a small number of device/delivery system/delivery parameter possibilities among the plethora available (and increasing in number). Lastly, it is important to consider that smoking cessation is the reason for use of ENDS in a declining minority of users (Ayers, 2017). Most users have no intent to quit smoking, but to only cut down in the false belief that reduced smoking is harm reducing. Because dual users (smoking plus ENDS) do not reduce their risk of harm, the majority of users therefore will not derive even any of the health benefits postulated.

The failure of governments in nearly every nation to regulate tobacco *the product* (advertising, packaging, misleading claims and smoke free areas are all strongly regulated) is not a sensible reason for removing ENDS from TGA regulation. To remove nicotine regulation from the TGA would be to learn nothing from the historic failure to regulate cigarettes. The argument being made by those urging this to happen is "cigarettes are an unregulated public health disaster and are freely available. Let's now take the same unregulated route with ENDS."

Other than injuries caused by exploding ENDS, the harms that may arise from their long term use are unlikely to manifest in the short term. This was of course the history of emerging knowledge about the harms of smoking. Anyone proposing that cigarette smoking was apparently safe 10 years after mass use commenced would have been revealed to have been very badly wrong. ENDS advocates make such parallel claims today. These may turn out to be true or to be recklessly irresponsible - all the more reason to defer to the TGA.

The TGA's regulatory assessment and scheduling powers will allow it to assess submissions for ENDS approval and to then calibrate scheduling that may be either strengthened or liberalised as evidence of harms and/or benefits emerge. Such flexibility is routine in the TGA and occurred (for example) with nicotine replacement therapy which was earlier a prescription only item and is now available in low doses over the counter.

Key questions for policy makers include:

- What is the net impact of the widespread use of ENDS?
- What might be the health effects of long term vaping?
- Does the proliferation in ENDS use tip more people permanently out of smoking than it holds in smoking because of widespread erroneous beliefs that cutting down cigarettes is harm reducing enough?
- Does it pull significant numbers of ex-smokers back into nicotine dependency?
- Does it see children and young people who may have never used any form of nicotine product start vaping or encouraged to think of vaping or smoking as normal and acceptable behaviour for them?

While some nations impose a ban on ENDS, the focus of this submission is on the case for regulating their content and availability through the established processes of the TGA

Note: Throughout, we use the acronym ENDS (Electronic Nicotine Delivery Systems) to refer to electronic cigarettes and all other vapourising systems used to vapourise nicotine and all other materials that are inhaled by their users.

We have arranged the material in our submission sequentially to address the Committee's Terms of Reference. Under each we have set out frequently asked questions often posed in the ENDS debate, and then addressed these. Appendices 1,2 and 4 are found at the end of this document. Appendix 3 is separately attached.
A study of smokers in 18 European nations published in *Preventive Medicine* [Fernandez et al, 2015] provides important data of direct relevance to the hardening hypothesis.

The most recognised way of measuring the "hardness" of smoking is the Heaviness of Smoking Index (HSI). This scores smokers out of a maximum of six, comprising a score of one to three for number of cigarettes smoked each day, and one to three on the time taken to lighting up the first cigarette of the day.

The European study, involving 5,136 smokers drawn from a total 18-country sample of more than 18,000 people, found that across the 18 nations, there was no statistically significant relationship between a nation's smoking prevalence and the HSI.

If the hardening hypothesis was correct, nations with low smoking prevalence would have had higher HSI scores in the remaining smokers. They would have been smoking more cigarettes and lighting up earlier in the morning in nations with low smoking prevalence than in those with high. But they were not.

Similar findings have been reported for the United States. Data on smoking in 50 US states for 2006–2007 indicate that the mean number of cigarettes smoked daily, the percentage of cigarette smokers who smoke within 30 minutes of waking, and the percentage who smoke daily were all significantly lower in US states with low smoking prevalence (see http://www.bridgingthegapresearch.org/_asset/vgm11t/Giovino_2009_TobaccoChartbook.pdf) . Again, this provides compelling evidence against the hardening hypothesis.

In Australia, a 2012 paper [Matthews, Hall & Gartner, 2010] examined three series of Australian surveys of smoking – the National Drug Strategy Household Survey (NDSHS), National Health Survey (NHS) and National Survey of Mental Health and Well-being (NSMHW) – that spanned seven to ten years.

The authors found that in two of the surveys (NDSHS and NHS), while smoking fell across the population, there was no change in the proportion of smokers who smoked less than daily, while in the NSMHW survey, that proportion increased from 6.9% in 1997 to 17.4% in 2007 (indicating a softening, not a hardening of smoking).

The authors concluded that the evidence presented:

> "weak evidence that the population of Australian smokers hardened as smoking prevalence declined."

Undeterred by this evidence, advocates for vaping centre their arguments around assumptions that there are many smokers who they claim are "unable" or "unwilling" to quit smoking. These are both very fluid and imprecise constructs.

Hundreds of millions have quit smoking

It is important to note that many hundreds of millions of smokers have quit smoking all over the world in the years before and since the evidence about the harms of smoking first began being publicised. Many very heavy smokers were among this population.

Most ex-smokers (between two-thirds and three-quarters) quit unassisted (i.e. without using any form of medication, nicotine replacement or getting professional assistance of any sort). [Chapman & McKenzie, 2010]. It is important to recall that nicotine replacement therapy (NRT) only became available in the early 1980s. Before that, a huge number of smokers stopped smoking permanently. [Smith & Chapman, 2014]. Those who stopped smoking without using NRT were not just light, non-addicted smokers but included many heavy and strongly addicted smokers.

In 1955, five years after Ernst Wynder and Evarts Graham's historic study of smokers and lung cancer was published in JAMA (see http://www.epidemiology.ch/history/PDF%20bg/Wynder%20and%20Graham%201950%20tobacco%20smoking%20as%20a%20possible%20etiologic.pdf) 7.7 million Americans (6.4% of the population) were former smokers. Ten years later, following widespread publicity surrounding the 1964 US Surgeon General's Report, this had ballooned to 19.2 million (13.5%) ex-smokers.

By 1975, 32.6 million Americans (19.4%) had stopped smoking.

In 1978, the then director of the US Office in Smoking and Health noted in a National Institute of Drug Abuse Monograph, "In the past 15 years, 30 million smokers have quit the habit, *almost all of them on their own*." (our emphasis) Many of these quitters had been very heavy smokers.

Today, quitting unaided (going "cold turkey") remains the most common way that most ex-smokers have quit, despite more than 20 years of the availability and heavy promotion of nicotine-replacement therapy and other drugs and many other promoted methods of quitting both before and since. One should be very circumspect about voices trying to downplay this major and enduring phenomenon and promoting the view that stopping smoking requires pharmacological or professional help.

"Unable" to stop?

The "unable" to quit group are said to be those who want to stop smoking, but who have tried many times unsuccessfully and are now described by some as "unable" to stop smoking. It is certainly correct that some smokers find it very hard to stop smoking. But it

is equally the case that there are very many ex-smokers who after a succession of failed attempts to stop, then succeed. Indeed, many smokers who quit do so after a number of previous attempts. Such people therefore cannot be described as being "unable" to stop. They might better be described as being those who found it difficult to stop, to varying degrees.

Many quit attempts are clearly not serious attempts to stop, much in the same way that many *attempts* to get fit, lose weight, drink less and so on are also not serious attempts. Research has shown that many smokers who have had few thoughts about quitting make spontaneous quit attempts, and that such attempts are more successful than planned attempts [West & Sohal, 2006; Resnicow et al 2014J

Any roles that ENDS play in assisting some who find it difficult to quit are a far different proposition than than that driving much vaping marketing which is to encourage as many smokers as possible to switch to ENDS. This would include many who may never have any serious difficulty in quitting.

Public policy on ENDS' role in cessation needs to consider how best to make any ENDS products that have been approved for safety and quality accessible to smokers genuinely in need of this form of assistance, without risking the proliferation of these nicotine delivery devices to those who are likely to be able to quit anyway, to those who have no intention of quitting, and to non-smokers (especially children and young people).

Most smokers want to quit, and messaging from vaping interests that they should instead vape (and perhaps merely *reduce* their smoking) is a message that can seriously threaten the 50 year historical momentum for smokers to quit which has seen smoking rates in Australia fall almost continuously since 1980. This of course, would be an outcome that would be very welcomed by the tobacco industry, in which all major companies have bought into the ENDS industry. (see http://vaping360.com/the-battle-for-the-electronic-cigarette-market/)

In this respect, a core message of ENDS marketing is little different to those promoted over many years by tobacco companies during the many years of the low tar fraud, encapsulated by an infamous promotion for an earlier alleged harm reduced tobacco product, the US cigarette brand *True* (see below).

The "unwilling" to stop group

The "unwilling" group are often said to be those who enjoy smoking , or who have no interest or intention of stopping. However, ENDS advocates claim that many in this group have a strong interest in discontinuing smoking (overwhelmingly because of their awareness of the harms of smoking that have been so effectively communicated by tobacco control campaigns, pack warnings and doctor-patient advice) but want to maintain their nicotine addiction through vaping. They believe (or hope) that vaping is far less dangerous than continuing to smoke (see the next term of reference below) and that nicotine is virtually benign in the exposures received by smokers or vapers (also see term of reference #2 for comments on this point).

While some 90% of smokers regret that they ever started to smoke [Fong et al, 2004] some smokers claim that they "enjoy" smoking. A large part of the "enjoyment" that smokers get from smoking is the very palpable experience of relief that smokers get when the nicotine receptors in their brains are replenished with a dose of nicotine. When nicotine dependent smokers go without nicotine they can experience distressing symptoms - "cravings" - which are rapidly relieved by nicotine.

In this way, the ”pleasure” of smoking is in large part the pleasure of avoiding the distress caused by the absence of nicotine in one's body. To refer to this as “pleasure” is like arguing that being beaten up every day is something you want to continue with, because it feels so good when the beating stops for a while. And clearly hundreds of millions of ex-smokers who experienced this “pleasure” decided that the risks it brought far out-weighed the benefits of continuing.

What is the quality of the evidence to date about ENDS assisting smokers to quit smoking?

In assessing evidence about any intervention in smoking cessation, a variety of evidence can be considered.

Randomised Controlled Trials

Those who research the quality of evidence refer to high and low quality evidence. The highest quality evidence that can be considered in answering the question of whether vapourisers are useful in smoking cessation is the randomised controlled trial (RCT). This is where smokers wanting to quit smoking would be randomised into several different study groups. Typically, these would be where some would be allocated to use nicotine containing vapourisers; some given another form of smoking cessation intervention (such as NRT or varenicline); and others would be given a non-nicotine vaporiser (placebo).

At the time of writing (June 2017), there is only one recognised RCT that reasonably complies with these basic methodological characteristics [Bullen et al, 2013]. As the authors stated:

> “657 people were randomised (289 to nicotine e-cigarettes, 295 to patches, and 73 to placebo e-cigarettes) . . .” At 6 months, verified (biochemically confirmed) abstinence was 7.3% (21 of 289) with nicotine e-cigarettes, 5.8% (17 of 295) with patches, and 4.1% (three of 73) with placebo e-cigarettes (risk difference with nicotine e-cigarette vs patches 1.51 [95% CI -2.49 – 5.51]; for nicotine e-cigarettes vs placebo e-cigarettes 3.16 [95% CI -2.29 – 8.61]). Achievement of abstinence was substantially lower than we anticipated for the power calculation, thus we had insufficient statistical power to conclude superiority of nicotine e-cigarettes to patches or to placebo e-cigarettes.”

Other significant methodological concerns with this trial included that the delivery of nicotine e-cigarettes to participants was, unrealistically, via courier, whereas the patches group had to take a voucher to a chemist in order to obtain their nicotine replacement

therapy. Perhaps unsurprisingly, there was a high loss-to-follow-up noted in the patches group. It is entirely feasible, therefore, that the study *overestimated* the very "modest" effect size of nicotine e-cigarettes, and *underestimated* the effect size of well-managed nicotine replacement therapy.

Another RCT assessing the efficacy of ENDS for smoking cessation (Caponnetto et al, 2013) involved a study of smokers, though, in contrast to the aforementioned RCT study, *not* seeking to quit smoking. It involved only placebo comparison groups, and found no consistent differences in smoking cessation between nicotine e-cigarette and placebo e-cigarette.

In September 2016, the Cochrane Collaboration published an updated review and meta-analysis of this evidence, and the usefulness of electronic cigarettes in smoking cessation. It concluded:

> "There is evidence from two trials that ECs help smokers to stop smoking in the long term compared with placebo ECs. However, the small number of trials, low event rates and wide confidence intervals around the estimates mean that our confidence in the result is rated 'low' by GRADE standards. The lack of difference between the effect of ECs compared with nicotine patches found in one trial is uncertain for similar reasons." (Cochrane Collaboration Hartmann-Boyce et al, 2016)

However, in contrast to this analysis demonstrating, at best, a very weak positive association between e-cigarette use and smokers stopping smoking, another meta-analysis of the current RCT data [El Dib et al, 2017], identifying the aforementioned high loss-to-follow-up issue, highlighted that another entirely feasible interpretation ("plausible worse case sensitivity analysis") is that e-cigarettes "fail to show a difference" in smoking cessation compared to placebo. As they point out:

> ". . . the 95% CI of the relative risk crossed 1.0 and a plausible worse case sensitivity analysis to assess the risks of bias associated with missing participant data yielded results that were inconsistent with the primary complete case analysis."

We understand that several RCTs are now under way. These should be important in increasing knowledge about ENDS' efficacy in cessation.

Cohort studies on cessation

A lower form of evidence than RCTs is the longitudinal cohort study. This is where a group of smokers are followed for a long period to determine what proportions using different methods of trying to quit are not smoking at different times of follow-up. Because of the

very common phenomenon of relapse in smoking cessation, studies which report long follow-up data are more important than those reporting short-term findings,

The aforementioned Cochrane Review did not apply meta-analysis to cohort data on ENDS. However, the El Dib review did (n=8 studies), and in fact noted a potential *suppression* of chances in successful quitting when people use ENDS: "Cohort studies provide very low-certainty evidence suggesting a possible reduction in quit rates with use of ENDS compared with no use of ENDS" [El Dib, 2017].

Cross-sectional studies

Cross-sectional studies are a still lower form of evidence. These are where "snapshot" surveys of the community are undertaken and data obtained on the proportion of smokers who answer that they are no longer smoking.

Weaknesses in relying on this type of data include, fundamentally (as any epidemiology 1 student knows) that causality can never be claimed from cross sectional studies. Because data from participants in a cross-sectional (snapshot) studies are recorded only once, inference of temporal associations between ENDS use and smoking outcomes cannot be made. Only associations, not causation can be inferred from cross sectional studies.

An example of cross-sectional data from which inappropriate claims *were* made about e-cigarette cessation effects was a secondary analysis of the 2014 Eurobarometer survey data by Farsalinos and others (2016). Claims were made that vaping "caused 6.1m European smokers to quit smoking" (recently repeated in an article in the *Sydney Morning Herald* by Dr. Colin Mendelsohn - http://www.smh.com.au/comment/ecigarettes-needed-to-get-more-adults-to-quit-smoking-20170625-gwybcb.html)

This causal factoid has been widely promoted through social media, but was demolished in the journal *Addiction* where it was published [Maziak & Taleb, 2016]. Among other criticisms, the critics in *Addiction* asked:

> "how many of those who claim that they have stopped with the aid of e-cigarettes would have stopped anyway, and how many of those who used an e-cigarette but failed to stop would have stopped had they used another method?"

They also noted that the questions asked in the survey would have allowed those who quit for only a short period to say they had "stopped".

Longitudinal studies with a minimum of 12 months follow-up of randomly selected cohorts have shown sobering results, a long way from the hype of vaping having the equivalent

efficacy of antibiotics (Nutt D, 2013: https://www.youtube.com/watch?v=8rYSFiyZhwQ). One such study reported that:

> "Daily use of e-cigarettes while smoking appears to be associated with subsequent increases in rates of attempting to stop smoking and reducing smoking, *but not with smoking cessation.*" (our emphasis, Brose et al, 2015)

A companion paper [Hitchman et al, 2015] reported that daily tank system users were the only type of ENDS which showed a significant improvement in smoking cessation, although, the number of self-reporting vapers using these systems in that study was only 19.

Further, there are data which demonstrate that, for England, there are important differences between self-reported abstinence and biochemically verified abstinence. As West et al note:

> "Self-reported cigarette and total tobacco smoking prevalence were assessed by means of the standard questions used . . . In subsamples, specimens were collected for analysis of cotinine (saliva, N = 1,613 in England . . .) providing an objective means of determining active smoking . . . Self-reported cigarette smoking prevalence using the standard methods underestimated true tobacco smoking prevalence by an estimated 2.8% in England . . . Cotinine concentrations in those misclassified as nonsmokers were indicative of high levels of smoke intake. Interpretation: Underestimation of smoking prevalence was significant in England . . .". [West et al, 2007]

The same study identified no such discrepancy in U.S. data, and therefore, the validity of English ENDS survey data not utilising biochemical verification should arguably be viewed with this evidence in mind.

Not approved as cessation devices in USA

The current scientific evidence base does not, therefore, support recommending these devices as effective in smoking cessation. They are not approved as cessation aids by the US FDA [Brandon et al, 2015], nor by the US Preventive Services Task Force (USPSTF) which concluded "that the current evidence is insufficient to recommend electronic nicotine delivery systems (ENDS) for tobacco cessation in adults, including pregnant women" [USPSTF, 2015], an analysis with which we fully agree.

What are the limitations of personal testimonies in establishing evidence?

"the plural of anecdote is not evidence".

Dr Tom Frieden, former Director of the US Centers for Disease Control and Prevention

The Committee will receive many testimonies from former smokers who will passionately explain that they were able to stop smoking by using ENDS. Many will argue that their experience self-evidently means that many others will, like them, also stop smoking after using an ENDS. Some of these will have been generated by tobacco companies such as Philip Morris, which have solicited such submissions to the inquiry. (see http://www.abc.net.au/radio/melbourne/programs/mornings/big-tobacco-spamming-punters-to-submit-to-government-inquiry/8667096)

Personal testimonies can also be found from ex-smokers on websites promoting smoking cessation strategies which are been shown under controlled research conditions to have very poor outcomes. These include acupuncture, "laser therapy" (see for example http://www.imaginelaserworks.com/additional-services/stop-quit-smoking/) and hypnosis, all of which have been assessed as being supported by very poor evidence of assisting smoking cessation. Those working in tobacco control are very familiar with a wide range of cessation approaches promoted by some quitters as the only or best approach because they worked for them. These range from astringents to herbal remedies to 5 Day Plans to clinics to books.

No one respectful of evidence gives any credibility to such personal testimony for cessation methods known from high quality reviews of evidence to be of poor efficacy. We should hold claims about the efficacy of ENDS in cessation to the same standards.

Those who quit smoking after using ENDS understandably attribute their smoking cessation to ENDS. Some want to spread their good news and encourage others to try to do what they have done. However, those who have tried and failed to quit using ENDS i.e. the substantial majority are far less likely to be as enthusiastic and evangelical. Positive personal testimonies represent flagrant self-selection bias about success and cannot be given any credibility when it comes to making generalisations about the success or otherwise of a cessation method.

What proportion of long-term users of vapourisers still smoke? ("dual use")

The significant majority of adult smokers who try ENDS to quit smoking stop using them [Simonavicius et al, 2017; UK Office for National Statistics, 2016]. Most adults who use ENDS continue to smoke conventional cigarettes ("dual users"). In 2014 in the US, 93% of ENDS users continued to smoke cigarettes [Patel et al, 2016], 83% in France [Andler et al, 2016], and 60% in the UK [UK Office for National Statistics, 2016].

It is essential to highlight here that even ardent advocates of ENDS point out that:

> ". . . concern(s) have been {partly} expressed that dual use" may encourage "smokers who could otherwise have quit elect for dual use instead, *in the mistaken belief that this generates significant health gains*" [our emphasis: Royal College of Physicians, 2016]

Professor Robert West (a leading figure in tobacco cessation research and director of the large *Smoking in England* national study told the BBC in February 2016, (http://www.bbc.co.uk/programmes/b070dq8h)

> "[This widespread use of e-cigarettes] raises an interesting question for us: If they were this game changer, if they were going to be – have this massive effect on everyone switching to e-cigarettes and stopping smoking *we might have expected to see a bigger effect than we have seen so far which has actually been relatively small*" [our emphasis]
>
> "We know that most people who use e-cigarettes are continuing to smoke and when you ask them they'll tell you that they're mostly doing that to try to cut down the amount they smoke. But we also know that if you look at how much they're smoking it's not really that much different from what they would have been doing if they weren't using an e-cigarette. *So I think as far as using an e-cigarette to reduce your harm while continuing to smoke is concerned there really isn't good evidence that it has any benefit*." [our emphasis]

As background to this statement, West et al (2016) estimated that between 16 000 and 22 000 extra smokers may have quit per year in England because of ENDS use, above and beyond the number who would have quit in the absence of ENDS. At a population level this equates to a change in smoking rates of 0.044-0.061%. This figure can be placed into perspective when looking at the average annual fall in smoking prevalence that Australia (which has insignificant ENDS use) in the 25 years between 1991 (29.5%) and 2016 (14.9%). Australia has achieved an average annual fall *10 fold greater* than the median estimate of 0.05% contribution calculated for ENDS by West et al. This ratio is similar if only the recent period 2010-2016 is examined. This small potential benefit would naturally have to be considered in conjunction with known ENDS harms.

	1991	1993	1995	1998	2001	2004	2007	2010	2103	2016
Daily	24.3	25	23.8	21.8	19.4	17.5	16.6	15.1	12,8	12.2
Weekly	2.8	2.3	1.6	1.8	1.8	1.6	1.3	1.5	1.4	1.3
< weekly	2.4	1.8	1.8	1.3	2	1.6	1.5	1.4	1.6	1.4
Total	29.5	29.1	27.2	25.9	22.2	20.7	19.7	18	15.8	14.9

Smoking in Australia, persons aged 14+ 1991-2016
Source: Australian Institute of Health and Welfare

West et al (2016) described their estimations thus:

> "Evidence from RCTs and from surveys in England indicate that using an e-cigarette in a quit attempt increases the probability of success on average by approximately 50% compared with using no aid or LNP bought from a shop—similar to use of a licensed medicine with limited behavioural support but less than medication plus specialist behavioural support [6,7].".

The two references the authors used here were the Cochrane Collaboration review [Cochrane, 2016] (which noted that the evidence for smoking cessation with ENDS was low to very low) and a cross-sectional study [Brown et al, 2014] which have the weaknesses we described above. With the caveats that must apply to these sources, we would submit that no firm conclusions as to effect size can be credible, considering the fragility of these data.

The Committee should therefore be most circumspect in considering claims that ENDS use in the UK has caused a dramatic fall in smoking rates.

Very recent data from England show that about half of daily ENDS users are also smoking (Figure 1 below) and that the rate at which English smokers have tried to stop was the lowest in 2016 (30.9%) than it had been since 2007 (42.5%) when the study began (Figure 2 below). The decline in those attempting to quit is 11.6% in absolute terms and 27.3% in proportional terms. These are very disturbing data which would greatly please those in the tobacco industry.

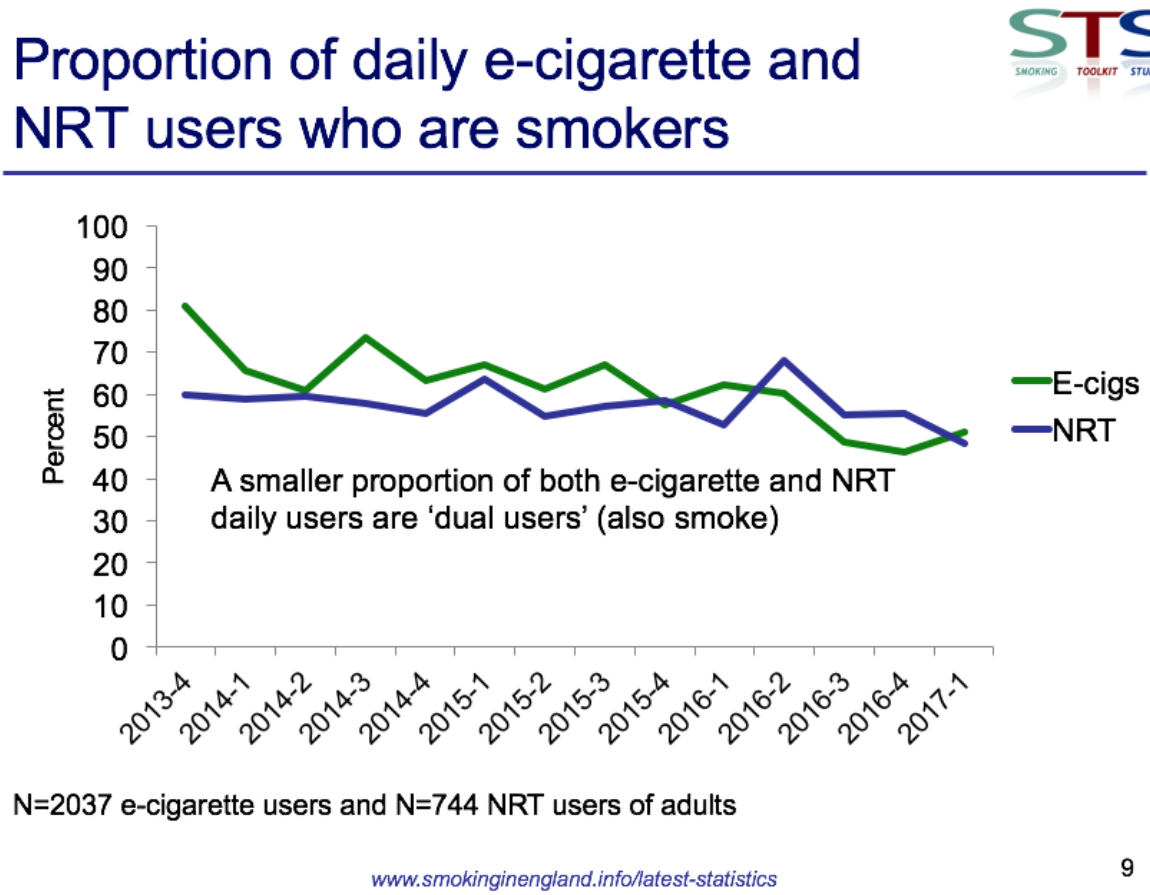

Figure 1: About half of daily e-cigarette users in England are currently also smoking cigarettes

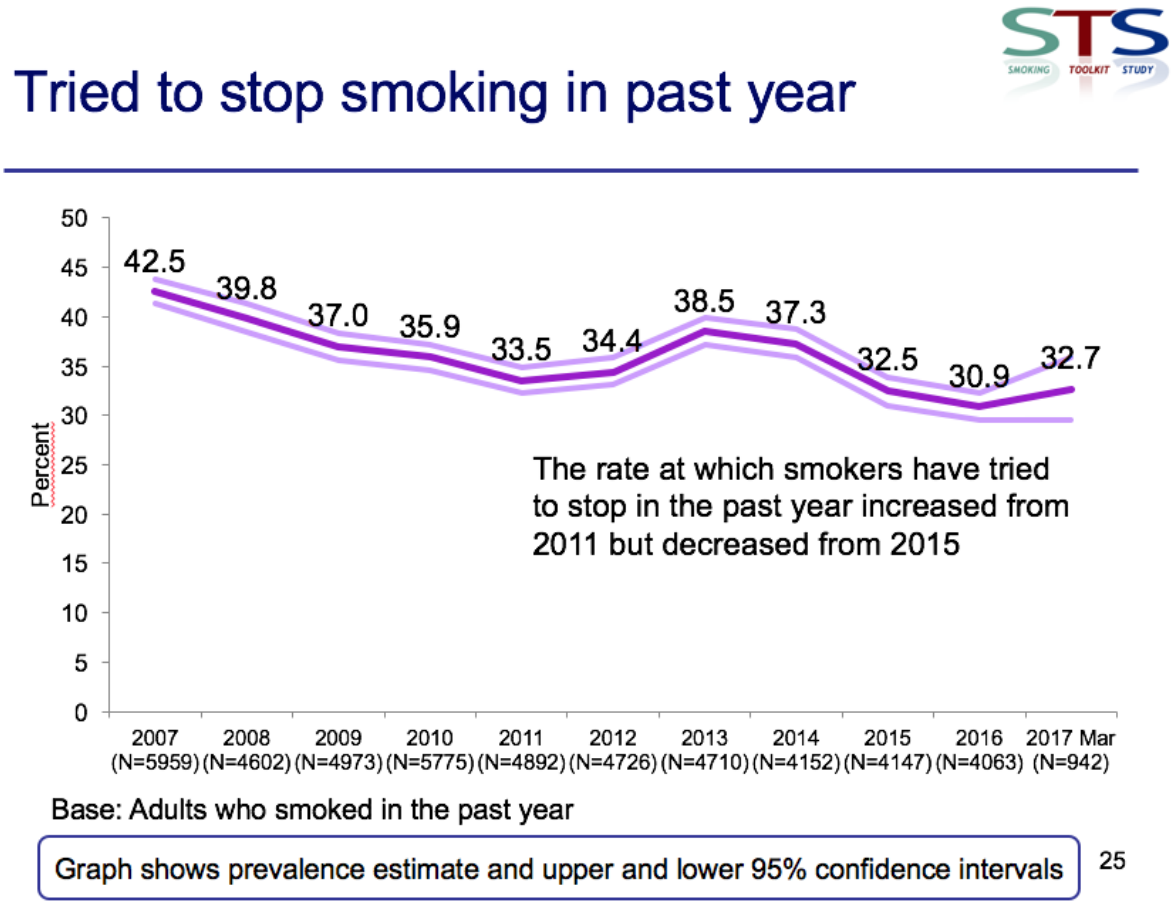

Figure 2: Continuing decline across 10 years in percentage of English smokers trying to stop smoking (e-cigarettes became available from around 2007)

These data raise important questions about whether ENDS may be holding many smokers in smoking even if they help some to quit. Moreover, new data concerningly suggest that non-daily vapers may actually *increase their consumption* of conventional cigarettes [Doran et al, 2017]. Further, it has been suggested that one of the key reasons for US cigarette consumption being higher higher in 2015 than in 2014 (the first time cigarette consumption increased since 1973) [Wang T et al. 2017], was because of continued dual use. Recent qualitative data, where dual users are asked about their continued smoking and vaping behaviours, suggests that dual users may find it harder to quit, as they do not actually view themselves as smokers [Vandrevala et al, 2017].

Key questions for public health therefore include: what is the net impact of the widespread use of ENDS? Does the proliferation in ENDS use tip more people permanently out of smoking than it holds in smoking? Does it pull significant numbers of ex-smokers back into nicotine dependency? Does it see children who may have never used any form of nicotine

product start vaping or encouraged to think of vaping or smoking as normal and acceptable behaviour for them? What might be the health effects of long term vaping?

Marketing

Interest groups promoting ENDS understandably wish to be allowed to promote their products to as wide an audience as possible. These groups are generally cognisant of the need to at least appear to be acting responsibly, by claiming they do not want children to use ENDS. However, the reality with ENDS at the retail level suggests the opposite. Results of a recent UK Chartered Trading Standards Institute investigation [CTSI, August 2016] identified that approximately 40% (246/634) of retailers illegally sold nicotine e-cigarettes and vaping liquids to children and young people, with 50% (68/137) specialist vaping shops "flouting" laws regarding the selling ENDS and nicotine e-liquids to children.

Another example of this was exposed recently by the UK Royal Society for Public Health [RSPH, 2017], which undertook an undercover investigation of 100 of the UK's 1700 independent vape shops. Nearly nine in 10 stores (87%) were either knowingly, or unwittingly, selling ENDS to people who have never smoked or vaped. As was highlighted by the RSPH:

> "Almost half (45%) of stores did not check whether new customers were current or former smokers."
>
> "Three quarters (76%) of those that did check continued to encourage the customer to start vaping, even once they knew they were a non-smoker."
>
> "This is in direct violation of the Independent British Vape Trade Association (IBVTA) code of conduct which states: "Vape products are for current or former smokers and existing users of vaping devices, therefore never knowingly sell to anyone who is not a current of former smoker, or a current vaper." (http://www.ibvta.org.uk/join-us/code-of-conduct)

"The code of conduct exists to ensure e-cigarettes are perceived as an effective aid for quitting smoking, rather than as a lifestyle product" [RSPH, 2017].

Allegations of "irresponsible" marketing tactics utilised by elements of the ENDS industry were recently made by Dr K Farsalinos, a vociferous advocate for the potential of ENDS to help adult smokers quit, who stated:

> "I wonder if there is anyone who thinks that the use of cartoons and funny graphics . . . is not going to be perceived as appealing, and an attempt to actively promote the products, to youth . . . this is absolutely unacceptable and a clear indication of irresponsible behaviour . . ." (Farsalinos, 2017)

Industry claims of being public health allies are obviously nothing but cynical public relations gestures because, like all industries, the future of ENDS commerce depends on new users. With ENDS, this means non-users of ENDS taking them up and becoming addicted to nicotine via ENDS. Smokers are an obvious target, but children are another which cannot be airbrushed out of public policy considerations (see Term of Reference #5 below).

The same tobacco companies which are now heavily investing in ENDS have always strenuously publicly denied that they do not want children to smoke.

Voluminous evidence from their own internal documents reveals that such statements were duplicitous public relations statements [Assunta & Chapman, 2004; Knight & Chapman, 2004]. If the ENDS industry is to survive, and flourish, it will need to attract new users: adult smokers, adult non-smokers and youth, which it appears to be attempting to do. It is manifestly in the interests of tobacco companies and any others involved in the e-cigarette industry that children and young people should view their products favourably and be encouraged to use them. Any denials on this issue carry as much credibility as tobacco industry denials over the decades.

The figure below shows an example of the sort of packaging and promotional appeals that have been seen in England recently. This link shows examples of ENDS promotions with major appeal to children in the USA
http://www.tobaccofreekids.org/tobacco_unfiltered/post/2015_06_17_ecig

Figure: child-attracting vaping products on sale in England, 2016

As the University of Bath Research team point out "E-cigarettes are being marketed in a way which emulates very successful tobacco advertising asserting an independent identity and a lifestyle choice, aligning oneself with celebrities, fashionable and youthful places and activities."

The current bill before the Senate presented by Senators Leyonhjelm and Roberts (Vaporised Nicotine Products Bill 2017) seeks to allow the advertising of ENDS through

changes to the Tobacco Advertising Prohibition Act 1992. There is no known form of advertising which can only be seen by adults but not by children. Should this Bill succeed, ENDS marketers would be effectively free to promote their products, brand names and corporate identities to the entire community, including (non-smokers as well as smokers, children and young people. We would doubtless witness the same farcical and totally ineffectual "safeguards" against this as we witnessed with assurances about non-appealing advertising and children with tobacco advertising in the 1980s and even earlier. It is indeed fifty years since the late Senator Robert Kennedy said in 1967,

> "If we were starting afresh, I would say the first line of action would be industry self-regulation of advertising. But we have witnessed a charade of purportedly self-regulation for some years. The codes of self-regulation have been largely ineffective, and I see little hope for change. The industry we seek to regulate is powerful and resourceful. Each new effort to regulate will bring new ways to evade".

Giving the tobacco industry or any others carte blanche to advertise e-cigarettes would be a catastrophic error - yet another demonstration of the need to respect the processes of the TGA.

Below are photographs taken in NSW of ENDS products being sold alongside confectionery at eye-level, where young children would easily see them. Tobacco products are required to be stored out-of-sight in all Australian states and territories. We believe the same regulations should apply to ENDS products.


Skittles
Skittles
Skittles
Wobl Bobba
Wobl Bobba

Term of Reference #2. The health impacts of the use of e-cigarettes and personal vaporisers

Unlike inhaling tobacco smoke from combusted tobacco products, inhaling vapour does not involve inhaling the smoke arising from combusted tobacco. That smoke contains carbon monoxide, tar, many carcinogens and co-carcinogens, toxicants and irritants. ENDS do not ignite the contents of the liquids which are vapourised. They instead heat them, and so there is no carbon monoxide or "tar".

From this, it has been argued that inhaling vapour will be eventually acknowledged to be of *far* less risk to health than smoking. However, many ENDS advocates are adamant that we know this to be true already, barely a decade after ENDS use began to be used widely in some countries.

They argue that there is no need to wait any longer before adopting policy based on assumptions that ENDS are all but benign, and accordingly ENDS should be treated as such.

They argue that smoking now kills 7 million people a year and will kill an estimated 1 billion during this century and that widespread use of ENDS will see such figures dramatically reduced. This would be self-evidently a wonderful thing if it their predictions were to be later shown to be correct. But as we will argue, the evidence that we have confidence that we currently have to inform these predictions is very scant. There is also overwhelming evidence that tobacco companies selling and promoting ENDS are indeed doing all they can to continue to aggressively promote cigarettes - and hence the deaths they cause - in both developing and developed countries.

Tobacco control has had a long history of wild, unbridled and commercially driven enthusiasms for purported reduced harm products (filters, asbestos filters, reduced carcinogen cigarettes, "low" tar, "lights", tobacco substitutes, etc). None of these were subsequently demonstrated to reduce harm is those who used them. [Parascandola, 2011}. It does not follow from this that ENDS will similarly be found to fail as harm reduction devices, but the long history of failure and the consequences of again promoting false hopes must give all responsible authorities strong pause for consideration.

This submission is not a formal, systematic review of the research literature on ENDS. However, our concern is to give some perspective to the obvious campaign by ENDS

advocates to present an entirely sanitized view of what is known about the health risks of ENDS use.

There is a rapidly growing toxicological research literature on the health effects of ENDS.

Appendix 1 below shows an indicative recent selection of such research. No one reading this research who had an open mind as to whether ENDS might be seriously harmful could form the view that they were free from serious concerns and should be sold as freely as grocery items, let alone widely promoted.

With respect, parliamentary committees are not in a position to assess the scientific quality of specialised toxicological research such as that we have highlighted in this submission and in Appendices 1 and 2 . In Australia, that is very obviously and properly the role of expert bodies like the TGA and the NHMRC which can convene and commission independent scientific expertise to advise governments.

Both have already done this with ENDS.

Is it too soon to know whether vapourisers are really far less dangerous than cigarettes?

It has been claimed, utterly bizarrely, by some that:

> "The paucity of evidence for serious harm to users of e-cigarettes over the years since they were first marketed in 2006, with millions purchased, in itself is evidence" that they do not cause such serious harm (Nutt et al, 2016).

The main diseases caused by smoking (cancers, respiratory and cardiovascular) are known as chronic diseases. While there can be some people who manifest smoking-caused health problems early, clinical signs of diseases like lung and heart diseases and cancers typically begin to show up in larger numbers several decades later. The harms of smoking do not manifest quickly in the ways that those resulting from exposure to infectious or acutely toxic agents do. The aforementioned claim by Nutt et al is, therefore, at odds with what is well established with conventional cigarettes.

Smoking skyrocketed when cheap, affordable cigarettes first appeared early in the twentieth century following the invention of mechanised cigarette rolling machines. Over the next 20 years, lung cancer remained an uncommon, even rare disease.

The US surgeon Alton Oschner, recalling attendance at his first lung cancer autopsy in 1919, was told he "might never see another such case as long as we lived". He saw no further cases until 1936 -- 17 years later - and then saw another nine cases in six months. Today lung cancer is (by far) the world's leading cause of cancer death.

The incidence of lung cancer rose rapidly in the decades 1930-1980 but it was not until 1950 that definitive evidence was published in the USA and the UK that long-term smoking caused lung cancer, by far the most common form of fatal cancer today. Knowledge about smoking's causal role in other diseases followed.

If any scientist had declared in 1920 that cigarette smoking was all but harmless, history would have judged their call as dangerously incorrect. But this is the reckless call that many ENDS advocates are making today, after just 10 years.

What is the provenance of the claim the e-cigarettes are "95% safer" than cigarettes?

This number was produced by a hand-picked group of 12 [Nutt D et al, 2014] who were asked to rank the health risks of 12 nicotine delivery products, including cigarettes. Several of the group had no research track record or expertise in tobacco control and some had histories of financial connections with manufacturers of ENDS and tobacco companies [Gornall, 2015]: a network diagram from the British Medical Journal (http://www.bmj.com/content/351/bmj.h5826/infographic) shows these interconnetions between some of the authors. The authors stated that "There was no formal criterion for the recruitment of the experts although care was taken to have raters from many different disciplines."

However, there were no toxicologists, cancer or cardiovascular specialists among the authors. The "95%" number was uncritically repeated in a Public Health England (2015) review and report, which amazingly even described e-cigarettes as "around 95% *safer* [not *less dangerous*] than smoking" (our emphasis). Incredulous toxicologists have since pointed out: "there is no *evidence* for the 95% estimate" [their emphasis, Combes & Balls, 2015]

Even the pro-ENDS activist Carl Phillips, who has a long history of support from tobacco manufacturers (see http://www.tobaccotactics.org/index.php/Carl_V_Phillips), summed up this study as follows:

> "This specific point estimate (synonymous with "5% as bad for you as smoking") has rapidly evolved into "fact" (in the political sense of that term). It is repeated in a large fraction of popular press reports and widely used in arguments, snipes, and broadsides from vaping advocates. *It seems to have emerged from nowhere* when the

> Public Health England report asserted the figure. That traced to what was *actually a huge misinterpretation of what was only a made-up number, from one junk-science journal article*." (our emphasis) https://antithrlies.com/2016/05/25/saying-e-cigarettes-are-95-less-harmful-is-a-very-bad-idea-part-143-of-10000/

Moreover, several UK organisations which have cited this paper as being central to their perspectives (e.g. Public Health England; Royal College of Physicians; NHS UK) appear not to have noticed that the group of twelve authors themselves stated that:

> "A limitation of this study is the lack of hard evidence for the harms of most products on most of the criteria."

So, a group of 12 people estimated that ENDS were 95% less dangerous than cigarettes, despite acknowledging themselves that they had a "lack of hard evidence of most products on most of the criteria" for their guess. This is hardly surprising, as this risk estimation exercise was carried out in the summer of 2013, just a few years after ENDS devices became readily available to consumers.

Bizarrely, the authors of the "study" subsequently attempted to respond [Nutt et al, 2016] to extensive criticism of it [Lancet, 2015] by attempting to counter the correct observation that their study suffered from, among other things, a lack of hard evidence. As noted above, they had, *themselves*, explicitly stated in the original article that this *was*, indeed, the case.

Didn't both the Public Health England and the Royal College of Physicians reports on e-cigarettes endorse the "95% safer" figure?

Yes they did, however, neither of these two groups provided any data, calculations or formal risk assessment to substantiate the production of the "95%" figure, nor indeed, any possible figure. They would have appeared to have just repeated the same, identical opinion-led "justifications" originally published by the Nutt et al group.

So what is the true risk of e-cigarettes compared with cigarettes?

We have often been asked "well, if you question the risk as being 95% less dangerous, what is *your* estimate?" Those asking this question appear to not understand that no estimate can be made currently that has any acceptable toxicological degree of accuracy. This is the opinion of expert toxicologists, who have noted:

> " . . . Public Health England and the Royal College of Physicians in the UK, largely relied on expert opinion and where evidence was considered it largely focused on studies of vaping aerosol and e-liquid composition with relatively few biomarker studies . . ."[Wilson et al, 2016]

Their subsequent analysis of the few recent relevant biomarker studies available at the time of their review revealed a:

> ". . . very diverse range of results . . . but all suggest lower levels of risk for vapers compared to tobacco smokers". However, "preliminary evidence . . . suggests that the effect of vaping on four . . . inflammatory markers of likely relevance to cardiovascular disease (CVD) and respiratory disease may be at least half that of tobacco smoking" and "The results for cancer-related toxicants were variable, from 0% to 23% of the levels observed for tobacco smokers, with most studies reporting between 14% and 23% – *a substantial level of exposure***"** [Wilson et al, 2016, our emphasis].

Because of the relatively few years in which people have vaped, it is not currently scientifically possible to provide a credible single figure estimate of risk. The World Health Organisation confirmed this when they stated:

> "The magnitude of these risks is likely to be smaller than from tobacco smoke although there is not enough research to quantify the relative risk of ENDS/ENNDS over combustible products. Therefore, no specific figure about how much "safer" the use of these products is compared to smoking can be given any scientific credibility at this time" [WHO, 2016]

Two toxicologists put it rather more bluntly, that to label ENDS as "low risk" products is:

> "*in the light of current knowledge*, a reckless and irresponsible suggestion" . . . such a view "ignores the possibilities that users might be repeatedly exposed to hitherto undetected contaminants and by-products, as well as to carcinogenic chemicals, or their precursors (which have been detected in solvent extracts and vapours, and which are derived from tobacco during solvent extraction or generated during solvent heating), that can have effects at very low dose levels, following repeat exposures, which can occur without clear threshold doses, thus necessitating zero-dose extrapolation." (their emphasis, Combes and Balls, 2015).

As key co-authors of the 2016 UK RCP "Nicotine without smoke" review stated at the same time that the RCP review was published, ENDS are highly unlikely to be harmless:

> "long term use is likely to be associated with long term sequelae, including an increased risk of chronic obstructive pulmonary disease, lung cancer, possibly cardiovascular disease, and some other long term conditions associated with smoking" [Britton et al, 2016; WHO, 2016] i.e. sequelae associated with the well-documented spectrum of harm caused by smoking conventional cigarettes .

Vaping advocates urge smokers to switch to ENDS. Those who fully switch are likely to experience reduced risk of premature death from smoking caused diseases, but the magnitude of that risk remains entirely speculative, in the absence of any large longitudinal population studies.

How often do vapers inhale vapour?

In 2014, the US tobacco company Lorillard posted on a website advising parents about how they could talk to their children about vaping, claiming, misleadingly and irresponsibly, that:

> *"The 'smoke' you see coming out of e-cigarettes isn't smoke -- it's WATER VAPOR.*"

(http://www.tobacco.ucsf.edu/sites/tobacco.ucsf.edu/files/u9/What%20you%20need%20to%20know%20about%20e-cigarettes%20%E2%80%93%20Infographic%20_%20Real%20Parents%20Real%20Answers_may31-2014.pdf *and*

http://www.tobacco.ucsf.edu/lorillard-maker-blu-ecigs-tells-parents-ecigs-just-emit-harmless-water-vapor-thats-not-true)

Vapers average about 200 inhalations a day, with a 2016 study [Martin et al, 2016] finding a range of 6 to 611 puffs, an average 73,050 deep lung bastings a year, up to 223,168. Like cigarette smoke, vape mist normally contains, as well as nicotine, normally, a cocktail of toxic contaminants and by-products, for example, proinflammatory fine, ultra-fine and nano-particles [Fouco et al, 2013], potentially harmful and carcinogenic metals and silicate [Williams et al, 2013; Hess et al, 2017], toxic and carcinogenic aldehydes [Kosmider et al, 2014], and potentially cytotoxic flavourings [Farsalinos et al, 2015]. It is *anything but* just like "inhaling steam in a shower", as some on vaping blogs have irresponsibly tried to describe it.

Lung Health

The primary target or site of inhaled ENDS vapour is the lung. The lungs have a combined surface area the size of a tennis court and are hugely exposed to vapourised products. For organic compounds, other chemicals and heavy metals, in vapour that can be absorbed into the lung circulation, there is a broad access avenue. Normally, the lungs have a critical surface fluid lining that is vanishingly thin so that the volume of this fluid is less than 5mls. At the conclusion of a vaping session, it has been estimated that half of the lining fluid composition is derived from the vaping inhaler. [Manigrasso, M., et al 2015]

This is critically different from an asthma spray. 99% of the propellant of an asthma spray is exhaled unaltered in gaseous form with the active drug in powder form being left behind (Leach, 2005).

Further, for the majority of ENDS users who are also current smokers, the altered lung lining fluid may actually increase exposures to toxins within cigarette smoke. Normal lining fluid is little more than salty water and fat-based toxins from smoke cannot dissolve in it. [Fröhlich, 2017]. In contrast, by its very nature, ENDS vapour is an excellent solvent. Changing the properties and constituents of lung lining fluid may, for example, change the absorption and effect of common treatments for asthma or alter in a very deleterious fashion cigarette smoke particle transit in the majority of ENDS users who continue to smoke .

That this change in the lung liquid interface is a real, and not just a theoretical, risk is supported by data from aviation safety training that shows changes in the basic properties of tear fluid in the eyes from propylene glycol [included in almost all ENDS] exposure in aviation safety training exercise.

A highly detailed review of the lung toxicity of ENDS has recently been published in the *American Journal of Physiology* [Chun et al, 2017]. This was funded by the US FDA and the National Cancer Institute. The review concludes:

> "In summary, there is a rapidly growing body of evidence derived from in vitro, animal, and human studies that e-cigarette use may have *significant pulmonary toxicity.*" (our emphasis)

Specific harms that the review addresses include:

A. Harms in adolescent ENDS users

In a study of 45,000 adolescents in Hong Kong, use of ENDS in the preceding 30 days doubled the risk of cough and phlegm in both ever smokers and never smokers [Wang et al 2016]. In a separate study of 40,000 adolescents in South Korea, ENDS use more than doubled the risk of asthma being diagnosed and more than trebled the frequency of school absence related to asthma.[Cho & Paik 2016] These harms are real, immediate and a cause for concern about protecting children from ENDS whether containing nicotine or otherwise.

B. Harms of flavourants and other vehicle compounds.

ENDS contain many flavourants that are approved for oral ingestion but not for inhalation. Further, the superheated environment in ENDS alters these chemicals to definite toxins and higher levels of toxins, equal to or greater than those seen in cigarette smoking. This can be seen when variable power devices are set to their highest setting. In particular the carcinogen formaldehyde and other aldehydes may be present in higher concentrations (Khlystov and Samburova, 2016).

C. Harms of heavy metal exposures

The heating coil for ENDS can easily decay or flake and cause toxic heavy metals to be included in solution or as a particle in the vaped aerosol. These include nickel, chromium and aluminium. All are carcinogens and all are better not inhaled. Silicates that are also carcinogenic may also be formed. [Williams et al 2013]

What do we know about the health consequences of inhaling nicotine many thousands of times a year?

ENDS advocates have sought to trivialise the health risks of nicotine, regularly sheltering behind the slogan:“People smoke for the nicotine but die from the tar” [Russell, M. 1991]

The inhalation of nicotine, however, may be anything but benign. The International Agency for Research on Cancer [IARC, 2014] recently noted that they had not previously evaluated electronic cigarettes and nicotine. They describe current evidence, and note that “recent evidence has indicated the potential for nicotine to cause DNA damage” and “In addition, exposure to nicotine has been shown to inhibit apoptosis, and stimulate cell proliferation and angiogenesis . . .”. Subsequently, due to their rapid uptake as consumer products in

many countries, the IARC declared that an evaluation of electronic cigarettes and nicotine is a "High Priority".

Appendix 2 lists recent research reports about the possible role of nicotine as a cancer promoter. This growing area of research underscores why it remains entirely appropriate that nicotine should remain within the regulatory oversight of the TGA in Australia.

There is no ENDS device that is a purely nicotine delivery system. Most ENDS deliver nicotine, which has its own toxicity as well as, clearly, the well documented effect of psychophysiological addiction. But they also deliver a variety of chemical vehicles/solvents, flavours etc that are separately and perhaps cumulatively toxic, and none of which are approved for inhalation in the form that they are included in solutions or in any chemically altered form that might emerge after superheating. As has been articulated by toxicologists:

> ". . . users might be repeatedly exposed to hitherto undetected contaminants and by-products, as well as to carcinogenic chemicals, or their precursors (which have been detected in solvent extracts and vapours, and which are derived from tobacco during solvent extraction or generated during solvent heating), that can have effects at very low dose levels, following repeat exposures, which can occur without clear threshold doses, thus necessitating zero-dose extrapolation" (Combes and Balls, 2015)

Many vapers reduce how much they smoke. Isn't reducing smoking obviously harm reducing?

Recent studies with small groups of subjects [Goniewicz et al, 2017; Shahab et al, 2017] indicate that smokers who fully switch from from cigarettes to ENDS reduce their exposure to various carcinogens and toxicants. They highlight, however, that "e-cigarettes are likely to be beneficial only if complete cessation of combustible cigarette smoking is achieved" [Shabab et al, 2017]. As we have discussed, large proportions of ENDS users are dual users and continue to smoke, so are highly unlikely to be reducing harm.

While there is strong evidence for a causal association between early uptake, amount smoked and duration (pack years) of smoking, the evidence on "reverse engineering" harm by continuing to smoke while cutting back is far from strong.

A Norwegian cohort of 51,210 people followed from the 1970s until 2003 found "no evidence that smokers who cut down their daily cigarette consumption by >50% reduce their risk of premature death significantly" [Tverdal & Bjartveit K. 2006]. A Scottish study [Hart et al, 2013] of two smaller cohorts followed from the 1970s to 2010 found no

evidence of reduced mortality in reducers, but clear evidence in quitters and concluded "that reducing cigarette consumption should not be promoted as a means of reducing mortality." The largest study, from Korea [Sung et al, 2008] and involving 479,156 men followed for 11 years , found no association between smoking reduction and all cancer risk but a significant decrease in risk of lung cancer, with the size of risk reduction "disproportionately smaller than expected".

A 2007 systematic review of the evidence on the health impact of reduction which included none of the above important studies, noted that most studies examined reductions in smoking of more than 50%. It found:

> "A substantial reduction in smoking seems to have a small health benefit, but more studies are needed to determine the long-term effects of smoking reduction" [Pisinger and Godtfredsen, 2007].

The apparently commonsense argument that it must be self-evidently true that continuing to smoke, but only smoking less than before, is harm reducing is therefore very poorly supported by research evidence.

What do we know about inflammation associated with vaping?

We have emphasised that it is far too soon to know at the population level whether widespread vaping will cause significant health problems, or health gains. We have further noted that vapers who stop smoking and fully switch to ENDS are exposed to much lower levels of many toxic and carcinogenic substances [Goniewicz et al, 2017; Shahab et al, 2017].

However, serious health effects can be observed when exposure to doses of such substances are very low [Combes & Balls, 2015]. For example, there is evidence that the dose-response curve for the potent lung carcinogen NNK, as identified in e-cigarette aerosol [Goniewicz et al, 2013] is highly nonlinear, has no clear threshold, with substantial increases in occurrence of lung cancer at very low doses [Hengstler et al, 2003, Figure 9, cited in Combes & Balls, 2015].

Recent independent comprehensive reviews of the current literature on health risks are available, and highlight both potential cardiovascular risks [Bhatnagar et al, 2016; Schweitzer et al, 2017)] and respiratory risks [Chun et al, 2017]. For example, Glycerol, one of the two solvent agents utilised in delivering nicotine and flavourants in e-cigarette fluid, when heated to even very low temperatures (relative to combustion temperatures), has been known for at least 90 years to thermally decompose and form, among other

chemicals, the highly toxic aldehyde acrolein [Lawrie, 1928]. The smell of burnt fat, when cooking oil is heated, is caused by glycerol in the burning fat breaking down into acrolein; there is growing evidence that chronic inhalation of such cooking fumes is related to lung disease [Juntarawijit C & Juntarawijit Y, 2017] . As the aforementioned reviews show, low dose acrolein has the potential to cause both respiratory and cardiovascular disease [Chun et al, 2017; Bhatnagar et al, 2016; Schweitzer et al, 2017]. Inhaled low dose acrolein has been strongly associated with causing chronic pulmonary inflammation i.e. COPD, a reduction of host respiratory defenses, neutrophil inflammation, mucus hypersecretion and protease mediated lung tissue damage [Moretto et al, 2012]. Moreover, "prolonged exposure to even low-dose . . . acrolein results in nonspecific inflammatory cardiac lesions" [Bhatnagar et al, 2016].

On the crucial issue of aldehyde exposure, a highly critical review of a key paper postulating that users of ENDS do not inhale significant levels of acrolein and other toxic aldehydes (e.g. formaldehyde, acetaldehyde) [Shihadeh et al, 2015] highlighted substantial problems with the paper. Shihadeh et al (scientists active in the field of electronic cigarettes, including exposures to aldehydes), highlighted that the criteria commonly considered during peer review (i.e. that "the method be described sufficiently so as to allow replication, results and data analytical techniques are presented thoroughly, and conclusions are based on the results presented") were "not met" by Farsalinos et al in 2015. [Farsalinos et al *Addiction*, 2015]

However, the Farsalinos et al (2015) study was uncritically cited by Public Health England 2015 as evidence that that puffs of ENDS aerosol, relatively rich in toxic aldehydes, are "instantly detected [by vapers] due to a distinctive harsh and acrid taste. This poses no danger to either experienced or novice vapers, because [such] dry puffs are aversive and are avoided rather than inhaled."

This presumption was based on only this one study of just seven vapers using unflavoured liquid. This flavouring issue is important, as some flavours are already known to potentially mask the harsh, acrid tastes of cigarettes, and therefore, potentially, ENDS [Alpert et al, 2015]. The original Farsalinos et al study itself recommended further studies to better understand interindividual differences in tasting perception. Longitudinal studies would further be needed in order to establish potential changes in perception: it has been correctly noted that some smokers, over time, learn to "overcome" and inhale puffs of cigarette smoke, rich in aldehydes [Rowell and Tarran, 2015]. These issues highlight the importance of: sticking to the scientific method; appropriate peer review; and of replication and expansion of results, *prior* to influential public health organisations making, in effect, unsubstantiated generalisations from one small study.

Highly reactive free radical production, also implicated in the causation of the irreversible inflammatory lung disease COPD from cigarette smoking, has also been identified in ENDS aerosol [Goel, 2015]. The volumes of highly reactive free radicals collected were, perhaps predictably, much less than those in found in cigarette smoke, presumably related to the absence of combustion in ENDS aerosol production. However, as the authors point out:

> "Since the overall levels of radicals are significantly lower than those observed in conventional cigarette smoke, it might be expected that the degree of damage might be less, but this depends on the identity and reactivity of the specific radicals produced" [Goel et al, 2015]

Research already carried out in human subjects (Martin et al, 2016) indicates that ENDS suppress genes involved in the immunity and inflammatory responses of users: the authors signal the necessity for further research into the respiratory consequences of vaping.

A very recent review of the potential cardiovascular risks of vaping concluded that:

> "The majority of studies found some evidence of a significant risk effect for e-cigarettes, although the evidence was not totally consistent within and between studies. Suggestive evidence also implicates a possible effect of e-cigarettes on inflammation processes. Levels of risk indicators for e-cigarettes were sometimes lower than those found for cigarettes but several studies showed comparable effects" [Schweitzer et al, 2017].

As noted above, ENDS work by creating an aerosol of ultrafine particles that carry nicotine deep into the lungs of users, and thereby into the bloodstream to the heart, and then to the brain. These particles are as small as – and sometimes smaller – than those in conventional cigarettes [Fuoco et al, 2014]. Importantly, these ultrafine particles are biologically active, and can trigger inflammatory processes that are directly implicated in causing cardiovascular disease, and acute cardiovascular events [Pope C et al, 2009]. The dose-response effect for exposure to these particles, similar to the above example of the potent lung carcinogen NNK, is nonlinear, with substantial increases in cardiovascular risk with even low levels of exposure to ultrafine particles [Pope et al, 2009]. There is some evidence, already emerging, of a potential link between ENDS use and increased risk of heart attacks [Temesgen et al, 2017. See link to full discussion of this new data in the Reference List].

ENDS expose users who fully switch to them to reduced levels of carcinogens, which may likely reduce their risk of cancer. However, it should be noted here that most of the premature, preventable deaths associated with smoking tobacco are related to cardiovascular and non-cancer respiratory disease, and not cancer [U.S. Department of

Health and Human Services, 2014], and that current interpretation implicates significant cardiovascular and non-cancer respiratory health risks .

Is it safe to inhale vapourised propylene glycol?

Propylene glycol (PG), like glycerol, is a chemical used in vaping liquid in which the nicotine and flavour chemicals are vapourised and transported into the lungs. There are some very old data on the effects of inhaled PG in animals [Robertson & Loosli, 1947], which are regularly cited in the literature relating to potential positive effects [e.g. Farsalinos and Polosa, 2014]. However, Dow Chemical, which manufactures PG, says unambiguously, reflecting data from *human* subjects (Weislander et al, 2001), that:

> ". . . breathing spray mists of these materials should be avoided. In general, Dow does not support or recommend the use of Dow's glycols in applications where breathing or human eye contact with the spray mists of these materials is likely…"
> (DOW, 2003)

Weislander et al highlighted that:

> "Short exposure to PG mist from artificial smoke generators may cause acute ocular and upper airway irritation in non-asthmatic subjects. A few may also react with cough and slight airway obstruction."

It has been incorrectly claimed by some that PG is a solvent utilised in the delivery of inhaled nebulised medications for asthma sufferers, and that, therefore, "it must be safe". **No standard asthma inhaler in Australia contains propylene glycol.** However, there is evidence that it is in fact the case that PG is used in this therapeutic fashion, although, it is "a commonly used drug solubilizer in topical, oral, and **a very limited number of i**njectable medications" (https://www.drugs.com/inactive/propylene-glycol-270.html).

This view has been articulated even by active advocates of vaping (Johnson L, 2016) who stated, subsequent to his own research, that he was completely unable to identify confirmatory evidence for PG being used in nebuliser therapy. He stated that the claim is fundamentally "misleading", and that, "as many vapers will know – some people find PG very irritating to the throat". Johnson continued to speculate on the genesis of the claim:

> "As for why this argument has gained so much traction, my only guess is for the same reason I want it to be true: it's so powerful to be able to say, "well, even asthmatics can inhale PG without problems, so worrying about it in e-cig vapor is

> silly." But when you really want something to be true, you don't have much motivation to go and check out whether or not it's really the case" [Johnson L, 2016]

Is it safe to inhale vapourised flavouring chemicals?

There are now some 8000 beguiling and often child-friendly flavours being sold in e-juice [Allen et al, 2016; Barrington-Trimis et al, 2014]. These have mostly been approved for ingestion as food additives, but have never been approved for inhalation. The U.S. flavouring industry has said about this issue:

> "The manufacturers and marketers of ENDS, and all other flavored tobacco products, and flavor manufacturers and marketers, should not represent or suggest that the flavor ingredients used in these products are safe because they have FEMA GRAS™ status for use in food because such statements are false and misleading." [see https://www.femaflavor.org/safety-assessment-and-regulatory-authority-use-flavors-focus-electronic-nicotine-delivery-systems]

For some flavourants, for example cinnamon, there is already evidence for cytotoxicity [Behar et al, 2014] and for the very commonly utilised additive diacetyl, which produces a pleasant, buttery taste in e-liquid, there is an association with the causation of the non-reversible respiratory condition Bronchiolitis Obliterans [Farsalinos et al, 2015; Allen et al, 2016]. The English National Centre for Smoking Cessation and Training has already recommended that users avoid cinnamon and diacetyl flavoured e-liquid [NCSCT, 2016]but these are still on sale. Cherry flavoured ENDS fluids have also been demonstrated, via the inhalation of the irritant benzaldehyde, to be a potential concern for long term users [Kosmider et al, 2016].

Our knowledge of the impact of long term inhalation, many times a day over many years, of vapour arising from the heating of these chemicals is in its infancy. We therefore recommend adopting the precautionary principle to issues related to the safety of ENDS.

What do we know about explosions that occur with vapourisers?

There are continuing reports of reports of dramatic explosions occurring with ENDS from around the world. Those working in trauma care have published case-series of serious burns and injuries and shotgun like injuries arising from these explosions [e.g. Jiwani et al, 2017; Bohr S et al, 2016; Shastry S et al, 2016]

There are now dozens of cases reported in medical journals of burns and other injury related to lithium-ion battery powered device malfunction. Explosive malfunction causes

three complications: blast injury, thermal burn from the device and superheated vaping liquid and corrosive burn from lithium. (Brownson et al, 2016)

Broadly, device-related injuries can be grouped into those when the device is not in use, most commonly when in a trouser pocket, and when in use near or in the mouth. Explosions in the vicinity of the mouth during use are potentially catastrophic. Reported consequences include major dental injury (Brooks et al, 2017; Harrison et al, 2016), injury to soft tissues in the mouth and pharynx and even fractures of C1/C2 vertebrae (Norii and Plate, 2017).

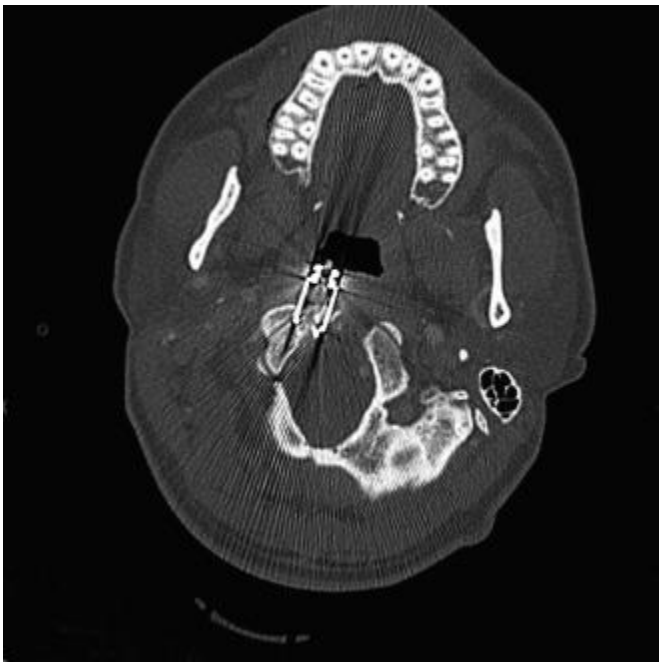

Image: Computed tomographic scan axial view showing fractures involving the superior cortex of the anterior arch of C1 at the posterior aspect of the foreign body. Source: Norri and Plate. Journal of Emergency Medicine, 2017. Volume 52, Issue 1, Pages 86–88.

Burn injuries are becoming so frequent that a classification system has been proposed (Patterson et al 2017) . Burns have most commonly been reported in the thigh area. Whereas first aid for thermal burn generally is based on water application, this may worsen the situation with lithium burn. The total burn area averages less than 10% but may include the external genitalia - an area that represents particular challenges for burns surgery and of course important long-term physical and psychological harms for the (generally) young person affected.

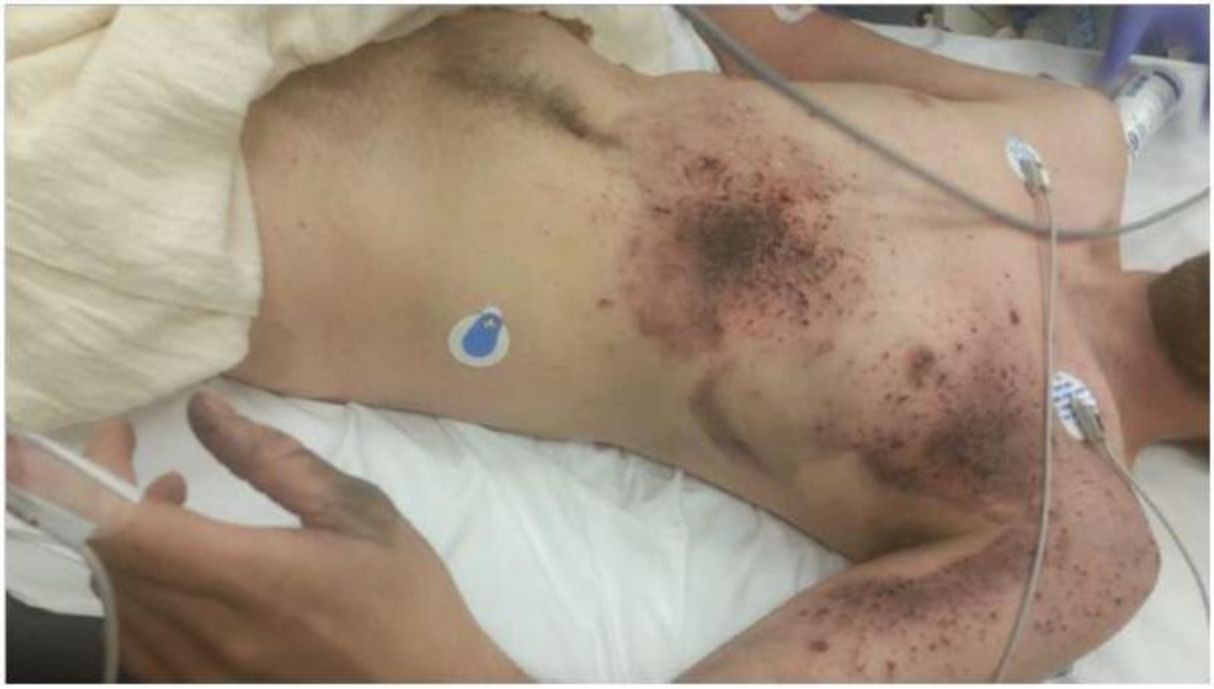

Image: Shrapnel-like injury from exploding ENDS device in a shirt pocket. Source: Shastry et al West J Emerg Med. 2016 Mar; 17(2): 177–180

ENDS advocates often note that other lithium battery-powered items like mobile phones and laptops have also exploded (often in far greater numbers than have ENDS), apparently implying from this that there is no need for concern about the safety of ENDS and their batteries. Explosions have occurred in pockets as well as during inhalation http://ecigone.com/featured/e-cigarette-explosions-comprehensive-list/

When mobile phones and computers explode, we see responsible industries suspend sales or enact global recalls, until they have rendered the product safe, as happened with the Samsung Galaxy Note 7 in 2016. At the time Samsung initiated its global recall, there had been only 35 cases of battery-related explosions - much less even than the number of cases of injury from exploding ENDS devices that have now been reported in medical journals alone.

In 2006, Dell computers recalled 4 million batteries (https://www.cnet.com/au/news/dell-to-recall-4-million-batteries/) and HP recalled 101,000 batteries in January 2017. We are very pleased that use of ENDS is banned on nearly every airline. There has been one report of an ENDS explosion and fire on board an aircraft (in an overhead locker) [http://www.star-telegram.com/news/local/community/fort-worth/article121150273.html]. Fortunately

this was extinguished by crew. An ENDS explosion in stowed luggage where it could not be extinguished could have catastrophic consequences.

The lack of regulatory standards for ENDS and their components stands in stark contrast to these other products.

Term of Reference #3. International approaches to legislating and regulating the use of E-cigarettes and personal vaporisers

Assertions have been made that there is widespread support for light touch regulation of ENDS, and that Australia is an outlier in its present policy position. This support is, however, far from universal among nations, health authorities and agencies. It is misleading to portray Australia as an outlier.

The "light touch" position is naturally favoured by those involved in ENDS manufacture and commerce, and accordingly is an approach supported by those conflicted with commercial objectives. It is also favoured by many who vape today.

Some experts have argued that that analysis of the International Tobacco Control Four Country surveys (i.e. data from the United States and Canada, the United Kingdom and Australia), demonstrate that:

> "Use of ECs in the real world during a quit attempt appears only effective for sustaining smoking abstinence in a less restrictive EC environment suggesting that the benefits of ECs [electronic cigarettes] for smoking cessation are likely highly dependent on the regulatory environment" [Yong et al, 2017].

This analysis has been strongly critiqued by Benmarhnia et al (2017), who identified that

> "there are at least three limitations in this paper that severely temper the conclusions reached by the authors and, in our view, cannot be addressed by the supporting data. Given the importance of the research question, it is equally important that firm conclusions be generated from appropriate data."

As they argued:

> "[firstly] . . the measurement of e-cigarette use was only valid in one of the ten waves of the data used" . . . secondly, that "the analyses suffer from inadequate sample size, drawing into question the generalizability of the sample to the population they are purported to represent. For instance, there are only 50 respondents from either Canada or Australia who reported using an e-cigarette over the entire 11-year period" . . . and thirdly, that "the authors consider how the association of e-cigarette use with 30-day cigarette abstinence varies across countries categorized according to their regulatory environment . . . , but the validity

of this proposed singular distinction has not been demonstrated" [Benmarhnia et al, 2017]

The Johns Hopkins Bloomberg School of Public Health has summarised ENDS regulation of 123 countries in a comprehensive website (see http://globaltobaccocontrol.org/node/14052). This summary reported that the sale of all types of ENDS is banned in 26 countries, 18 countries regulate ENDS as medicinal products, 26 countries regulate ENDS as tobacco products (or imitation/derivative/substitute products) and four countries regulate ENDS containing nicotine as poisons. Use of ENDS is banned in three countries (Cambodia, Jordan and the United Arab Emirates). As of February 2016, 71 countries had been identified that regulate ENDS.

Global

Among leading health agencies with strong concerns about ENDS are the World Health Organization, the US Surgeon General, the, the US FDA,, Australia's National Health and Medical Research Council and the TGA.

USA

- US Food and Drug Administration (see regulations here https://www.fda.gov/tobaccoproducts/labeling/productsingredientscomponents/ucm456610.htm#regulation)

- US Surgeon General (see https://e-cigarettes.surgeongeneral.gov/documents/2016_sgr_full_report_non-508.pdf)
-

Thes 51 US groups listed below have all urged the US political administration to support the Food and Drug Administration's regulation of ENDS (see http://www.tobaccofreekids.org/press_releases/post/2017_05_17_fda)

Action on Smoking & Health
American Academy of Family Physicians
American Academy of Oral and Maxillofacial Pathology
American Academy of Pediatrics
American Association for Cancer Research
American Association for Dental Research
American Association for Respiratory Care
American Cancer Society Cancer Action Network
American College of Cardiology
American College of Occupational and Environmental Medicine

American College of Physicians
American College of Preventive Medicine
American Congress of Obstetricians and Gynecologists
American Dental Association
American Heart Association
American Lung Association
American Medical Association
American Psychological Association
American Public Health Association
American School Health Association
American Society of Addiction Medicine
American Society of Clinical Oncology
American Thoracic Society
Americans for Nonsmokers' Rights
Asian Pacific Partners for Empowerment, Advocacy and Leadership
Association of Women's Health, Obstetric & Neonatal Nurses
Big Cities Health Coalition
Campaign for Tobacco-Free Kids
ClearWay Minnesota
Community Anti-Drug Coalitions of America
Eta Sigma Gamma - National Health Education Honorary
March of Dimes
National African American Tobacco Prevention Network
National Association of County and City Health Officials
National Association of Pediatric Nurse Practitioners
National Center for Health Research
National Hispanic Medical Association
National Network of Public Health Institutes
National Physicians Alliance
Oncology Nursing Society
Prevention Institute
Prevention Partners
Public Health Solutions
Society for Cardiovascular Angiography and Interventions
Society for Public Health Education
Students Against Destructive Decisions
The Society of State Leaders of Health and Physical Education
Tobacco Control Legal Consortium
Trust for America's Health
Truth Initiative

United Methodist Church- General Board of Church and Society

Australia

In Australia, the NHMRC, the Cancer Council, the Heart Foundation, the Australian Medical Association, Lung Foundation Australia, Thoracic Society of Australia and New Zealand and the Public Health Association of Australia and New Zealand have all expressed support for TGA regulation of ENDS.

UK

The Public Health England agency claims there is a consensus in England regarding the safety and usefulness of ENDS. This ignores the fact that prominent health organisations and scientists within the UK are not part of it, and have demonstrably disagreed with at least some of PHE's position. For example:

1. The British Heart Foundation: "There is a lack of empirical research regarding the effectiveness of e-cigarettes as a smoking cessation aid . . .". [https://www.bhf.org.uk/publications/policy-documents/e-cigarettes-policy-statement
2. Public Health Wales: "Confectionery-like' flavours of e-liquid should not be permitted, in order to reduce the appeal of ENDS to children and young people". [http://www.wales.nhs.uk/sitesplus/888/news/43873]
3. ASH Scotland e.g. ". . . widely varying estimates demonstrate the difficulty of attributing a meaningful value to {the health} risk {of e-cigarettes} without long-term studies of health of e-cig users." (http://www.ashscotland.org.uk/media/627028/e-cigarettes-march-2017.pdf
4. Professor Helen Stokes-Lampard, Chair of the Royal College of General Practitioners "Vaping should not be allowed in public places where cigarette smoking is banned". (http://www.rcgp.org.uk/news/2016/december/vaping-should-not-be-allowed-in-public-places-where-cigarette-smoking-is-banned-says-rcgp-chair.aspx)
5. The British Medical Association: "There is some evidence in other countries that e-cigarettes may be acting as a gateway to smoking" http://www.bma.org.uk/-/media/files/pdfs/working%20for%20change/policy%20and%20lobbying/pa-e-cigarettesbriefing-03-12-2014.pdf (see Term of Ref 5 below)
6. The Royal Pharmaceutical Society: "We have expressed concern over possible safety issues of using e-cigarettes, as well as a lack of evidence of their efficacy when used for smoking cessation" . . . "We recommend that policy-makers must do everything they can to avoid a new generation of people becoming addicted to nicotine. This is particularly important in light of the current lack of evidence in relation to long-term health effects of using e-cigarettes, and their secondhand emissions" (https://www.rpharms.com/making-a-difference/policy-a-z/e-cigarettes)

7. English toxicologists Dr Robert Combes and Emeritus Professor Michael Balls' comprehensive critique of the position of Public Health England is self-explanatory [Combes & Balls, 2015].

Seven policy approaches to ENDS regulation were outlined in Section 4 of a report prepared for the Commonwealth Department of Health in 2016 (the Committee secretariat has been sent a copy).
These policy approaches are not meant to be mutually exclusive.

The seven possible policy approaches are as follows:
Policy approach 1: Maintain the status quo
Policy Approach 2: Increase awareness and enforcement of and compliance with existing legislation
Policy approach 3: Regulate ENDS as medicines
Policy approach 4: Regulate ENDS as tobacco products
Policy approach 5: Regulate ENDS as consumer products
Policy approach 6: Develop an ENDS regulatory framework
Policy approach 7: Adopt measures to ban ENDS

We commend that report for the Committee's consideration (Note: author Chapman contributed a section to that report)

Term of Reference #4: The appropriate regulatory framework for E-cigarettes and personal vaporisers in Australia

Australia introduced modern approaches to drug regulation in 1963 following the thalidomide tragedy. The Therapeutic Goods Administration (TGA) and its predecessors have had responsibility for the evaluation, regulation and scheduling of any product where therapeutic claims are made.

The TGA

> " safeguards and enhances the health of the Australian community through effective and timely regulation of therapeutic goods". It is well recognised as a crucial and meticulous component of Australia's health system. Its activities include "ensuring that therapeutic goods available for supply in Australia are safe and fit for their intended purpose". The full role and approaches taken by the TGA are set out on the TGA website (https://www.tga.gov.au/)

We have consistently argued that ENDS should remain subject to the TGA process. Nobody could take seriously any suggestion that they are not being promoted as cessation aids. There is simply no worthwhile case for bypassing the TGA other than that some groups or individuals may not be comfortable with the outcomes of rigorous, objective scientific review.

Further, bypassing the TGA on the basis of lobbying by sectional interests would set a potentially disastrous precedent, indicating a lack of confidence in the TGA and opening the door to similar lobbying and bypassing for many other products where companies or individuals wish to avoid proper scrutiny.

Quack claims about alleged cures for deadly and common diseases like cancers, HIV/AIDS and asthma have long been with us. But we do not allow those with an alleged cancer cure to by-pass the TGA assessment process and sell and promote a substance as cancer-curing simply on the strength of either commercial lobbying or emotional rhetoric.

We are aware of an argument that if ENDS makers had to convince the TGA on safety and effectiveness, only the pharmaceutical and tobacco industries could afford to conduct the research to the standards required. This in itself is open to debate. But the alternative -- to allow any backyard "kitchen chemist" maker of vaping equipment and ingredients to sell

and promote their products without TGA regulation – is an irresponsible proposal that would both put the health of consumers at risk and set a very dangerous precedent.

As noted in an article in the Medical Journal of Australia co-authored by McKee, Chapman and Daube:

> "In Australia, anyone considering importing or supplying e-cigarettes as a cessation aid must submit an application to the Therapeutic Goods Administration (TGA) with evidence of their safety and efficacy. The TGA then considers the evidence before determining whether the product may be sold, and, if so, under what conditions." [McKee, Chapman & Daube, 2016]

This is the approach that should be taken in relation to ENDS. It may be important to stress in this context that our position is not, as has sometimes been falsely stated, simple "opposition" to new approaches. It is that proper processes should be followed; the role of the TGA should be supported; and any determinations by the TGA should be respected.

In 2016-17 the TGA considered proposals to bypass poison controls to enable access to liquid nicotine for vaping. Following extensive consultations, submissions and reviews the TGA concluded that "the scheduling for nicotine remains appropriate". (see https://www.tga.gov.au/book-page/21-nicotine-0)The TGA comments and final decisions set out a wide range of concerns and conclusions leading to this decision, including those summarised under the headings "Delegates' interim decision" and "Delegates' final decision". We recognise that some who make submissions to the Inquiry may not like the verdict of this impartial and authoritative referee, but we urge the Committee to recognise, support and uphold the integrity and authority of the TGA.

It is further relevant to note that the nation's highest medical authority, the National Health and Medical Research Council, has also carefully reviewed the evidence on e-cigarettes/ENDS, with two CEO statements, first in 2015, then an updated statement as recently as April 2017. The 2017 statement reports that while "Electronic cigarettes (e-cigarettes, also known as electronic nicotine delivery systems (ENDS) or electronic non-nicotine delivery systems (ENNDS)) are often marketed as a method to assist smokers to quit, or as a 'safe alternative' to conventional tobacco cigarettes", ".....there is currently insufficient evidence to support claims that e-cigarettes are safe and further research is needed to enable the long-term safety, quality and efficacy of e-cigarettes to be assessed".

We recognise that, as in relation to the TGA, some groups or individuals may not be comfortable with the outcomes of rigorous, objective scientific review, but that should not be allowed to undermine the authority of the NHMRC or its advice, any more than this

should occur on the basis of representations from commercial interests or enthusiasts in any other area.

Refusing to accept the umpire's decision

Indeed, we find it disturbing that there are clearly some who wish to bypass both the TGA and NHMRC despite the crucial role both these bodies play in ensuring that Australian governments and community receive the best possible advice, and that the health of the public is well protected, with appropriate safeguards.

The TGA is in every sense Australia's national "umpire" on claims about therapeutic product safety and efficacy. Its processes and decisions over decades have given Australia one of the world's best and most envied therapeutic regulatory systems. Those who have been working to try and have the TGA circumvented as this umpire are challenging its authority on the flimsiest of pretexts. They have refused to accept the TGA umpire's decision, a course of action which brings them great discredit.

Many of those who have been prominent in this exercise have little if any serious track record or experience in population-focussed tobacco control. They, and some from overseas, may not be aware of the roles and critical importance of the TGA and NHMRC.

ENDS use in Australia today: very low

In considering policy options for ENDS, the we believe that the Committee should be mindful of the size of the likely demand for ENDS, and also of the potential risks of ENDS becoming popular with Australian children and young people should their accessibility and promotion move in the directions being advocated by the ENDS and tobacco industries.

ENDS are widely available for sale in Australia, although e-juice containing nicotine must be imported. This is very easily done (as easily as ordering books, clothing or other consumer goods is today on-line). Despite this, ENDS use is a very marginal activity in Australia today. The AIHW 2013 national survey (the largest survey on smoking and ENDS use available for Australia) reported that:

Year	Ever used e-cigarettes	Among daily smokers
2013	4.5% of all persons 1.8% of 14+ non-smokers 18.8% of 14+ smokers	

2016	8.8% of all persons 4.9% of 14+ non-smokers 31% of 14+ smokers	**A. Of smokers** 1.5% of daily smokers 1.2% of at least weekly smokers 0.7% of at least monthly smokers 1.0% of less than monthly smokers 6.8% used to use, but no longer do 19.9% tried it once or twice 69% never tried B. 0.8% **of ex-smokers**

Source: **http://www.aihw.gov.au/alcohol-and-other-drugs/data-sources/ndshs-2016/data/** (from Tables 8 & 9)

12.2% of the Australian population aged 14 years and over smoke daily. Yet only 1.5% of these are vaping daily (ie 0.186% of all Australians aged 14 and over). It is *far* more common (17.8 times more common) for daily smokers to have experimented with or used and then stopped using ENDS than for daily smokers to be using them today.

Only 0.8% of ex-smokers are vaping. We do not know what proportion of these are recent smokers who quit and are now vaping, and what proportion may be longer term ex-smokers who took up vaping long after quitting.

There are two main Australian on-line forums for vapers; Aussie vapers (http://forums.aussievapers.com/forum.php with 1,781 active members as at 26 June, 2017 and Vaper Cafe www.vapercafeaustralia.com/ with only 931 members on the same date. Many members belong to both. It is not known how many of these are Australian members and how many are from abroad.

These numbers provide no evidence that anything other than transient curiosity vaping is widespread in Australia. By far the largest numbers of people who have vaped are smokers who have tried it a few times and did not then go on to vape regularly (some 20% of smokers). There is no evidence that there are large numbers of smokers in Australia who want to vape but cannot do so, given the ease with which those who are vaping now are able to obtain both vaping equipment and nicotine containing e-juice.

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Term of Reference #5. Any other related matter

Two issues deserve the Committee's careful attention.

Does ENDS use predict later uptake of smoking?

Earlier, we were critical of claims made by those involved in ENDS manufacture and commerce that they had no interest in seeing children use ENDS. We argued that this is a commercially disingenuous claim, made entirely for public relations purposes. No industry concerned for its longevity would claim that it had no interest in fomenting strong interest in its products among future users.

Australia currently has the lowest rate of smoking among children ever recorded in this country. Only 2% of Australian children and young people aged 12-17 have ever smoked 100 or more cigarettes (see http://www.aihw.gov.au/2016-national-drug-strategy-household-survey/).
This is the lowest level ever recorded and is a huge testimony to the effectiveness of Australian tobacco control over the decades. Given that there is no evidence of any significant use of nicotine replacement therapy among youth, we are confident that regular exposure to nicotine in any form is fast becoming a thing of the past among Australian youth.

This is disastrous news for both tobacco companies and ENDS companies alike. With the former, the search for acceptable routes into nicotine addiction that might see young ENDS users also start smoking would be front of mind.

Appendix 3 is a Powerpoint presentation of evidence prepared by a colleague, A/Prof Stacey Carter, found in tobacco industry documents, about their intense interest in children and the duplicitous efforts they took to publicly deny that interest. All companies will have done elementary calculations about the need to attract starters among young people to expand the user base. Why contain the appeal of ENDS just to the dwindling number of smokers when the prospects of interesting the far more numerous non-smokers beckon?

ENDS as presursor or catalyst to smoking
As at February 2017, there were nine longitudinal studies suggesting that children starting nicotine use with ENDS and transitioning to smoking conventional cigarettes [Soneji et al, 2017]. These studies all considered youth who had not smoked a conventional cigarette, and then compared smoking between youth who did and did not use ENDS at baseline.

Critics of these studies often dismiss them by saying that all they show is that "children who are going to smoke in the future, will smoke in the future". They argue that all these studies do is show that those children likely to become smokers are do so. However, such studies do attempt to control for relevant confounders:

> "They [the critics] miss the fact that the studies controlled for variables that are defining characteristics of high-risk youth, including risk-taking, impulsiveness, negative affect, low parental support, and affiliation with deviant peers, and the effect of e-cigarette use for smoking onset was independent of these confounders. Moreover, recent research with different designs has shown that e-cigarettes are most strongly related to smoking onset among lower-risk adolescents, thus specifically contradicting the confounding hypothesis." (Wills, 2017)

The extent of this gateway or catalytic effect of initial ENDS use on later smoking uptake has now been shown in a meta-analysis of all these studies, appropriately adjusting and allowing for demographic, psychosocial, and behavioral risk factors for cigarette smoking, found that the odds of subsequent cigarette smoking were quadrupled among e-cigarette users [Soneji et al, 2017]. E-cigarette users are 5 times more likely to smoke but this is reduced to *only* a three-fold increased risk after adjusting for the relevant confounding factors typically highlighted by critics. Unless critics of these findings propose another confounding factor to which they have not previously alluded the Soneji et al evidence is compelling.

These findings and opinions further substantiate the concerns raised regarding the use of electronic cigarettes by youth and young adults in the US by the Surgeon General in late 2016, a comprehensive scientific report, generated from the input of approximately 150 experts in this field [US Surgeon General, 2016].

We are completely unimpressed the with the circularity of the response often made by ENDS advocates to findings about the possibility that ENDS use may act as a catalyst to subsequent smoking. A typical glib reply is that "kids who are going to try stuff, try stuff" made to any suggestion of vaping being an important predisposer to smoking. Here, they act as if the possibility that we may ever identify critical factors other than a circular "those who will smoke, will smoke" insight that increase the probability of someone taking up smoking is somehow preposterous.

We have had no problem with research that has often identified factors that promote smoking uptake and which governments then try to influence with policy or programs (eg: low price, tobacco advertising, parental smoking, smoking by teachers, etc.). But when

research suggests that using ENDS might condition some children into thinking "I wonder what the 'real thing' [ie smoking] is like?", we see some extraordinary responses.

Professor Peter Hajek, a long time advocate of ENDS, has said about the Soneji et al meta-analysis:

> "People who drink white wine are more likely to also try red wine than teetotallers, but common sense would not suggest that this means that removing the white will reduce the drinking of the red."

(http://www.sciencemediacentre.org/expert-reaction-to-review-of-e-cigarettes-and-smoking-in-young-adults/)

This is an inept analogy, as one of the authors of the *JAMA* meta-analysis exposed with the following salient point.

> "Young people report that there is a lot of pressure among e-cigarette only users to smoke a 'real' cigarette. It may be somewhat analogous to the fact that teens who use flavored alcohol are often pressured socially to step up their game to harder forms of alcohol." (see https://www.reuters.com/article/us-health-teens-vaping-idUSKBN19H292)

ENDS, with their many teen-friendly flavours, their less harsh "throat grab", the ease with which they can be used inconspicuously (little smell, rapidly secretable), and their hyped "almost totally safe' propaganda have considerable appeal to youth compared with smoking. But, just as a large proportion of adults who experiment with ENDS do not continue using them, finding them unsatisfying [eg:Pepper et al 2014] so too it is likely that some young people may move on to cigarettes, with ENDS abandoned as "training wheels".

Schneider & Diehl (2015) considered the inadequacies of crude "gateway" hypotheses and posited a compelling "catalyst" model for researchers and policy makers to consider about how initial ENDS use may stimulate later smoking. Their

> "results indicate that the perceived health risks, specific product characteristics (such as taste, price and inconspicuous use), and higher levels of acceptance among peers and others potentially make e-cigarettes initially more attractive to adolescents than tobacco cigarettes. Later, increasing familiarity with nicotine could lead to the reevaluation of both electronic and tobacco cigarettes and subsequently to a potential transition to tobacco smoking."

ENDS advocates have pointed out that cross-sectional surveys of smoking in the USA and England show that as ENDS use is rising, smoking prevalence is falling in adolescents. From this, they imply that there therefore cannot be any significant problem of ENDS use causing an increase in smoking among youth. But this does not follow at all.

There are multiple reasons for both the rise and the fall in smoking prevalence. If the impact of all factors driving smoking down in youth is greater than the impact of any putative ENDS "gateway" effect on smoking, smoking prevalence among youth would be falling.

But such a fall could nonetheless mask considerable smoking uptake caused by any ENDS gateway effects that were not widespread enough to stop the net fall in smoking prevalence still occurring. For this reason, longitudinal cohort studies such as those meta-analysed by Soneji et al (2017) are critical in understanding whether ENDS are an important catalyst for smoking among youth. As we have emphasised, that analysis shows that E-cigarette users are 5 times more likely to smoke but this is reduced to *only* a three-fold increased risk after adjusting for the relevant confounding factors typically highlighted by critics.

Should restrictions be placed on where vaping can occur?

Policy on smoking in public spaces is a state and territory matter, so beyond the remit of this Committee, other than in locations controlled by Commonwealth law such as some airports. In Appendix 4 [Chapman, Daube, Maziak, 2017] , we set out several reasons why ENDS use should not be allowed in any setting where cigarette smoking is not allowed. These include:

- Exposure of the public to harmful particles, particularly in enclosed environments with high concentration of persons vaping (see this video https://www.youtube.com/watch?v=VxiEZeFE2Zs and the Figure below
- Risks of catastrophic explosions (especially on aircraft -- see earlier)
- Triggering relapse in former smokers
- Renormalisaing the smoking "performance"

Both the American Indoor Hygiene Association's 2014 *White Paper: Electronic Cigarettes in the Indoor Environment*, subsequent to their full independent scientific review here https://www.aiha.org/government-affairs/PositionStatements/Electronc%20Cig%20Document_Final.pdf and the American Society of Heating Refrigeration and Air-conditioning Engineers 2016 *Standards 62.1 & 62.2; The Standards for Ventilation and Indoor Air Quality* here https://www.ashrae.org/resources--publications/bookstore/standards-62-1--62-2 confirm that there are potential health risks and concerns related to bystanders and passive vaping in indoor public areas, especially for susceptible groups such as the old and young, those with pre-existing health issues e.g. cardiac and respiratory, pregnant mothers. They strongly recommend that e-cigarettes should be treated the same as conventional cigarettes in such areas. The American Indoor Hygiene Association stated that:

> "e-cigarettes are not emission-free and that their pollutants could be of health concern for users and those who are exposed secondhand. … [T]heir use in the indoor environment should be restricted, consistent with current smoking bans, until and unless research documents that they will not significantly increase the risk of adverse health effects to room occupants" [AIHA, 2014].

Data confirm the need for this precautionary policy standpoint, showing that levels of fine particulate matter ($PM_{2.5}$) in a large hotel event room (4023 m^3) increased from 2-3 $\mu g/m^3$

to as high as 819 μg/m^3 μg/m^3 (interquartile range: 761-975 μg/m^3) when 59 to 86 people were using their e-cigarettes (Soule et al, 2017): a level comparable to a very smoky bar or casino. These levels substantially exceeded the US Environmental Protection Agency annual time-weighted standard for $PM_{2.5}$ of 12μg/m^3.

Tangentially, It has been argued by Bauld et al (2016) that

> "if and when vapour products with a medicinal license become available, it will be important to allow their use indoors, just as asthma inhalers, which dispense a drug and propellants into the atmosphere, can be used indoors."

The comparison and conclusion here is fundamentally inappropriate, and misleading. Newman et al showed, as long ago as 1991, that the amount of dosed drug exhaled by asthmatics using inhalers ranged from just 0.2%-1.7% across different puffing behaviours [Newman et al, 1991]. A typical person who uses an asthma reliever therapy puffer e.g. Salbutamol 100mcg would not normally be recommended to use it more than 2 puffs four times a day (8 puffs/day), as the UK National Institute for Health and Clinical Excellence recommend the prescription of salbutamol, with reference to British National Formulary (https://bnf.nice.org.uk/drug/salbutamol.html#indicationsAndDoses). Conversely, vapers can take up to, and therefore exhale, 610 puffs a day, with an average of around 200 puffs [Martin et al, 2016].

There is simply no comparison between what the asthma medication and propellant, and what one or even a few asthmatics might exhale into, for example, a crowded bar over a few hours, and what potentially dozens of vapers could generate in the sort of exuberant cloud chasing sessions that vaping in bars can entail. Furthermore, unlike vapers, asthmatics obviously do not participate in asthma puffer social events and competitions.

In conclusion:

Smoking remains Australia's largest single preventable cause of death and disease.

Trends among adults and children in Australia have been encouraging over time as a result of consensus action based on recommendations from health authorities. As a consequence, Australia is one of the world's leading countries in reducing smoking in adults and onset of smoking among children and young people. It is especially encouraging that 98% of those aged 12 – 17 are classified as never-smokers.

There is a strong evidence base for action that will further reduce smoking and its harms in both the community as a whole and disadvantaged groups.

There should be caution about introducing new products, with inevitable consequent promotion, that may distract from further evidence-based action, introduce new risks to the community, and undermine the progress that has been made.

The evidence supporting e-cigarettes as a cessation aid is weak; there is some evidence that they may be counter-productive; and there are significant concerns about potential harms that may arise from use of e-cigarettes and related products, including renormalising smoking behaviour and acting as a catalyst for smoking among children and young people. There is further concern at the enormous range of products and flavours being developed and promoted, with lack of information as to their consequences.

Leading health authorities such as the World Health Organization and the US Surgeon General have supported the case for a cautionary approach, which has also been adopted by many other countries.

The National Health and Medical Research Council (NHMRC) has recently concluded that "there is currently insufficient evidence to support claims that e-cigarettes are safe and further research is needed to enable the long-term safety, quality and efficacy of e-cigarettes to be assessed". The Therapeutic Goods Administration (TGA) has also recently concluded that "unlike Nicotine Replacement Therapy (NRT) products, which have been rigorously assessed for efficacy and safety and, therefore, approved by the Therapeutic Goods Administration for use as aids in the withdrawal from smoking, no assessment of electronic cigarettes has been undertaken and, therefore, the quality and safety of electronic cigarettes is not known."

E-cigarettes, as any other products claimed or promoted as therapeutic products to help smokers quit or reduce their harms should remain subject to the processes of the TGA, whose role, independence and integrity should be strongly supported, as should that of the NHMRC.

Recognising Article 5.3 of the WHO Framework Convention on Tobacco Control, to which the Australian Government is a signatory, any considerations on this issue should be protected from direct or indirect influences by commercial and other vested interests of the tobacco industry.

Appendix 1: Recent publications reporting findings about potential harm of exposure to e-cigarettes

Electronic cigarette aerosols suppress cellular antioxidant defenses and induce significant oxidative DNA damage.

Ganapathy V, Manyanga J, Brame L, McGuire D, Sadhasivam B, Floyd E, Rubenstein DA, Ramachandran I, Wagener T, Queimado L.

PLoS One. 2017 May 18;12(5):e0177780. doi: 10.1371/journal.pone.0177780.

BACKGROUND:

Electronic cigarette (EC) aerosols contain unique compounds in addition to toxicants and carcinogens traditionally found in tobacco smoke. Studies are warranted to understand the public health risks of ECs.

OBJECTIVE:

The aim of this study was to determine the genotoxicity and the mechanisms induced by EC aerosol extracts on human oral and lung epithelial cells.

METHODS:

Cells were exposed to EC aerosol or mainstream smoke extracts and DNA damage was measured using the primer anchored DNA damage detection assay (q-PADDA) and 8-oxo-dG ELISA assay. Cell viability, reactive oxygen species (ROS) and total antioxidant capacity (TAC) were measured using standard methods. mRNA and protein expression were evaluated by RT-PCR and western blot, respectively.

RESULTS:

EC aerosol extracts induced DNA damage in a dose-dependent manner, but independently of nicotine concentration. Overall, EC aerosol extracts induced significantly less DNA damage than mainstream smoke extracts, as measured by q-PADDA. However, the levels of oxidative DNA damage, as indicated by the presence of 8-oxo-dG, a highly mutagenic DNA lesion, were similar or slightly higher after exposure to EC aerosol compared to mainstream smoke extracts. Mechanistically, while exposure to EC extracts significantly increased ROS, it decreased TAC as well as the expression of 8-oxoguanine DNA glycosylase (OGG1), an enzyme essential for the removal of oxidative DNA damage.

CONCLUSIONS:

Exposure to EC aerosol extracts suppressed the cellular antioxidant defenses and led to significant DNA damage. These findings emphasize the urgent need to investigate the potential long-term cancer risk of exposure to EC aerosol for vapers and the general public.

E-cigarettes induce toxicological effects that can raise the cancer risk.

Canistro D, Vivarelli F, Cirillo S, Babot Marquillas C, Buschini A, Lazzaretti M, Marchi L, Cardenia V, Rodriguez-Estrada MT, Lodovici M, Cipriani C, Lorenzini A, Croco E, Marchionni S, Franchi P, Lucarini M, Longo V, Della Croce CM, Vornoli A, Colacci A, Vaccari M, Sapone A, Paolini M.

Sci Rep. 2017 May 17;7(1):2028. doi: 10.1038/s41598-017-02317-8.

Abstract

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CONCLUSIONS:

Exposure to EC aerosol extracts suppressed the cellular antioxidant defenses and led to significant DNA damage. These findings emphasize the urgent need to investigate the potential long-term cancer risk of exposure to EC aerosol for vapers and the general public.

Benzene formation in electronic cigarettes.
Pankow JF, Kim K, McWhirter KJ, Luo W, Escobedo JO, Strongin RM, Duell AK, Peyton DH.
PLoS One. 2017 Mar 8;12(3):e0173055. doi: 10.1371/journal.pone.0173055.

Abstract

BACKGROUND/OBJECTIVE:
The heating of the fluids used in electronic cigarettes ("e-cigarettes") used to create "vaping" aerosols is capable of causing a wide range of degradation reaction products. We investigated formation of benzene (an important human carcinogen) from e-cigarette fluids containing propylene glycol (PG), glycerol (GL), benzoic acid, the flavor chemical benzaldehyde, and nicotine.

METHODS/MAIN RESULTS:
Three e-cigarette devices were used: the JUULTM "pod" system (provides no user accessible settings other than flavor cartridge choice), and two refill tank systems that allowed a range of user accessible power settings. Benzene in the e-cigarette aerosols was determined by gas chromatography/mass spectrometry. Benzene formation was ND (not detected) in the JUUL system. In the two tank systems benzene was found to form from propylene glycol (PG) and glycerol (GL), and from the additives benzoic acid and benzaldehyde, especially at high power settings. With 50:50 PG+GL, for tank device 1 at 6W and 13W, the formed benzene concentrations were 1.9 and 750 μg/m3. For tank device 2, at 6W and 25W, the formed concentrations were ND and 1.8 μg/m3. With benzoic acid and benzaldehyde at ~10 mg/mL, for tank device 1, values at 13W were as high as 5000 μg/m3. For tank device 2 at 25W, all values were ≤~100 μg/m3. These values may be compared with what can be expected in a conventional (tobacco) cigarette, namely 200,000 μg/m3. Thus, the risks from benzene will be lower from e-cigarettes than from conventional cigarettes. However, ambient benzene air concentrations in the U.S. have typically been 1 μg/m3, so that benzene has been named the largest single known cancer-risk air toxic in the U.S. For non-smokers, chronically repeated exposure to benzene from e-cigarettes at levels such as 100 or higher μg/m3 will not be of negligible risk.

E-cigarettes as a source of toxic and potentially carcinogenic metals.
Hess CA, Olmedo P, Navas-Acien A, Goessler W, Cohen JE, Rule AM.
Environ Res. 2017 Jan;152:221-225. doi: 10.1016/j.envres.2016.09.026.

Abstract

BACKGROUND AND AIMS:

The popularity of electronic cigarette devices is growing worldwide. The health impact of e-cigarette use, however, remains unclear. E-cigarettes are marketed as a safer alternative to cigarettes. The aim of this research was the characterization and quantification of toxic metal concentrations in five, nationally popular brands of cig-a-like e-cigarettes.

METHODS:

We analyzed the cartomizer liquid in 10 cartomizer refills for each of five brands by Inductively Coupled Plasma Mass Spectrometry (ICP-MS).

RESULTS:

All of the tested metals (cadmium, chromium, lead, manganese and nickel) were found in the e-liquids analyzed. Across all analyzed brands, mean (SD) concentrations ranged from 4.89 (0.893) to 1970 (1540) μg/L for lead, 53.9 (6.95) to 2110 (5220) μg/L for chromium and 58.7 (22.4) to 22,600 (24,400) μg/L for nickel. Manganese concentrations ranged from 28.7 (9.79) to 6910.2 (12,200) μg/L. We found marked variability in nickel and chromium concentration within and between brands, which may come from heating elements.

CONCLUSION:

Additional research is needed to evaluate whether e-cigarettes represent a relevant exposure pathway for toxic metals in users.

Detection of 5-hydroxymethylfurfural and furfural in the aerosol of electronic cigarettes.
Soussy S, El-Hellani A, Baalbaki R, Salman R, Shihadeh A, Saliba NA.
Tob Control. 2016 Nov;25(Suppl 2):ii88-ii93. doi: 10.1136/tobaccocontrol-2016-053220.

Abstract

SIGNIFICANCE:

The wide availability of sweet flavours has been hypothesised as a factor in the popularity of electronic cigarette (ECIG), especially among youth. Saccharides, which are commonly used to impart a sweet flavour to ECIG liquids, thermally degrade to produce toxic compounds, like aldehydes and furans. This study investigates the formation of furanic compounds in aerosols when ECIG liquid solutions of varying sweetener concentrations are vaped under different power and puff duration.

METHODS:

Liquids are prepared by mixing aqueous sucrose, glucose or sorbitol solutions to a 70/30 propylene glycol/glycerin solution. Aerosols are generated and trapped on filter pads using a commercially available ECIG operating at 4.3 and 10.8 W and 4 and 8 s puff duration. Extraction, elimination of matrix interference and quantification are achieved using novel

solid phase extraction and gas chromatography tandem mass spectrometry methods (GC-MS).

RESULTS:

Well-resolved GC peaks of 5-hydroxymethylfurfural (HMF) and furfural (FA) are detected. Both HMF and FA are quantified in the aerosols of sweet-flavoured e-liquids under various vaping conditions. Levels of furan emissions are significantly correlated with electric power and sweetener concentration and not with puff duration. Unlike saccharides, the formation of HMF and FA from a sugar alcohol is negligible.

CONCLUSIONS:

The addition of sweeteners to ECIG liquids exposes ECIG user to furans, a toxic class of compounds. Under certain conditions, the per-puff yield of HMF and FA in ECIG emissions is comparable to values reported for combustible cigarettes.

Nicotine and Carbonyl Emissions From Popular Electronic Cigarette Products: Correlation to Liquid Composition and Design Characteristics.

El-Hellani A, Salman R, El-Hage R, Talih S, Malek N, Baalbaki R, Karaoghlanian N, Nakkash R, Shihadeh A, Saliba NA.

Nicotine Tob Res. 2016 Oct 7. pii: ntw280

Abstract

INTRODUCTION:

Available in hundreds of device designs and thousands of flavors, electronic cigarette (ECIG) may have differing toxicant emission characteristics. This study assesses nicotine and carbonyl yields in the most popular brands in the U.S. market. These products included disposable, prefilled cartridge, and tank-based ECIGs.

METHODS:

Twenty-seven ECIG products of 10 brands were procured and their power outputs were measured. The e-liquids were characterized for pH, nicotine concentration, propylene glycol/vegetable glycerin (PG/VG) ratio, and water content. Aerosols were generated using a puffing machine and nicotine and carbonyls were, respectively, quantified using gas chromatograph and high-performance liquid chromatography. A multiregression model was used to interpret the data.

RESULTS:

Nicotine yields varied from 0.27 to 2.91 mg/15 puffs, a range corresponding to the nicotine yield of less than 1 to more than 3 combustible cigarettes. Nicotine yield was highly correlated with ECIG type and brand, liquid nicotine concentration, and PG/VG ratio, and to a lower significance with electrical power, but not with pH and water content. Carbonyls, including the carcinogen formaldehyde, were detected in all ECIG aerosols, with total carbonyl concentrations ranging from 3.72 to 48.85 µg/15 puffs. Unlike nicotine, carbonyl concentrations were mainly correlated with power.

CONCLUSION:

In 15 puffs, some ECIG devices emit nicotine quantities that exceed those of tobacco cigarettes. Nicotine emissions vary widely across products but carbonyl emissions showed little variations. In spite of that ECIG users are exposed to toxicologically significant levels of carbonyl compounds, especially formaldehyde. Regression analysis showed the importance of design and e-liquid characteristics as determinants of nicotine and carbonyl emissions.

IMPLICATIONS:

Periodic surveying of characteristics of ECIG products available in the marketplace is valuable for understanding population-wide changes in ECIG use patterns over time.

Respiratory bronchiolitis-associated interstitial lung disease secondary to electronic nicotine delivery system use confirmed with open lung biopsy.

Flower M, Nandakumar L, Singh M, Wyld D, Windsor M, Fielding D.

Respirol Case Rep. 2017 Apr 3;5(3):e00230. doi: 10.1002/rcr2.230. eCollection 2017 May.

Abstract

As a modern phenomenon, there is currently limited understanding of the possible toxic effects and broader implications of electronic nicotine delivery systems (ENDS). Large volumes of aerosolized particles are inhaled during "vaping" and there are now an increasing number of case reports demonstrating toxic effects of ENDS, as well as human studies demonstrating impaired lung function in users. This article presents a case of respiratory bronchiolitis interstitial lung disease (RB-ILD) precipitated by vaping in a 33-year-old male with 10 pack years of traditional cigarette and prior treatment for mixed germ cell tumour. The patient had started vaping 10-15 times per day while continuing to smoke 10 traditional cigarettes per day. After 3 months of exposure to e-cigarette vapour, chest computed tomography demonstrated multiple new poorly defined pulmonary nodules with fluffy parenchyma opacification centred along the terminal bronchovascular units. Video-assisted thoracoscopy with lung biopsy of the right upper and right middle lobes was undertaken. The microscopic findings were overall consistent with RB-ILD. This

case demonstrates toxicity with use of ENDS on open lung biopsy with resolution of radiographic findings on cessation. We believe that this is the first case where open lung biopsy has demonstrated this and our findings are consistent with RB-ILD.

Cytotoxic and Genotoxic Effects of Electronic Cigarette Liquids on Human Mucosal Tissue Cultures of the Oropharynx.
Welz C, Canis M, Schwenk-Zieger S, Becker S, Stucke V, Ihler F, Baumeister P.
J Environ Pathol Toxicol Oncol. 2016;35(4):343-354.

Abstract

The popularity of electronic cigarettes (ECs) is rapidly growing and ECs are claimed to be an uncritically regarded alternative to conventional cigarettes. The mucosal tissue of the upper aerodigestive tract (UADT) is the first contact organ for xenobiotics such as liquids of ECs. The aim of this study is to investigate the bimolecular effects of e-liquids on human pharyngeal tissue cultures to evaluate whether e-liquids and their components present a risk factor for head and neck squamous cell carcinoma. Fresh tissue samples of healthy oropharyngeal mucosa were assembled into mucosal tissue cultures. Two fruit-flavored liquids (FLs), one tobacco-flavored liquid (TL) (all containing nicotine), and the corresponding base mixtures (free of nicotine and flavor) were used in three different dilutions. Cytotoxicity was assessed using the water-soluble tetrazolium-8 assay. DNA fragmentation was quantified using alkaline microgel electrophoresis. All liquids caused a significant reduction in cell viability. FLs especially showed a higher toxicity than TL. DNA fragmentation significantly increased by incubation with FL, whereas treatment with TL did not show serious DNA damage. E-liquids are cytotoxic to oropharyngeal tissue, and some liquids can induce relevant DNA damage. Thus, mutagenicity for mucosa of the UADT and e-liquids as risk factors for head and neck cancer cannot entirely be ruled out. Only the implementation of standards and regulations for liquid production and distribution can ensure a valid scientific investigation and assessment of carcinogenic potential of long-term EC use.

Flavoring Compounds Dominate Toxic Aldehyde Production during E-Cigarette Vaping.
Khlystov A, Samburova V.
Environ Sci Technol. 2016 Dec 6;50(23):13080-13085. Epub 2016 Nov 8.

The growing popularity of electronic cigarettes (e-cigarettes) raises concerns about the possibility of adverse health effects to primary users and people exposed to e-cigarette vapors. E-Cigarettes offer a very wide variety of flavors, which is one of the main factors that attract new, especially young, users. How flavoring compounds in e-cigarette liquids affect the chemical composition and toxicity of e-cigarette vapors is practically unknown.

Although e-cigarettes are marketed as safer alternatives to traditional cigarettes, several studies have demonstrated formation of toxic aldehydes in e-cigarette vapors during vaping. So far, aldehyde formation has been attributed to thermal decomposition of the main components of e-cigarette e-liquids (propylene glycol and glycerol), while the role of flavoring compounds has been ignored. In this study, we have measured several toxic aldehydes produced by three popular brands of e-cigarettes with flavored and unflavored e-liquids. We show that, within the tested e-cigarette brands, thermal decomposition of flavoring compounds dominates formation of aldehydes during vaping, producing levels that exceed occupational safety standards. Production of aldehydes was found to be exponentially dependent on concentration of flavoring compounds. These findings stress the need for a further, thorough investigation of the effect of flavoring compounds on the toxicity of e-cigarettes.

Toxicity evaluation of e-juice and its soluble aerosols generated by electronic cigarettes using recombinant bioluminescent bacteria responsive to specific cellular damages.
Bharadwaj S, Mitchell RJ, Qureshi A, Niazi JH.
Biosens Bioelectron. 2017 Apr 15;90:53-60. doi: 10.1016/j.bios.2016.11.026. Epub 2016 Nov 12.

Abstract

Electronic-cigarettes (e-cigarette) are widely used as an alternative to traditional cigarettes but their safety is not well established. Herein, we demonstrate and validate an analytical method to discriminate the deleterious effects of e-cigarette refills (e-juice) and soluble e-juice aerosol (SEA) by employing stress-specific bioluminescent recombinant bacterial cells (RBCs) as whole-cell biosensors. These RBCs carry luxCDABE-operon tightly controlled by promoters that specifically induced to DNA damage (recA), superoxide radicals (sodA), heavy metals (copA) and membrane damage (oprF). The responses of the RBCs following exposure to various concentrations of e-juice/SEA was recorded in real-time that showed dose-dependent stress specific-responses against both the e-juice and vaporized e-juice aerosols produced by the e-cigarette. We also established that high doses of e-juice (4-folds diluted) lead to cell death by repressing the cellular machinery responsible for repairing DNA-damage, superoxide toxicity, ion homeostasis and membrane damage. SEA also caused the cellular damages but the cells showed enhanced bioluminescence expression without significant growth inhibition, indicating that the cells activated their global defense system to repair these damages. DNA fragmentation assay also revealed the disintegration of total cellular DNA at sub-toxic doses of e-juice. Despite their state of matter, the e-juice and its aerosols induce cytotoxicity and alter normal cellular functions, respectively that raises concerns on use of e-cigarettes as alternative to traditional cigarette. The ability of

RBCs in detecting both harmful effects and toxicity mechanisms provided a fundamental understanding of biological response to e-juice and aerosols.

A decade of e-cigarettes: Limited research and unresolved safety concerns.
Kaisar MA, Prasad S, Liles T, Cucullo L.
Toxicology. 2016 Jul 15;365:67-75. doi: 10.1016/j.tox.2016.07.020. Epub 2016 Jul 28.
Review.

Abstract

It is well known that tobacco consumption is a leading cause of preventable deaths worldwide and has been linked to major diseases ranging from cancer to chronic obstructive pulmonary disease, atherosclerosis, stroke and a host of neurological/neurodegenerative disorders. In the past decade a number of alternative vaping products have hit the market, rapidly gaining consumers especially among the younger population. Electronic nicotine delivery systems or e-cigarettes have become the sought-after product due to the belief that they are much safer than traditional cigarettes. However, inadequate research and lack of regulatory guidelines for both the manufacturing process and the content of the vaping solution of the e-cigarette has become a major concern. Highly debated and unresolved questions such as whether e-cigarettes may help smokers quit and whether e-cigarettes will promote the use of nicotine among non-smokers add to the confusion of the safety of e-cigarettes. In this review article, we summarize the current understanding (and lack thereof) of the potential health impacts of e-cigarettes. We will also highlight the most recent studies (in vivo/in vitro) which seem to conflict with the broad safety claims put forward by the manufacturers. Finally, we provide potential solutions to overcome the research gap of the short and long-term health impact of e-cigarettes.

Appendix 2: Recent studies relevant to concerns about nicotine as a cancer promoter.

Grando SA. Connections of nicotine to cancer. Nature Reviews Cancer (2014) 14:419-429 doi:10.1038/nrc3725 http://www.nature.com/nrc/journal/v14/n6/pdf/nrc3725.pdf

This Opinion article discusses emerging evidence of direct contributions of nicotine to cancer onset and growth. The list of cancers reportedly connected to nicotine is expanding and presently includes small-cell and non-small-cell lung carcinomas, as well as head and neck, gastric, pancreatic, gallbladder, liver, colon, breast, cervical, urinary bladder and kidney cancers. The mutagenic and tumour-promoting activities of nicotine may result from its ability to damage the genome, disrupt cellular metabolic processes, and facilitate growth and spreading of transformed cells. The nicotinic acetylcholine receptors (nAChRs), which are activated by nicotine, can activate several signalling pathways that can have tumorigenic effects, and these receptors might be able to be targeted for cancer therapy or prevention. There is also growing evidence that the unique genetic makeup of an individual, such as polymorphisms in genes encoding nAChR subunits, might influence the susceptibility of that individual to the pathobiological effects of nicotine. The emerging knowledge about the carcinogenic mechanisms of nicotine action should be considered during the evaluation of regulations on nicotine product manufacturing, distribution and marketing.

Nordenvall C, Nilsson PJ, Ye W, Andersson TM, Nyrén O. Tobacco use and cancer survival: A cohort study of 40,230 Swedish male construction workers with incident cancer. Int J Cancer 2013; 132 (1):155-61. http://onlinelibrary.wiley.com/doi/10.1002/ijc.27587/epdf (full text)

On theoretical grounds, nicotine has been implicated as a modifier of cancer progression. We investigated possible associations of smoking or use of Scandinavian moist snuff (snus) with survival after cancer among Swedish male construction workers. Snus use is associated with substantial exposure to nicotine but not to the combustion products in smoke. Among 336,381 workers with detailed information on tobacco use in 1971–1992, we observed 40,230 incident cancers. Complete follow-up through 2007 was accomplished through linkage to population and health registers. Hazard ratios (HRs) and 95% confidence intervals (CIs) for death from any cause, cancer-specific death and death from other causes were derived from Cox proportional hazards regression models adjusted for

age at diagnosis, body mass index at study entry and period of diagnosis. Never users of any tobacco served as reference. Increased risks of cancer-specific death were observed both among exclusive smokers ($HR_{all\ cancer}$ 1.15, 95% CI: 1.10–1.21) and never-smoking snus users (1.15, 95% CI: 1.05–1.26). As regards deaths due to other causes, exclusive smokers had higher relative risks than exclusive snus users (p = 0.03). A history of tobacco use, even exclusive use of the seemingly benign snus, is associated with moderately increased cancer-specific mortality. Although nicotine might play a role, the mechanisms warrant further investigation.

Bavara JH, Tae H, Settlage RE, Garner HR. Characterizing the Genetic Basis for Nicotine Induced Cancer Development: A Transcriptome Sequencing Study. PLoS One 2013; Jun 18
DOI: 10.1371/journal.pone.0067252
Nicotine is a known risk factor for cancer development and has been shown to alter gene expression in cells and tissue upon exposure. We used Illumina® Next Generation Sequencing (NGS) technology to gain unbiased biological insight into the transcriptome of normal epithelial cells (MCF-10A) to nicotine exposure. We generated expression data from 54,699 transcripts using triplicates of control and nicotine stressed cells. As a result, we identified 138 differentially expressed transcripts, including 39 uncharacterized genes. Additionally, 173 transcripts that are primarily associated with DNA replication, recombination, and repair showed evidence for alternative splicing. We discovered the greatest nicotine stress response by HPCAL4 (up-regulated by 4.71 fold) and NPAS3 (down-regulated by -2.73 fold); both are genes that have not been previously implicated in nicotine exposure but are linked to cancer. We also discovered significant down-regulation (-2.3 fold) and alternative splicing of NEAT1 (lncRNA) that may have an important, yet undiscovered regulatory role. Gene ontology analysis revealed nicotine exposure influenced genes involved in cellular and metabolic processes. This study reveals previously unknown consequences of nicotine stress on the transcriptome of normal breast epithelial cells and provides insight into the underlying biological influence of nicotine on normal cells, marking the foundation for future studies.
Cardinal A, Nastrucci C, Cesario A, Russo P. Nicotine: specific role in angiogenesis, proliferation and apoptosis. *Critical Reviews in Toxicology*, 2012; 42(1): 68–89
http://www.ncbi.nlm.nih.gov/pubmed/22050423

Nowadays, tobacco smoking is the cause of ~5-6 million deaths per year, counting 31% and 6% of all cancer deaths (affecting 18 different organs) in middle-aged men and women, respectively. Nicotine is the addictive component of tobacco acting on neuronal nicotinic receptors (nAChR). Functional nAChR, are also present on endothelial, haematological and epithelial cells. Although nicotine itself is regularly not referred to as a carcinogen, there is an ongoing debate whether nicotine functions as a 'tumour promoter'. Nicotine, with its specific binding to nAChR, deregulates essential biological processes like regulation of cell

proliferation, apoptosis, migration, invasion, angiogenesis, inflammation and cell-mediated immunity in a wide variety of cells including foetal (regulation of development), embryonic and adult stem cells, adult tissues as well as cancer cells. Nicotine seems involved in fundamental aspects of the biology of malignant diseases, as well as of neurodegeneration. Investigating the biological effects of nicotine may provide new tools for therapeutic interventions and for the understanding of neurodegenerative diseases and tumour biology.

Momi N, Kaur S, Ponnusamy MP, Kumar S, Wittel UA, Batra SK. Interplay between smoking-induced genotoxicity and altered signaling in pancreatic carcinogenesis. Carcinogenesis. 2012 Sep;33(9):1617-28. doi: 10.1093/carcin/bgs186. Epub 2012 May 23.

Despite continuous research efforts directed at early diagnosis and treatment of pancreatic cancer (PC), the status of patients affected by this deadly malignancy remains dismal. Its notoriety with regard to lack of early diagnosis and resistance to the current chemotherapeutics is due to accumulating signaling abnormalities. Hoarding experimental and epidemiological evidences have established a direct correlation between cigarette smoking and PC risk. The cancer initiating/promoting nature of cigarette smoke can be attributed to its various constituents including nicotine, which is the major psychoactive component, and several other toxic constituents, such as nitrosamines, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, and polycyclic aromatic hydrocarbons. These predominant smoke-constituents initiate a series of oncogenic events facilitating epigenetic alterations, self-sufficiency in growth signals, evasion of apoptosis, sustained angiogenesis, and metastasis. A better understanding of the molecular mechanisms underpinning these events is crucial for the prevention and therapeutic intervention against PC. This review presents various interconnected signal transduction cascades, the smoking-mediated genotoxicity, and genetic polymorphisms influencing the susceptibility for smoking-mediated PC development by modulating pivotal biological aspects such as cell defense/tumor suppression, inflammation, DNA repair, as well as tobacco-carcinogen metabolization. Additionally, it provides a large perspective toward tumor biology and the therapeutic approaches against PC by targeting one or several steps of smoking-mediated signaling cascades.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3514894/
Petros WP, Younis IR, Ford JN, Weed SA. Effects of tobacco smoking and nicotine on cancer treatment. Pharmacotherapy. 2012 Oct;32(10):920-31. doi: 10.1002/j.1875-9114.2012.01117. http://www.ncbi.nlm.nih.gov/pubmed/23033231
A substantial number of the world's population continues to smoke tobacco, even in the setting of a cancer diagnosis. Studies have shown that patients with cancer who have a history of smoking have a worse prognosis than nonsmokers. Modulation of several physiologic processes involved in drug disposition has been associated with long-term

exposure to tobacco smoke. The most common of these processes can be categorized into the effects of smoking on cytochrome P450-mediated metabolism, glucuronidation, and protein binding. Perturbation in the pharmacokinetics of anticancer drugs could result in clinically significant consequences, as these drugs are among the most toxic, but potentially beneficial, pharmaceuticals prescribed. Unfortunately, the effect of tobacco smoking on drug disposition has been explored for only a few marketed anticancer drugs; thus, little prescribing information is available to guide clinicians on the vast majority of these agents. The carcinogenic properties of several compounds found in tobacco smoke have been well studied; however, relatively little attention has been given to the effects of nicotine itself on cancer growth. Data that identify nicotine's effect on cancer cell apoptosis, tumor angiogenesis, invasion, and metastasis are emerging. The implications of these data are still unclear but may lead to important questions regarding approaches to smoking cessation in patients with cancer.

Catassi A, Servent S, Paleari L, Cesario A, Russo P. Multiple roles of nicotine on cell proliferation and inhibition of apoptosis: implications on lung carcinogenesis. Mutat Res. 2008 Sep-Oct;659(3):221-31. doi: 10.1016/j.mrrev.2008.04.002. Epub 2008 Apr 11.
The genotoxic effects of tobacco carcinogens have long been recognized, the contribution of tobacco components to cancerogenesis by cell surface receptor signaling is relatively unexplored. Nicotine, the principal tobacco alkaloid, acts through nicotinic acetylcholine receptor (nAChR). nAChR are functionally present on human lung airway epithelial cells, on lung carcinoma [SCLC and NSCLC] and on mesothelioma and build a part of an autocrine-proliferative network that facilitates the growth of neoplastic cells. Different nAChR subunit gene expression patterns are expressed between NSCLC from smokers and non-smokers. Although there is no evidence that nicotine itself could induce cancer, different studies established that nicotine promotes in vivo the growth of cancer cells and the proliferation of endothelial cells suggesting that nicotine might contribute to the progression of tumors already initiated. These observations led to the hypothesis that nicotine might be playing a direct role in the promotion and progression of human lung cancers. Here, we briefly overview the role and the effects of nicotine on pulmonary cell growth and physiology and its feasible implications in lung carcinogenesis.

Slotkin TA. If nicotine is a developmental neurotoxicant in animal studies, dare we recommend nicotine replacement therapy in pregnant women and adolescents? Neurotoxicol Teratol. 2008 Jan-Feb;30(1):1-19.
Tobacco use in pregnancy is a leading cause of perinatal morbidity and contributes in major ways to attention deficit hyperactivity disorder, conduct disorders and learning disabilities that emerge in childhood and adolescence. Over the past two decades, animal models of prenatal nicotine exposure have demonstrated that nicotine is a neurobehavioral teratogen that disrupts brain development by preempting the natural, neurotrophic roles

of acetylcholine. Through its actions on nicotinic cholinergic receptors, nicotine elicits abnormalities of neural cell proliferation and differentiation, promotes apoptosis and produces deficits in the number of neural cells and in synaptic function. The effects eventually compromise multiple neurotransmitter systems because of the widespread regulatory role of cholinergic neurotransmission. Importantly, the long-term alterations include effects on reward systems that reinforce the subsequent susceptibility to nicotine addiction in later life. These considerations strongly question the appropriateness of nicotine replacement therapy (NRT) for smoking cessation in pregnant women, especially as the pharmacokinetics of the transdermal patch may actually enhance fetal nicotine exposure. Further, because brain maturation continues into adolescence, the period when smoking typically commences, adolescence is also a vulnerable period in which nicotine can change the trajectory of neurodevelopment. There are also serious questions as to whether NRT is actually effective as an aid to smoking cessation in pregnant women and adolescents. This review considers the ramifications of the basic science findings of nicotine's effects on brain development for NRT in these populations.

Egleton RD, Brown KC, Dasgupta P. Nicotinic acetylcholine receptors in cancer: multiple roles in proliferation and inhibition of apoptosis. Trends Pharmacol Sci. 2008 Mar;29(3):151-8. doi: 10.1016/j.tips.2007.12.006. Epub 2008 Feb 11.
Nicotinic acetylcholine receptors (nAChRs) constitute a heterogeneous family of ion channels that mediate fast synaptic transmission in neurons. They have also been found on non-neuronal cells such as bronchial epithelium and keratinocytes, underscoring the idea that they have functions well beyond neurotransmission. Components of cigarette smoke, including nicotine and NNK [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone], are agonists of nAChRs. Given the association of tobacco use with several diseases, the non-neuronal nAChR signaling pathway has considerable implications for cancer and cardiovascular disease. Recent studies have shown that alpha7 is the main nAChR subunit that mediates the proliferative effects of nicotine in cancer cells. As a result, alpha7 nAChR might be a valuable molecular target for therapy of cancers such as lung cancer and mesothelioma. Future studies involving the design of nAChR antagonists with improved selectivity might identify novel strategies for the treatment of tobacco-related cancers. Here we review the cellular roles of non-neuronal nAChRs, including regulation of cell proliferation, angiogenesis, apoptosis, migration, invasion and secretion.
Zeilder R, Albermann K, Lang S. Nicotine and apoptosis. Apoptosis. 2007 Nov;12(11):1927-43.
Cigarette smoking is associated with a plethora of different diseases. Nicotine is the addictive component of cigarette but also acts onto cells of the non-neuronal system, including immune effector cells. Although nicotine itself is usually not referred to as a carcinogen, there is ongoing debate whether nicotine functions as a 'tumor enhancer.' By binding to nicotinic acetylcholine receptors, nicotine deregulates essential biological

processes like angiogenesis, apoptosis, and cell-mediated immunity. Apoptosis plays critical roles in a wide variety of physiologic processes during fetal development and in adult tissue and is also a fundamental aspect of the biology of malignant diseases. This review provides an overlook how nicotine influences apoptotic processes and is thus directly involved in the etiology of pathological conditions like cancer and obstructive diseases.

Wickström R. Effects of nicotine during pregnancy: human and experimental evidence. Curr Neuropharmacol. 2007 Sep;5(3):213-22. doi: 10.2174/157015907781695955.
Prenatal exposure to tobacco smoke is a major risk factor for the newborn, increasing morbidity and even mortality in the neonatal period but also beyond. As nicotine addiction is the factor preventing many women from smoking cessation during pregnancy, nicotine replacement therapy (NRT) has been suggested as a better alternative for the fetus. However, the safety of NRT has not been well documented, and animal studies have in fact pointed to nicotine per se as being responsible for a multitude of these detrimental effects. Nicotine interacts with endogenous acetylcholine receptors in the brain and lung, and exposure during development interferes with normal neurotransmitter function, thus evoking neurodevelopmental abnormalities by disrupting the timing of neurotrophic actions. As exposure to pure nicotine is quite uncommon in pregnant women, very little human data exist aside from the vast literature on prenatal exposure to tobacco smoke. The current review discusses recent findings in humans on effects on the newborn of prenatal exposure to pure nicotine and non-smoke tobacco. It also reviews the neuropharmacological properties of nicotine during gestation and findings in animal experiments that offer explanations on a cellular level for the pathogenesis of such prenatal drug exposure. It is concluded that as findings indicate that functional nAChRs are present very early in neuronal development, and that activation at this stage leads to apoptosis and mitotic abnormalities, a total abstinence from all forms of nicotine should be advised to pregnant women for the entirety of gestation.
Full text here http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2656811/

Grozio A, Catassi A, Cavalieri Z, Paleari L, Cesario A, Russo P.
Nicotine, lung and cancer. Anticancer Agents Med Chem. 2007 Jul;7(4):461-6.
The respiratory epithelium expresses the cholinergic system including nicotinic receptors (nAChRs). It was reported that normal human bronchial epithelial cells (BEC), which are the precursor for squamous cell carcinomas, and small airway epithelial cells (SAEC), which are the precursor for adenocarcinomas, have slightly different repertoires of nAChRs. Studies show that nAChRs expressed on lung carcinoma or mesothelioma form a part of an autocrine-proliferative network facilitating the growth of neoplastic cells; others demonstrated that nicotine can promote the growth of colon, gastric, and lung cancers. Nicotine and structurally related carcinogens like NNK [4-(methylnitrosoamino)- 1-(3-

pyridyl)-1-butanone] and NNN (N'-nitrosonornicotine) could induce the proliferation of a variety of small cell lung carcinoma cell lines and endothelial cells and nicotine in non-neuronal tissues -including lung- induces the secretion of growth factors (bFGF, TGF-alpha, VEGF and PDGF), up regulation of the calpain family proteins, COX-2 and VEGFR-2, causing the eventual activation of Raf/MAPK kinase/ERK (Raf/MEK/ERK) pathway contributing to the growth and progression of tumors exposed to nicotine through tobacco smoke or cigarette substitutes. It has been demonstrated that nicotine promotes the growth of solid tumors in vivo, suggesting that might induce the progression of tumors already initiated. While tobacco carcinogens can initiate and promote tumorigenesis, the exposure to nicotine could confer a proliferative advantage to early tumors but there is no evidence that nicotine itself provokes cancer. This is supported by the findings that nicotine can prevent apoptosis induced by various agents - such as chemotherapeutic in NSCLC, conferring a survival advantage as well.

Wu WK, Cho CH. The pharmacological actions of nicotine on the gastrointestinal tract. J Pharmacol Sci. 2004 Apr;94(4):348-58.
Increasing use of tobacco and its related health problems are a great concern in the world. Recent epidemiological findings have demonstrated the positive association between cigarette smoking and several gastrointestinal (GI) diseases, including peptic ulcer and cancers. Interestingly, smoking also modifies the disease course of ulcerative colitis (UC). Nicotine, a major component of cigarette smoke, seems to mediate some of the actions of cigarette smoking on the pathogenesis of GI disorders. Nicotine worsens the detrimental effects of aggressive factors and attenuates the protective actions of defensive factors in the processes of development and repair of gastric ulceration. Nicotine also takes part in the initiation and promotion of carcinogenesis in the GI tract. In this regard, nicotine and its metabolites are found to be mutagenic and have the ability to modulate cell proliferation, apoptosis, and angiogenesis during tumoriogenesis through specific receptors and signalling pathways. However, to elucidate this complex pathogenic mechanism, further study at the molecular level is warranted. In contrast, findings of clinical trials give promising results on the use of nicotine as an adjuvant therapy for UC. The beneficial effect of nicotine on UC seems to be mediated through multiple mechanisms. More clinical studies are needed to establish the therapeutic value of nicotine in this disease.

Zhu B-Q, Heeschen C. Sievers RE, Karliner JS, Parmley WW, Glantz SA, Cooke JP.
Second hand smoke stimulates tumor angiogenesis and growth. Cancer Cell 2003; Sept 191-196.

http://ac.els-cdn.com/S1535610803002198/1-s2.0-S1535610803002198-main.pdf?_tid=ad1f8084-a439-11e5-b823-00000aab0f6c&acdnat=1450300512_9ba5bb948ad346910e374692a9b5715a (full text)

Exposure to second hand smoke (SHS) is believed to cause lung cancer. Pathological angiogenesis is a requisite for tumor growth. Lewis lung cancer cells were injected subcutaneously into mice, which were then exposed to sidestream smoke (SHS) or clean room air and administered vehicle, cerivastatin, or mecamylamine. SHS significantly increased tumor size, weight, capillary density, VEGF and MCP-1 levels, and circulating endothelial progenitor cells (EPC). Cerivastatin (an inhibitor of HMG-coA reductase) or mecamylamine (an inhibitor of nicotinic acetylcholine receptors) suppressed the effect of SHS to increase tumor size and capillary density. Cerivastatin reduced MCP-1 levels, whereas mecamylamine reduced VEGF levels and EPC. These studies reveal that SHS promotes tumor angiogenesis and growth. These effects of SHS are associated with increases in plasma VEGF and MCP-1 levels, and EPC, mediated in part by isoprenylation and nicotinic acetylcholine receptors.

And also:

England LJ, Bunnell RE, Pechacek TF, Tong VT, McAfee TA. Nicotine and the Developing Human: A Neglected Element in the Electronic Cigarette Debate A 2015 Aug;49(2):286-93. doi: 10.1016/j.amepre.2015.01.015.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4594223/pdf/nihms724908.pdf

The elimination of cigarettes and other combusted tobacco products in the U.S. would prevent tens of millions of tobacco-related deaths. It has been suggested that the introduction of less harmful nicotine delivery devices, such as electronic cigarettes or other electronic nicotine delivery systems, will accelerate progress toward ending combustible cigarette use. However, careful consideration of the potential adverse health effects from nicotine itself is often absent from public health debates. Human and animal data support that nicotine exposure during periods of developmental vulnerability (fetal through adolescent stages) has multiple adverse health consequences, including impaired fetal brain and lung development, and altered development of cerebral cortex and hippocampus in adolescents. Measures to protect the health of pregnant women and children are needed and could include (1) strong prohibitions on marketing that increase youth uptake; (2) youth access laws similar to those in effect for other tobacco products; (3) appropriate health warnings for vulnerable populations; (4) packaging to prevent accidental poisonings; (5) protection of non-users from exposure to secondhand electronic cigarette aerosol; (6) pricing that helps minimize youth initiation and use; (7) regulations to reduce product addiction potential and appeal for youth; and (8) the age of legal sale.

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From: [redacted]
To:

Cc:

Date: Tuesday, July 10, 2018 11:22AM
Subject: Ecigs as bad as cigarettes for CVD

History: ➪ This message has been forwarded.

Why would any sensible Health Department even consider legalizing these nicotine addiction enhancing Improvised Explosive Devices?

https://gizmodo.com/florida-fire-officials-say-exploding-vape-pen-may-have-1825814558

https://www.thesun.co.uk/news/6716018/dad-todger-blasted-off-e-cigarette-explosion/

https://www.youtube.com/watch?v=IvFEUb9rV_E

Attachments:

Ecigs-as-bad-as-cigarettes-CVD.pdf

New study finds that e-cigarettes increase cardiovascular risk as much as cigarettes

eurekalert.org/pub_releases/2018-07/s-nsf070918.php

Public Release: 9-Jul-2018

SAGE

The usage of e-cigarettes containing nicotine has a significant impact on vascular functions claims new study. Research published in the SAGE journal, *Vascular Medicine*, has brought new research to light on the significant health risks of e-cigarettes with nicotine. The study revealed that smokers of e-cigarettes experienced the same, if not higher level of cardiovascular elevation for prolonged periods after smoking the e-cigarette. The findings have significant implications for our understanding of the use of e-cigarettes on long-term cardiovascular risk.

Conducted by Franzen et al., results were obtained by monitoring participant's vitals during and after they had smoked a cigarette, e-cigarette, or nicotine-free e-cigarette. The smoking lasted for one cigarette, at least 5 minutes, and the vaping lasted for one session for 5 minutes. Vitals were monitored for 2 hours from when smoking commenced.

Researchers found that using e-cigarettes and cigarettes, in comparison to nicotine-free e-cigarettes, had the same significant impact on vitals, with participant's blood pressure and heart rate being affected. Peripheral systolic blood pressure was raised significantly for 45 minutes after using an e-cigarette and 15 minutes after smoking a cigarette. Heart rate also remained elevated for 45 minutes for e-cigarettes, with the increase being higher than 8% for the first 30 minutes. In comparison, traditional cigarettes only raised heart rate for 30 minutes and there was again no change when using nicotine-free e-cigarettes. Franzen et al. use this data to state that the e-cigarettes can be as dangerous as cigarettes, simply concluding that:

"The increased parameters within the nicotine containing devices might be a link to an increased cardiovascular risk which is well known for cigarettes."

As one of the first trials studying blood pressure and heart rate elevation in relation to e-cigarette use, the authors emphasized the need for further studies in the area, stating:

"Future trials should focus on chronic effects of vaping nicotine-containing or nicotine free liquids on peripheral and central blood pressures as well as on arterial stiffness. Since no endothelial dysfunction nor gender differences were described for three different arms in literature, it would be important for future trials to address these items."

Along with highlighting further areas of discussion the study has provided clear evidence of the potential cardiovascular issues from acute e-cigarette use and diminishes the common thought that e-cigarettes are a lower risk than tobacco products.

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The article, *E-Cigarettes and Cigarettes worsen peripheral and central hemodynamics as well as arterial stiffness: A randomized, double-blinded pilot study* by Klaas Franzen, et al., in *Vascular Medicine*, can be accessed here.

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Original Article

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E-cigarettes and cigarettes worsen peripheral and central hemodynamics as well as arterial stiffness: A randomized, double-blinded pilot study

Klaas Frederik Franzen[1*], Johannes Willig[1*], Silja Cayo Talavera[1*], Moritz Meusel[2], Friedhelm Sayk[3], Michael Reppel[4], Klaus Dalhoff[1,5], Kai Mortensen[6*] and Daniel Droemann[1,5*]

Abstract

The introduction of electronic cigarettes has led to widespread discussion on the cardiovascular risks compared to conventional smoking. We therefore conducted a randomized cross-over study of the acute use of three tobacco products, including a control group using a nicotine-free liquid. Fifteen active smokers were studied during and after smoking either a cigarette or an electronic cigarette with or without nicotine (eGo-T CE4 vaporizer). Subjects were blinded to the nicotine content of the electronic cigarette and were followed up for 2 hours after smoking a cigarette or vaping an electronic cigarette. Peripheral and central blood pressures as well as parameters of arterial stiffness were measured by a Mobil-O-Graph® device. The peripheral systolic blood pressure rose significantly for approximately 45 minutes after vaping nicotine-containing liquid ($p<0.05$) and for approximately 15 minutes after smoking a conventional cigarette ($p<0.01$), whereas nicotine-free liquids did not lead to significant changes during the first hour of follow-up. Likewise, heart rate remained elevated approximately 45 minutes after vaping an electronic cigarette with nicotine-containing liquid and over the first 30 minutes after smoking a cigarette in contrast to controls. Elevation of pulse wave velocity was independent from mean arterial pressure as well as heart rate in the electronic cigarette and cigarette groups. In this first of its kind trial, we observed changes in peripheral and central blood pressure and also in pulse wave velocity after smoking a cigarette as well as after vaping a nicotine-containing electronic cigarette. These findings may be associated with an increased long-term cardiovascular risk.

Keywords

arterial stiffness, cigarette, electronic cigarette (e-cigarette), pulse wave velocity, risk stratification, smoking, vaping

Introduction

Tobacco use is considered to be one of the leading causes of preventable death and disease in Western Europe and the United States.[1] In this context, the working group of Shaw published data indicating that each smoked cigarette shortens life by 11 minutes.[2] Recent data differentiate smoking from other types of nicotine products. In addition to cigarettes and traditional tobacco products, the electronic cigarette (e-cigarette) has become more popular. In addition to rising attention and distribution in print and internet media, lifetime and 30-day prevalence use of e-cigarettes is also increasing. Current data show there are 13 million users of e-cigarettes all over the world.[3]

On the one hand, publications postulate that vaping is less harmful than smoking.[4–6] On the other, publications describe the health impact of e-cigarettes or cast a scrutinizing view on them.[7–10] In addition, e-cigarettes are discussed as a tool for smoking cessation,[11] although long-term efficacy data are still missing.[12]

In general, smoking is accepted as one of the most significant risk factors for cardiovascular events.[13,14] Apart from the importance of nicotine as a risk factor, smoking is one of the most modifiable ones.[15]

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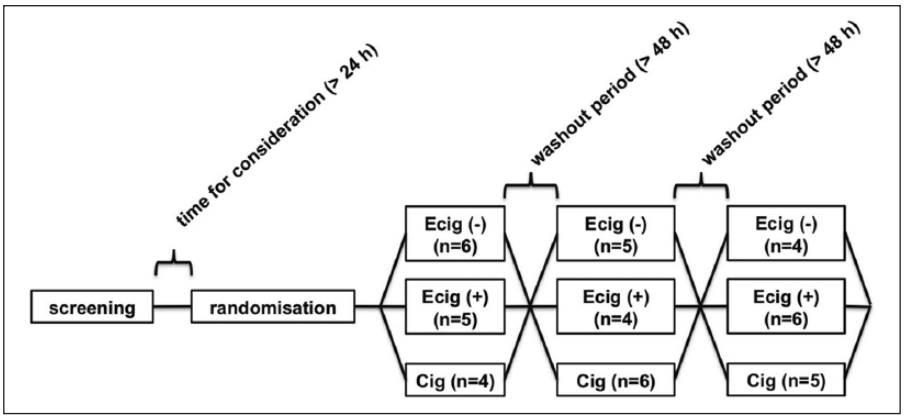

Figure 1. Study design.
Ecig, e-cigarette; cig, cigarette.

Several trials have evaluated the chronic effect of smoking on cardiovascular events. Based on the guidelines of the European Society of Hypertension, as well as the European Society of Cardiology, measurement of arterial stiffness and endothelial dysfunction may be used as an assessment of subclinical end organ damage as an indication of developing cardiovascular disease.[16]

We therefore aimed to determine the acute effects of vaping nicotine-containing or nicotine-free liquids versus cigarette smoking on both peripheral and central blood pressures including arterial stiffness.

Methods

Study cohort and design

This single-center pilot study included 15 young, active, traditional cigarette smokers. The trial was designed as a cross-over study of the acute use of three tobacco products. The subjects were blinded to the nicotine content of the e-cigarette.

The participants were randomized to one of the three study groups during the first visit by drawing pieces of paper from a closed envelope (Figure 1). The envelope contained three pieces of numbered paper (one to three); participants' order was moved by drawing three times. The numbers denoted e-cigarette with nicotine, e-cigarette without nicotine, or cigarette.

The participants were recruited from amongst students from the University of Luebeck. During screening, all participants were checked for exclusion criteria: (i) non-smoking or non-vaping; (ii) mental disorders; (iii) cardiovascular diseases; (iv) thyroid disease; (v) diabetes; (vi) abnormalities during physical examination; (vii) hypertension and/or (viii) elevated cholesterol or triglycerides. Furthermore, pregnancy excluded female participants. Participants were excluded if previously enrolled in any other kind of study and if they declared being strict non-smokers before they were given a written informed consent form. The study had the permission of the local ethics committee and was registered on German Register Clinical Trials (DRKS) (DRKS00012919).

In accordance with previous studies using arterial stiffness,[17,18] alcohol and/or smoking cigarettes were not allowed 24 hours prior to the measurements. The smoking-free phase was tested by Micro^{+}™ Smokerlyzer (Bedfont Scientific Ltd, Maidstone, UK) with a cut-off of 6 ppm CO. This phase was necessary to show the acute effects of each intervention. Furthermore, an elapse of 48 hours was scheduled between each test day to avoid any acute interaction between devices.

The three different study groups were the following: (1) smoking a cigarette and inhaling into the lungs (Cig) (Philip & Morris, New York, USA); (2) vaping an e-cigarette with nicotine (ECig (+)) (DIPSE, eGo-T CE4 vaporizer (third generation), SSR Produkt GmbH & Co KG, Oldenburg, Germany, 3.3 volts, 1.5 ohms and 7.26 watts; 24 mg/mL nicotine, 55% propylene glycol and 35% glycerin, tobacco flavor); and (3) vaping an e-cigarette without nicotine (ECig (–)) (0 mg/mL nicotine, 55% propylene glycol and 35% glycerin, tobacco flavor). Both investigators and participants were blinded (i.e. both were unaware of the kind of liquid used). The participants were asked to smoke the cigarette and inhale into the lungs. During the study, smokers who were inexperienced in the use of e-cigarettes were introduced to vaping and trained to use an e-cigarette by an experienced e-cigarette user. All participants had to vape the e-cigarette with a minimum of one puff every 30 seconds for 10 puffs, in accordance with different publications.[19] Every puff had to last for 4 seconds for this study. Each participant had to fulfill all three conditions to complete the study and to be analyzed.

Generally, measurements were started at least 30 minutes before vaping or smoking. Blood pressure were measured by a Mobil-O-Graph® (I.E.M., Stollberg, Germany)[20–22] every 5 minutes and with a conventional blood pressure monitor (Omron MIT Elite Plus®; Omron, Kyoto, Japan) every 15 minutes. Measurements discontinued not less than 2 hours after the application. The three measurements were taken around the same time of day to avoid change due to circadian rhythms.

Measurement of peripheral and central blood pressures and arterial stiffness

The blood pressure measurements with additional parameters were performed with the validated Mobil-O-Graph (software version HMS CS 4.2; I.E.M.), which allows recording of central pressures and arterial stiffness parameters

Table 1. Baseline characteristics (n=15).

Characteristics			
		Min	Max
Sex, male/female	5/10		
Age, years	22.9 ± 3.5	18.0	30.0
Height, m	1.7 ± 0.1	1.6	2.0
Weight, kg	70.0 ± 10.7	58.0	90.0
BMI, kg/m^2	23.2 ± 2.6	19.5	29.1
Waist, cm	75.2 ± 6.0	68.0	84.0
Hip, cm	93.7 ± 4.4	89.0	101.0
Smoking	100%		
Smoking, pack years	2.9 ± 1.5	1	6
Anemia	0%		
Elevated liver enzyme	0%		

Data are expressed as mean ± SD.
BMI, body mass index.

as transmitted.[20,21,23] Briefly, the Mobil-O-Graph uses the oscillometric technique with a standard blood pressure cuff at the arteria brachialis.[20] Central systolic blood pressure was determined from brachial waveforms, recorded with the cuff at the level of diastolic blood pressure and processed with the ARCSolver transfer function. Using the derived central waveforms, pulse waveform analysis is performed and pulse wave velocity (PWV), augmentation index (AIx) and augmentation pressure are estimated.[21,22] Measurements started 30 minutes before smoking or vaping in a sitting position. Therefore, the mean values of baseline were calculated from three measurements every 5 minutes directly before smoking or vaping. These mean values were used as references for statistical analyses.

Statistical analysis

Statistical analyses were performed with IBM SPSS statistical software, version 23 (IBM Corp., Armonk, NY, USA), graphs were edited with SigmaPlot 8.0 (SYSTAT Software Inc., San Jose, CA, USA) and prepared for publication with CorelDRAW 11.0 (Corel Inc., Mountain View, CA, USA). Baseline mean values were taken for statistical references of blood pressure as well as arterial stiffness. During the observation period of 2 hours, measurements were performed in intervals of 5 minutes. Mean values were calculated of three measuring points to form 15-minute intervals for statistical analyses. The investigator who analyzed the vascular data was blinded to the order of the devices, as well as the study intervention.

Before further analyses of the blood pressure, peripheral as well as central hemodynamics were analyzed for normal distribution by Kolmogorov–Smirnov tests. Because of the cross-over design, we calculated a two-way repeated measures analysis of variance (ANOVA) evaluating for an interaction between time and type of tobacco product used. Accordingly we did post hoc tests (Bonferroni) by G*Power if there was an interaction. In addition, the data were analyzed via paired Student's t-tests corrected for multiple testing and the Wilcoxon test where appropriate to compare individual time points within the three test settings. ANOVA was used to analyze the differences at the different time points between the three different groups, respectively. Where applicable a multivariate analysis of variance (MANOVA) was performed correcting for age, mean arterial pressure (MAP), heart rate (HR) and sex. If not stated otherwise, all data are expressed as mean ± standard deviation (SD). A p-value of < 0.05 was defined as statistically significant.

Results

Baseline characteristics

Baseline characteristics for all subjects are presented in Table 1. The participants did not show any significant clinical differences between the initial three groups formed by the randomization to the different order (data not shown). The participants were all smokers without a history of vaping or dual use. All participants finished the trial. The number of participants in each group is presented in Figure 1.

Cigarettes and e-cigarettes with nicotine increased SBP (Mobil-O-Graph)

The two-way repeated measures ANOVA showed a significant difference between the three study groups for the type of study group ($p < 0.05$), which remained statistically significant after post hoc testing. Using additional statistics, the systolic blood pressure (SBP) was increased significantly within the Cig and ECig (+) groups by more than + 3% ($p < 0.05$; Figure 2) and the three groups differed significantly from each other ($p < 0.05$; Figure 2). There were no significant changes of SBP within ECig (–) during follow-up ($p > 0.05$; Figure 2).

The three groups showed significant differences for peripheral diastolic blood pressure (DBP) from each other within the two-way repeated measures ANOVA for the type of study group, which remained statistically significant after post hoc testing ($p < 0.05$; Figure 3), too. Furthermore, DBP was significantly increased by more than 5% in the Cig arm using additional statistics ($p < 0.05$; Figure 3). In contrast to these findings, in ECig (–), DBP decreased by more than 4%, significantly after 30 minutes ($p < 0.05$; Figure 3).

No significant difference for the peripheral pulse pressure (PP) was found between the three groups within the two-way repeated measures ANOVA ($p > 0.05$; Figure 4), although PP showed a similar result to the SBP, with an increase at the first measuring points in the Cig and ECig (+) arms after smoking or vaping (Figure 4) using additional statistics.

HR was significantly elevated by smoking and vaping with nicotine

The HR of the three groups differed significantly for the type of study group as well as for time within the two-way repeated measures ANOVA ($p < 0.05$; Figure 5). Using additional statistics, there was a significant effect after

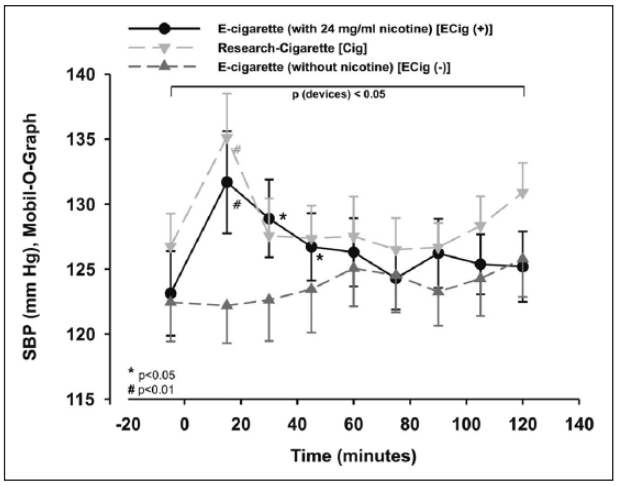

Figure 2. Peripheral SBP was increased significantly within Cig and ECig(+). Two-way measured ANOVA showed a significance between the devices ($p < 0.05$).
Asterisks indicate a significant change of individual values as compared to baseline, corrected for multiple testing. Data are expressed as mean ± SE. ANOVA, analysis of variance; SBP, systolic blood pressure; SE, standard error.

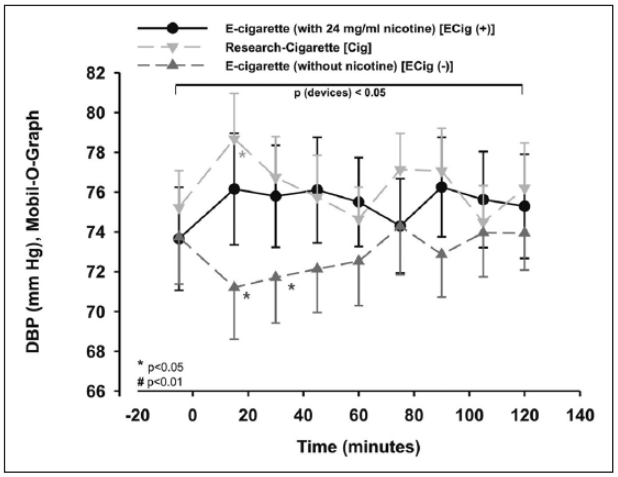

Figure 3. Peripheral DBP was changed significantly for Cig and ECig (-). Two-way measured ANOVA showed a significance between the devices ($p < 0.05$), which remains after post hoc testing.
Asterisks indicate a significant change of individual values as compared to baseline, corrected for multiple testing. Data are expressed as mean ± SE. ANOVA, analysis of variance; DBP, diastolic blood pressure; SE, standard error.

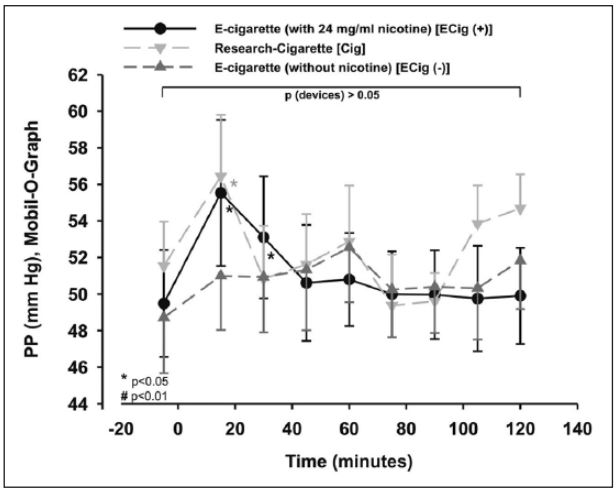

Figure 4. Peripheral PP was increased significantly within Cig and ECig (+) using additional statistics. Two-way measured ANOVA did not show a significance between the devices ($p < 0.05$), which remains after post hoc testing.
Asterisks indicate a significant change of individual values as compared to baseline, corrected for multiple testing. Data are expressed as mean ± SE. ANOVA, analysis of variance; PP, pulse pressure; SE, standard error.

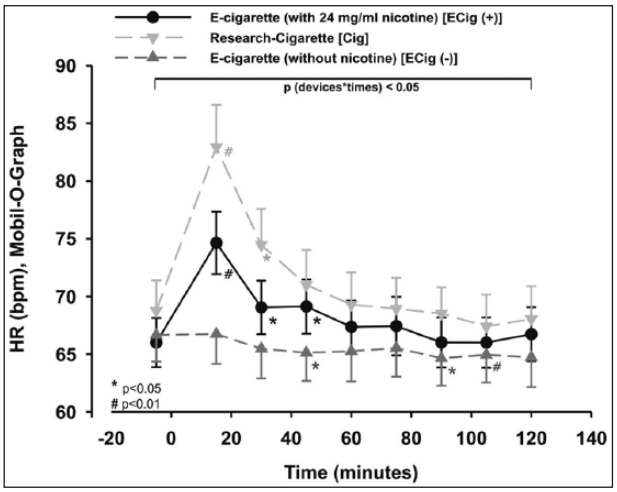

Figure 5. HR was increased within Cig and ECig (+). Two-way measured ANOVA showed a significance between the devices and time ($p < 0.05$), which remains after post hoc testing.
Asterisks indicate a significant change of individual values as compared to baseline, corrected for multiple testing. Data are expressed as mean ± standard error (SE). ANOVA, analysis of variance; HR, heart rate; SE, standard error.

vaping over 45 minutes (+12%; $p < 0.05$; Figure 5). HR was increased by more than 8% during the first 30 minutes after smoking a cigarette ($p < 0.05$; Figure 5).

Vaping with nicotine changed central hemodynamics

The two-way repeated measures ANOVA showed a trend without reaching significance between the different study groups (p=0.053) within central systolic blood pressures (cSBP). The cSBP increased after vaping with ECig (+) and smoking a cigarette, showing a trend without reaching significance (p=0.088/p=0.084; Figure 6) using additional statistics. ECig (–) did not show any significant changes of cSBP during the 2 hours of observation after vaping ($p >$ 0.05; Figure 6).

The two-way repeated measures ANOVA for central diastolic blood pressure (cDBP) showed a significant difference between the different study groups as well as for time ($p < 0.05$). Using additional statistics, the cDBP of ECig (–) was significantly decreased during the first 30 minutes after smoking or vaping ($p < 0.01$ and p=0.005; Figure 7), and showed a trend of increasing within the Cig group without reaching significance within the first 15 minutes (p=0.064; Figure 7). However, there was no significant difference at any time point in the ECig (+) group ($p > 0.05$; Figure 7).

All three groups differed significantly from each other, as analyzed by the two-way repeated measures ANOVA ($p <$ 0.05) for AIx, which was adjusted for a HR of 75 beats per minute (AIx75). In more detail, using additional statistics, the AIx75 increased in the ECig (+) significantly 15 minutes

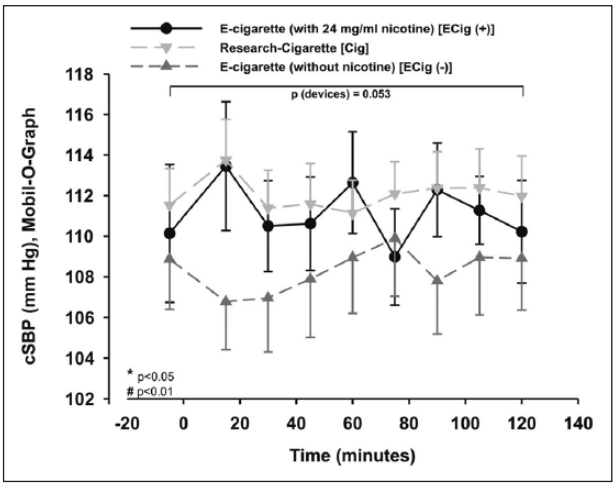

Figure 6. cSBP was not change significantly in the three different groups. Two-way measured ANOVA showed a trend without reaching significance between the devices (p=0.053).
Asterisks indicate a significant change of individual values as compared to baseline, corrected for multiple testing. Data are expressed as mean ± SE. ANOVA, analysis of variance; cSBP, central systolic blood pressure; SE, standard error.

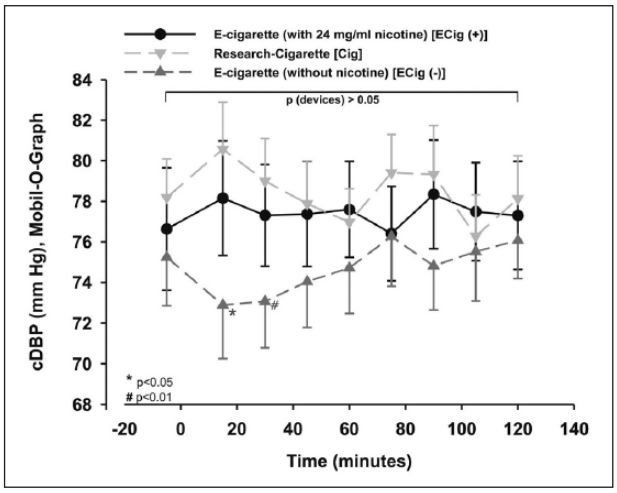

Figure 7. cDBP was decreased within ECig (-) using additional statistics. Two-way measured ANOVA showed a significant difference between the devices ($p < 0.05$).
Asterisks indicate a significant change of individual values as compared to baseline, corrected for multiple testing. Data are expressed as mean ± SE. ANOVA, analysis of variance; cDBP, central diastolic blood pressure; SE, standard error.

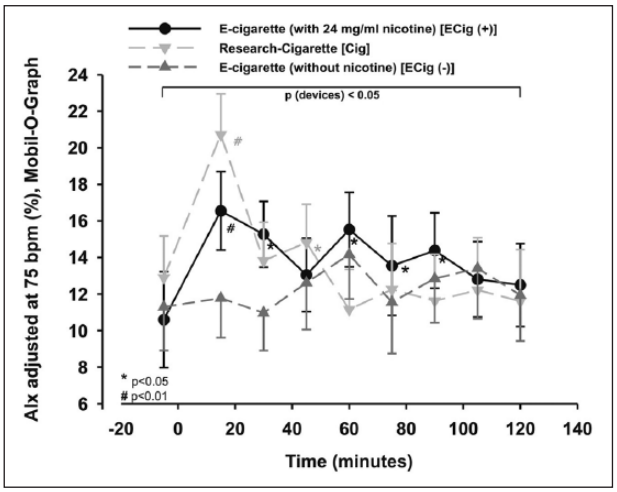

Figure 8. AIx adjusted for a heart rate of 75 bpm (AIx75). Two-way measured ANOVA showed a significance between the devices ($p < 0.05$), which remains after post hoc testing.
Asterisks indicate a significant change of individual values as compared to baseline corrected for multiple testing. Data are expressed as mean ± SE. AIx, augmentation index; ANOVA, analysis of variance; bpm, beats per minute; SE, standard error.

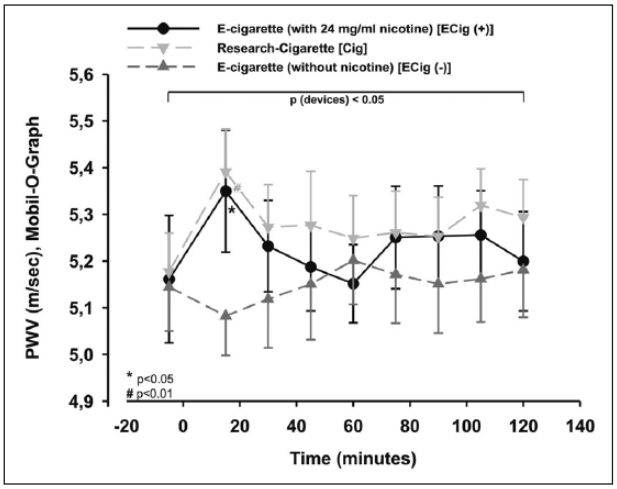

Figure 9. PWV was increased significantly within Cig and ECig (+). Two-way measured ANOVA showed a significance between the devices ($p < 0.05$), which remains after post hoc testing.
Asterisks indicate a significant change of individual values as compared to baseline corrected for multiple testing. Data are expressed as mean ± SE. ANOVA, analysis of variance; PWV, pulse wave velocity; SE, standard error.

after vaping (p=0.001), 30 minutes after vaping ($p < 0.05$), 60 minutes after vaping ($p < 0.05$), 75 minutes after vaping ($p < 0.05$) and 90 minutes after vaping ($p < 0.05$), and showed a trend to an increase without reaching significance 45 minutes after vaping (p=0.064; Figure 8). The Cig group showed a significant increase after the first ($p < 0.01$) and the third 15-minute interval ($p < 0.05$; Figure 8). There was no significance in the ECig (–) arm ($p > 0.05$; Figure 8).

The PWV showed a significant difference between the study arms within the two-way repeated measures ANOVA ($p < 0.01$). In addition, the PWV showed a significant alteration after 15 minutes for ECig (+) ($p < 0.05$; Figure 9) and Cig ($p < 0.01$; Figure 9), whereas no significant change occurred within the ECig (–) arm ($p > 0.05$; Figure 9). ECig (–) was lowered compared to both of the other groups, showing a lowering trend without reaching significance for the first 15 minutes (p=0.086; Figure 9). After calculating multivariate analysis of PWV changes during the 15-minute intervals, changes remained significant in relation to blood pressure or HR (Box test: $p > 0.05$; Levene's test: $p < 0.05$; multivariate tests (Wilks' lambda): $p < 0.05$) for the ECig (+) and Cig arms.

Discussion

In addition to published studies, this is the first study that has observed the effects of using cigarettes, e-cigarettes with nicotine, or e-cigarettes without nicotine – the latter

used as a control group. In the present study, we demonstrate acute changes in peripheral and central blood pressure for a short period of time after vaping a liquid with nicotine or smoking conventional cigarettes. This is in line with previous data on cigarettes and e-cigarettes published by, for example, Vlachopoulos et al.[24–28]

The temporary lowering of DBP can be explained by a relaxation caused by the use of a device or cigarette which supports the finger–mouth coupling (i.e. there will be a short-term relaxation in the group with the nicotine-free liquid). Furthermore, this relaxation inhibits the expected increase in the other two groups. The expected increase is based on the data published by the working group of Mahmud and Feely.[29] The acute increase in SBP and arterial stiffness, especially for AIx75, could be explained by different mechanisms. These mechanisms could be triggered by an increase in circulating and local catecholamines and by nicotine. As already published, nicotine stimulates sympathetic ganglia and therefore increases sympathetic neuronal discharge-impaired nitric oxide production in the central nervous system.[29–31]

The pathogenesis of coronary heart disease and, consecutively, cardiovascular events, are triggered by a stiffening of the arteries.[22,32] Besides the arterial stiffness, central blood pressures seem to be more important compared to peripheral blood pressures.[18,33,34]

Recently published trials have demonstrated discrepant results of the effects induced by vaping e-cigarettes.[25,26] The working group of Szoltysek-Boldys did not show any significant effect of vaping or smoking on SBP, DBP or HR in a study on 15 healthy smokers.[25] However, they showed an increase of the Stiffness Index and Reflection Index. In contrast to this study, Vlachopoulos and colleagues analyzed a group of smokers. The authors showed that vaping an e-cigarette with nicotine-containing liquid had an impact on central hemodynamics as well as on peripheral blood pressure.[26] As previously shown,[27,28,35] both cigarettes and e-cigarettes with a nicotine-containing liquid led to higher SBP, HR, PWV and adjusted AIx75, although the DBP decreased after vaping e-cigarettes with a nicotine-free liquid in our study.

In contrast to the published trials, there were trends and changes within all three different groups within the second half of the observation phase. The changes within the second hour ultimately remained unclear and could not be attributed to the effects of nicotine. This is due, among other things, to the physiological effect of nicotine on the body. One explanation could be that the subjects became restless during observation and looked forward to the end of the test. A passive and therefore secondhand exposure seemed unlikely due to air conditioning. In addition, each of the participants was examined individually and therefore distraction from another participant seemed unlikely.

Study limitations

Unlike the recently published trial,[26] this study was limited by consisting of three different study arms but the number of individuals tested was still limited. As a further limitation, the intensity of vaping the e-cigarette could not be standardized for the depth of breath of each puff. However, to avoid differences being too large, the frequency of puffs was defined. Furthermore, the e-cigarette without nicotine formally contained flavoring agents with the taste of tobacco and propylene was used. Both the liquid with and the liquid without nicotine did not contain the same number of additives as the cigarette. This should be considered in further studies. Another aspect, which has to been taken into account, was the fact that the concentration of nicotine (24 mg/mL) was quite high. However, we have chosen this concentration to illustrate expected effects.

Conclusion

This is the first trial to evaluate the acute changes in peripheral and central hemodynamics as well as PWV using an e-cigarette without nicotine as a control group. The increased parameters within the nicotine-containing devices might be a link to an increased cardiovascular risk, which is well known for cigarettes. Future trials should focus on the chronic effects of vaping nicotine-containing or nicotine-free liquids on peripheral and central blood pressures, as well as on arterial stiffness.

Since no endothelial dysfunction or sex differences have been described for the three different arms in the literature, it would be important for future trials to address these items. The number of laboratory values should be extended to include, for example, catecholamines.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Date: Tuesday, July 10, 2018 12:56PM
Subject: Youth or Young Adults: Which Group Is at Highest Risk for Tobacco Use Onset

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This study shows that due to advertising restrictions, US youth turned away from tobacco and took up e-cigarettes.

Numerous studies have already shown e-cigarettes are a gateway to smoking since they were advertised frequently on social and digital media and were not regulated like tobacco products. Even though e-cigs are now supposed not to be sold to U18's by law (U21 in some States), there were 1.7 million adolescent US e-cig users in 2016. Now this number will be far higher given the JUUL epidemic. JUUL is raising USD 1.2 billion to fuel its worldwide release. The pods hold a massive 59mg/ml nicotine salts. Imperial Brands is now copying the JUUL nicotine/benzoic salts idea in its latest product.

These astounding cohort results show how allowing access to alternate tobacco replacement products has created a young adult .cohort aged 18-24 whose tobacco product multiple product usage now far outstrips adolescent usage.

E-cigarettes have achieved the combustible tobacco usage that nicotine addiction leads to.

These products are for the promotion of nicotine addiction, not for smoking cessation.

This learning lesson is obvious.

Ban e-cigarettes and ban shisha use.

Both end up as proof of the gateway effect to cigarettes, and not just adolescents, as the study shows.

Attachments:

10.1016@j.jadohealth.2018.04.011.pdf

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Original article

Youth or Young Adults: Which Group Is at Highest Risk for Tobacco Use Onset?

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A B S T R A C T

Purpose: Historically, adolescence has been regarded as the time when most tobacco use initiation occurs. This study examines the initiation of tobacco product use, including cigarettes, e-cigarettes, cigar products, and hookah, among contemporary youth and young adults, to determine whether the developmental timing (youth vs. young adulthood) of initiation has changed.
Methods: Three cohort studies were used to examine the onset of ever use and current (past 30 days) use of each tobacco product among never-using youth (11 to <17 years) and young adults (18–24 years) at baseline (2013–2015) to one-year follow-up (2015–2016). These studies include the national Population Assessment of Tobacco and Health Study, and two Texas cohort studies, the Texas Adolescent Tobacco and Marketing Surveillance System (TATAMS), and the Marketing and Promotions Across Colleges in Texas (M-PACT) project. Estimations of onset were computed using generalized linear mixed models for TATAMS and M-PACT. The rates of initiation in Population Assessment of Tobacco and Health Study were compared to standardized incidence rates from TATAMS to M-PACT.
Results: Young adults had significantly higher incidence rates than youth to initiate ever and current use of each/all tobacco products for all comparisons.
Conclusions: These findings extend prior research on the timing of the onset of tobacco use by using longitudinal analyses from three contemporary cohort studies to include not just cigarettes, but also e-cigarettes, cigar products, and hookah. Among those who were never-users of tobacco products, young adults began to ever and currently use all tobacco products more than youth in these samples, a marked departure from prior decades of research.

IMPLICATIONS AND CONTRIBUTION

This study reveals that the initiation of tobacco products among never-using young adults at the national and regional levels is now greater than among youth. This recent, unprecedented change suggests that young adults should receive greater attention so that their tobacco use does not become long-term with associated health consequences.

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Historically, the developmental stage of adolescence is the time when cigarette smoking is initiated and progression to daily smoking is observed [1,2]. The first major conclusion of the 1994 Surgeon General's Report stated: "Nearly all first use of tobacco occurs before high school graduation; this finding suggests that *if adolescents can be kept tobacco-free, most will never start using tobacco*" (p.5). The conclusion was informed by data from the 1991 National Household Surveys on Drug Abuse. Among adults, ages 30–39, who had ever smoked daily, 89% first tried a cigarette and 71% began to smoke daily by age 18 (p. 65) [2]. These analyses were replicated for the 2012 Surgeon General's Report (p. 136) [1]. These data strongly suggest that the onset and regular use of cigarettes began in adolescence for adults who were smokers in 1991 and 2010 [1]. However, these data are somewhat limited since they are retrospective data from adults. Other prospective data, from the Add Health longitudinal study, are consistent with this conclusion (p. 248) [1].

There have been several major changes in tobacco-related products, marketing methods, and policies in the past decade [3,4], that could affect the ways in which youth and young adults initiate and use tobacco products. The most notable change is the introduction of new tobacco products, particularly electronic cigarettes (e-cigarettes), to the U.S. market in 2007, and their rapid adoption by adolescents and young adults [4]. Data from the National Youth Tobacco Survey indicate that 37.7% of high school students had ever used e-cigarettes and 16% were current users in 2015 [5]. Among young adults, ages 18–24, from the National Adult Tobacco Survey in 2013–2014, 35.8% had ever used e-cigarettes and 13.6% were current users [6]. A second change in the past decade involves increased access to and exposure to digital media, including marketing of a variety of products, including tobacco products, via digital and social media [7]. The iPhone's introduction in 2007 and other smartphones have made access to digital media and marketing nearly ubiquitous [8,9]. Unfortunately, exposure to digital marketing appears to affect subsequent tobacco use [10–12], with adolescents who reported seeing e-cigarette marketing on the internet having 2.2 times the odds of being current e-cigarette users six months later (compared with those who did not report exposure) [11]. A third change involves the implementation of the Family Smoking Prevention and Tobacco Control Act (TCA), which gave the Food and Drug Administration (FDA) the authority to regulate the manufacturing, distribution, and marketing of tobacco products [13]. The TCA originally included cigarettes, smokeless, and loose tobacco, but FDA's authority was extended to all tobacco products in 2016 [14]. One of the major charges of the TCA is to reduce tobacco use among adolescents under the age of 18. For example, the TCA banned some flavors of cigarettes and sponsorship at entertainment/sports events, prohibited free sampling of tobacco products and nontobacco branded items, and required manufacturers to seek approval or exemptions from FDA before introducing new tobacco products [15]. These regulations, in addition to those placed on marketing to youth by the 1998 Master Settlement Agreement, have all changed the potential for tobacco companies to market or appeal to youth [16]. As a possible response to these changes, among high school students, from 2011 to 2016, the use of cigarettes, cigars, and smokeless tobacco significantly decreased, while the use of e-cigarettes and hookah significantly increased [17].

Importantly, Thompson and colleagues [18] analyzed cross-sectional national data from 2006 to 2013, on adolescent (12–17 years old) and young adult (18–25 years old) cigarette use, using the National Survey on Drug Use and Health. They found that the rate of onset of cigarette smoking among adolescents was significantly less (1.9%) than onset among young adults (6.3%) during this time. Because this is such a notable departure from decades of research on the age of the onset of cigarette use, the current study extends this work by analyzing data from our ongoing longitudinal studies of youth and young adults in Texas, as well as the national Population Assessment of Tobacco and Health (PATH) study. The current study builds on prior work, by using contemporary data, from 2013 forward, examining the onset of ever and current (past 30 days) use of tobacco by age group (youth vs. young adults) and by product type (cigarettes, e-cigarettes, cigar products, and hookah). If young adults have become a higher risk group for tobacco use onset, then greater attention to preventing use prior to consolidation and addiction in adulthood will be crucial to future efforts to prevent tobacco-related morbidity and mortality.

Methods

Study design

Data in this study are derived from three longitudinal studies described below. These studies include two parallel, longitudinal studies of youth and young adults living in the five counties surrounding the four largest cities in Texas (Austin, Dallas/Fort Worth, Houston, San Antonio) between 2014-15 and 2016. The third study provides nationally-representative data on youth and young adults between 2013-14 and 2014-2015.

The Texas Adolescent Tobacco and Marketing Surveillance System (TATAMS) surveyed 6th, 8th, and 10th grade students at wave 1 (October 2014 to June 2015; n = 3,907), wave 2 (March 2015 to September 2015), and wave 3 (November 2015 to January 2016). Since there was an overlap in the overall timing of the first two waves of data collection, the TATAMS student surveys at wave 2 began at two time points to accommodate the long survey period in wave 1. The average time between waves for all students was 6 months. At wave 3, there was a 70% retention rate (n = 2,733; N = 308,460). TATAMS applies sampling weights to account for the complex design and to represent the population of the five counties [19]. Students completed the wave 1 survey using tablets in the 79 participating schools; participants in waves 2–3 responded to survey questions administered and completed online. Active, informed consent, and assent were obtained from parents and students.

The Marketing and Promotions Across Colleges in Texas project (M-PACT) surveyed students from 24 two-year and four-year colleges who were 18–29 years old (n = 5,482 at wave 1). The students were surveyed online at wave 1, and every six months thereafter, for waves 2–3, during similar dates as TATAMS, and from the same cities/counties. There was a 79% response rate at wave 3 (n = 4,321) [20]. Active and informed consent were obtained from young adults in M-PACT.

PATH study is a nationally-representative study of the civilian noninstitutionalized population of the United States who are 12 years and older. The sample size at baseline included 9,112 young adults of ages 18–24, and 13,651 youth of ages 12–17 [21]. Wave 1 data were collected via interviews with subjects from September 2013 to December 2014. Wave 2 data were collected one year later, 2014–2015 [21]. Data for this study come from the public and restricted use PATH data files [21].

From the PATH studies, subjects in our study were defined as "youth" if at baseline (wave 1) they were ≥12 years old and <17 years old. From the TATAMS study, subjects were defined as youth if at wave 1 they were ≥11 and <17 years old. TATAMS surveyed students by grade level, whereas PATH used age (rather than grade) as an inclusion criteria. Therefore, we excluded .3% of the TATAMS participants who were <11 years old and 1.3% who were ≥17 or older in wave 1, but retained those >11 because they comprise a large proportion of the sixth grade sample. In PATH, we excluded 16.5% of youth participants who were ≥17. This means that all youth were, at one-year follow-up, ≥12 and <18 years old, and all were strictly youth (<18) if/when they initiated tobacco use. "Young adults" were defined as those who were 18–24 at wave 1 in either PATH or M-PACT.

All study protocols and procedures were approved by the University of Texas Health Science Center at Houston's and the University of Texas at Austin's institutional review boards.

Measures

At each wave, subjects in all three studies were asked if they had "ever used" and if they had "used in the past 30 days" each of these tobacco products: cigarettes, e-cigarettes, cigars (little filtered cigars, cigarillos, and large cigars), and hookah. For this study of the onset of tobacco use, only never-users of each tobacco product at wave 1 were included. We then examined what percent of never-users at wave 1 of each cohort were ever users or past 30-day (current) users of each product at one-year follow-up, by wave 3 (for TATAMS and M-PACT), and at wave 2 for PATH. For TATAMS and M-PACT, participants were considered current users if they reported current use by wave 3 (either wave 2 or wave 3). Covariates included race/ethnicity (Hispanic, non-Hispanic white, non-Hispanic black, Asian, and other), sex (male and female), and age, using standardized measures [21–23]. These covariates were selected since significant differences by race/ethnicity, sex, and age have recently been documented for tobacco use at the national level [24].

Data analysis methods

Weighted estimates are reported from PATH [25] and TATAMS [19] accounting for their complex design and nonresponse. M-PACT estimates account for the cluster and design effect from participants within colleges. Wave 1 descriptive statistics are shown in Table 1 for the cohorts—before restricting the data to never-users—for reference purposes.

In TATAMS, sampling weights from all three waves were normalized to conduct the longitudinal estimation of the prevalence of new tobacco product use at one-year follow-up (by wave 3) among never-users at wave 1. Estimates are reported for both ever use or current use of each one of the five tobacco product categories (cigarettes, e-cigarettes, cigars, hookah, and any tobacco product), after controlling for race/ethnicity, sex, age, and design effects. Therefore, ten (2×5) generalized linear mixed models (GLMM) of waves 1–3, with a logit link using 150 quadrature points, were used to estimate these prevalence rates; data for wave 3 are reported to compare with PATH.

In M-PACT, similar to TATAMS, 10 separate GLMMs, with a logit link using 150 quadrature points, were used to estimate the prevalence of tobacco use initiation, for either ever use or current use of each of the five tobacco product categories, after controlling for race/ethnicity, sex, age, and design effects (college attended; and type of college, two-year or four-year).

In PATH, after appropriate weighting, the proportion of never-users at wave 1 who became ever users and current users by wave 2 (one-year follow-up) was used for comparisons.

Because TATAMS is a representative sample of the five previously mentioned counties in Texas, while M-PACT is a convenience sample of students in colleges within the five counties, the two samples were not deemed comparable. Instead, we utilize PATH estimates as the national reference standard, and then examine how youth and young adults differed in comparison to those in PATH. All analyses estimating the prevalence of tobacco use by wave 3 were conducted using SAS 9.4 [26].

Comparisons of youth and young adults

Youth and young adult onset (of ever and current use among wave 1 never-users) of each tobacco product category—cigarettes, e-cigarettes, cigar products, hookah, and any (of these) tobacco products—was assessed using five comparisons. First, we compared the difference in proportions at wave 2, between the prevalence of new ever and current users among PATH youth (12 to <17, wave 1) and PATH young adults (18–24, wave 1). Second, we evaluated whether the estimated prevalence rates of tobacco use initiation at wave 2 from PATH young adults (18–24) (population estimate) was inside the standardized 95% confidence interval (CI) for prevalence rates from TATAMS youth (11 to <17) by wave 3. Third, we evaluated whether the estimated prevalence rates of tobacco use initiation (population estimate) from PATH youth (12 to <17) was inside the standardized 95% CI for the prevalence rates from TATAMS youth (11 to <17) by wave 3. Fourth, we evaluated whether the prevalence of tobacco use initiation from PATH youth (12 to <17) (population estimate) at wave 2 was within the 95% CI for the prevalence rates for M-PACT young adults (18–24) by wave 3. Fifth, we evaluated whether the prevalence of tobacco use initiation from PATH young adults (18–24) (population estimate) at wave 2 was within the 95% CI for proportions for M-PACT young adults by wave 3.

Importantly, we used the 2014 population estimates of the United States [27] to standardize the prevalence estimates from TATAMS and M-PACT by gender and ethnicity. TATAMS data are standardized to correspond to the U.S. population of 11 to <17 years old in 2014; M-PACT data are standardized to correspond to the U.S. population of 18–24 years old in 2014. PATH data are also standardized by design of the national study [25].

Results

Table 2 provides the demographic data for the analytic samples of never-users of any tobacco product at wave 1 for PATH youth, PATH young adults, TATAMS youth, and M-PACT young adults. PATH youth and young adults were older than TATAMS youth and M-PACT young adults, respectively. While the youth populations of PATH and TATAMS were nearly evenly split between males and females; the young adult populations of PATH and M-PACT had a higher proportion of females among the never-users. PATH youth and young adults were predominantly white (>50%), followed by Hispanic and non-Hispanic black participants. TATAMS youth were predominantly Hispanic (>50%), followed by white, and non-Hispanic black. M-PACT young adults were more likely to be white, Hispanic or Asian (>25% each). Comparisons of demographic characteristics of other sub-groups (never-users of cigarettes,

Table 1
Demographic characteristics and tobacco use prevalence of the entire sample of PATH, TATAMS, and M-PACT youth and young adults at wave 1

	PATH (Ages 12 to <17) n = 11,539[d] (N = 20,754,826)	PATH (Ages 18–24) n = 9,112 (N = 30,706,753)	TATAMS (Ages 11 to <17) n = 3,830 (N = 452,449)	M-PACT (Ages 18–24) n = 5,073
Mean age (standard error)	14.0 (.00015)[d]	21.1 (.03)[c]	13.4 (.17)	20.0 (.02)
	(N) **%**	n(N) **%**	n(N) **%**	n **%**
Sex				
Female	5,616(10,098,250) **48.6**[d]	4,496(15,272,700) **49.7**[e]	2,147(221,310) **48.9**	3,227 **63.6**
Male	5,923(10,656,575) **51.4**[d]	4,614(15,434,053) **50.3**[e]	1,683(231,139) **51.1**	1,843 **36.4**
Race/ethnicity				
White	5,539(11,280,395) **54.4**[d]	4,712(16,842,509) **54.9**[e]	1,201(97,816) **21.6**	1,785 **35.2**
Hispanic	2,454(3,384,235) **16.3**[d]	1,575(4,736,149) **15.4**[e]	1,466(247,768) **54.8**	1,593 **31.4**
Black/African-American	1,777(3,162,062) **15.2**[d]	1,529(4,487,878) **14.6**[e]	608(77,304) **17.1**	408 **8.0**
Asian	348(1,002,007) **4.8**[d]	1,294(4,640,217) **15.1**[e]	555(29,561) **6.5**	902 **17.8**
Other[a]	1,421(1,926,126) **9.3**[d]			385 **7.6**
Any Tobacco product use[b]				
Ever use	2,043(3,623,622) **17.5**[d]	7,277(20,318,527) **66.5**[e]	813(109,100) **24.1**	3,355 **66.1**
Current use	920(1,632,810) **7.9**[d]	4,706(11,840,597) **39.0**[e]	309(46,343) **10.3**	1,788 **35.3**
Cigarettes				
Ever use	1,227(2,158,164) **10.4**[d]	5,963(16,339,145) **53.2**[e]	329(48,199) **10.7**	2,337 **46.1**
Current use	378(655,138) **3.2**[d]	3,593(8,839,176) **28.8**[e]	85(15,853) **3.5**	1,010 **19.9**
E-cigarette use				
Ever use	998(1,778,388) **8.6**[d]	3,887(9,834,710) **32.1**[e]	661(87,056) **19.2**	2,396 **47.2**
Current use	274(494,047) **2.4**[d]	1,516(3,818,883) **12.5**[e]	249(33,657) **7.5**	848 **16.7**
Cigars				
Ever use	571(992,549) **4.9**[d]	5,092(13,760,119) **45.4**[e]	189(26,773) **5.9**	1,723 **34.0**
Current use	174(294,601) **1.5**[d]	1,933(4,737,429) **15.7**[e]	63(8,634) **1.9**	479 **9.2**
Hookah				
Ever use	612(1,098,915) **5.3**[d]	5,061(13,621,120) **44.4**[e]	195(27,471) **6.1**	2,721 **53.6**
Current use	130(229,804) **1.7**[d]	1,261(3,295,066) **10.7**[e]	64(10,722) **2.4**	865 **17.1**

M-PACT = Marketing and Promotions Across Colleges in Texas; PATH = Population Assessment of Tobacco and Health Study; TATAMS = Texas Adolescent Tobacco and Marketing Surveillance System.

[a] Other (TATAMS and PATH Young Adults) includes Asian, other, and multiple race/ethnicity.

[b] Any product use includes cigarettes, e-cigarettes, cigars, and hookah.

[c] PATH restricted file received disclosure to publish: May 19, 2017. United States Department of Health and Human Services. National Institutes of Health. National Institute on Drug Abuse, and United States Department of Health and Human Services. Food and Drug Administration. Center for Tobacco Products. Population Assessment of Tobacco and Health (PATH) Study [United States] Restricted-Use Files. ICPSR36231-v13. Ann Arbor, MI: Inter-university Consortium for Political and Social Research [distributor], June 19, 2017. https://doi.org/10.3886/ICPSR36231.v13.

[d] PATH restricted file received disclosure to publish: January 18, 2018. United States Department of Health and Human Services. National Institutes of Health. National Institute on Drug Abuse, and United States Department of Health and Human Services. Food and Drug Administration. Center for Tobacco Products. Population Assessment of Tobacco and Health (PATH) Study [United States] Restricted-Use Files. ICPSR36231-v13. Ann Arbor, MI: Inter-university Consortium for Political and Social Research [distributor], June 19, 2017. https://doi.org/10.3886/ICPSR36231.v13.

[e] PATH public file: United States Department of Health and Human Services. National Institutes of Health. National Institute on Drug Abuse, and United States Department of Health and Human Services. Food and Drug Administration. Center for Tobacco Products. Population Assessment of Tobacco and Health (PATH) Study [United States] Public-Use Files. ICPSR36498-v6. Ann Arbor, MI: Inter-university Consortium for Political and Social Research [distributor], June 14, 2017. https://doi.org/10.3886/ICPSR36498.v6.

e-cigarettes, cigars, and hookah) were similar to the never-users of any tobacco product within each of the studies (data not shown). Because of these demographic differences between the studies, all comparisons with PATH, using TATAMS and M-PACT data are: (1) standardized to the U.S. population in 2014 (for comparable age groups, and by gender and ethnicity) and (2) adjusted for age, sex, and race/ethnicity in analyses.

Table 3 presents the data comparing PATH youth (12 to <17) and PATH young adults (18–24) who were never-users of any product, and each product, at wave 1, and who became ever users or current users of each tobacco product (or any tobacco product) by wave 2. *PATH young adults were significantly more likely to initiate ever and current use of all tobacco products than PATH youth by wave 2: cigarettes, e-cigarettes, cigar products, and hookah (and all combined).*

Table 4 presents the data comparing PATH youth (12 to <17) and young adults (18–24) and TATAMS youth (11 to <17), who were never-users at these ages at wave 1, and who became ever users or current users at wave 2 (PATH) or by wave 3 (TATAMS). Importantly, *PATH young adults at wave 2 were significantly more likely than TATAMS youth by wave 3 to ever use, and currently use, any tobacco product and each tobacco product.*

In addition, at one-year follow-up, PATH youth were significantly more likely than TATAMS youth to ever use: any tobacco product, e-cigarettes, and hookah. PATH youth and TATAMS youth were equally likely to ever use cigarettes and cigars. In addition, at follow-up, PATH youth were significantly more likely than TATAMS youth to currently use any tobacco product and cigarettes. They were equally likely to currently use e-cigarettes, cigars, and hookah.

Table 5 presents the data comparing PATH youth (12 to <17) and PATH young adults (18–24) with M-PACT young adults (18–24), who were never-users at wave 1, and who became ever users or current users at wave 2 (PATH) or by wave 3 (M-PACT). *M-PACT young adults were significantly more likely than PATH youth to ever and currently use: any tobacco product, cigarettes, e-cigarettes, cigars, and hookah at one-year follow-up.*

M-PACT young adults (wave 3) were significantly *more* likely than PATH young adults (wave 2) to ever use: any tobacco product, cigarettes, cigars, and hookah by one-year follow-up. M-PACT

Table 2
Demographic characteristics of the analysis sample PATH, TATAMS, and M-PACT youth and young adult never users of any tobacco product at wave 1

	PATH (ages 12 to <17) n = 9,314 (N = 16,805,457)	PATH (ages 18–24) n = 1,804 (N = 10,231,916)	TATAMS (ages 11 to <17) n = 3,025 (N = 344,679)	M-PACT (ages 18–24) n = 1,718
Mean age (standard error)	13.8 (.01)[b]	20.7 (.06)[b]	13.1 (.17)	19.6 (.04)
	n(N) **%**	n(N) **%**	n(N) **%**	n **%**
Sex				
Female	4,565(8,243,620) **49.2**[b]	1,046(5,654,157) **55.4**	1,728(168,038) **48.8**	1,131 **65.8**
Male	4,719(8,508,887) **50.8**[b]	755(4,557,669) **44.6**[b]	1,297(176,641) **51.2**	587 **34.2**
Race/ethnicity				
White	4,339(8,862,003) **56.3**[b]	838(5,150,278) **52.3**[b]	1,020(81,001) **23.5**	558 **32.5**
Hispanic	2,194(3,046,220) **19.3**[b]	361(1,705,306) **17.3**[b]	1,103(182,397) **52.9**	443 **25.8**
Black/African American	1,270(2,290,511) **14.6**[b]	328(1,510,181) **15.3**[b]	455(58,037) **16.8**	145 **8.4**
Asian	249(807,401) **5.1**[b]	109(1,146,976) **11.6**[b]	447(23,245) **6.7**[a]	444 **25.8**
Other	563(741,779) **4.7**[b]	91(343,358) **3.5**[b]		128 **7.5**

M-PACT = Marketing and Promotions Across Colleges in Texas; PATH = Population Assessment of Tobacco and Health Study; TATAMS = Texas Adolescent Tobacco and Marketing Surveillance System.

[a] Includes Asian, other, and multiple race/ethnicity.

[b] PATH restricted file received disclosure to publish: February 12, 2017. United States Department of Health and Human Services. National Institutes of Health. National Institute on Drug Abuse, and United States Department of Health and Human Services. Food and Drug Administration. Center for Tobacco Products. Population Assessment of Tobacco and Health (PATH) Study [United States] Restricted-Use Files. ICPSR36231-v13. Ann Arbor, MI: Inter-university Consortium for Political and Social Research [distributor], June 19, 2017. https://doi.org/10.3886/ICPSR36231.v13.

young adults were equally likely as PATH young adults to be current users of each and any tobacco product.

Discussion

Our findings extend prior research on the timing of the onset of tobacco use by using longitudinal analyses from three contemporary cohort studies to include not just cigarettes, but also e-cigarettes, cigar products, and hookah. Among those who were never-users of tobacco products, young adults, from 2013 to 2016, began to ever and currently use all tobacco products more than youth in these samples—a marked departure from prior decades of research on when tobacco use was initiated, and contrary to the conclusion that adolescence is the primary developmental stage of highest risk of onset [1,2].

One factor that may account for the shift from youth to young adult onset, is that tobacco marketing methods are less appealing, or have less exposure, to youth than to young adults, after coming under regulation [13,17]. Now, tobacco company marketing is more explicitly aimed at their youngest legal target group, young

Table 3
Comparing the prevalence of PATH youth and young adult use of tobacco products at wave 2 (one-year follow-up) among wave 1 never users of each product

Of wave 1 never users of:	Youth[b] (ages 12 to <17) n(N) **% users** at wave 2	Young adults[c] (Ages 18–24) n(N) **% users** at wave 2	Difference in proportions[d] youth–adults (95% CI), SE	*p* value of chi square statistic for test of independence
Any Tobacco product[a]				
Ever use by follow-up	829(1,703,309) **10.5**[e]	215(1,369,565) **13.9**[e]	−.034 (−.0593, −.0088), .0127	.0048[e]
Current use by follow-up	276(567,314) **3.5**[e]	125(774,671) **7.9**[e]	−.0437 (−.0625, −.0249), .0095	<.0001[e]
Cigarettes				
Ever use by follow-up	333(683,138) **3.8**[e]	215(945,559) **6.8**[e]	−.0297 (−.0414, −.018), .0059	<.0001[e]
Current use by follow-up	137(280,898) **1.6**[e]	146(625,208) **4.5**[e]	−.0291 (−.0381, −.0201), .0045	< .0001[e]
E-cigarettes				
Ever use by follow-up	808(1,675,248) **9.2**[e]	740(2,947,552) **14.6**[e]	.1204 (.1118, .129), .0043	<.0001[e]
Current use by follow-up	217(457,997) **2.5**[e]	227(901,931) **4.5**[e]	−.02 (−.0294, −.0105), .0048	<.0001[e]
Cigars				
Ever use by follow-up	267(566,752) **3.1**[e]	290(1,172,870) **7.4**[e]	−.043 (−.0544, −.0317), .0057	<.0001[e]
Current use by follow-up	78(159,062) **.9**[e]	183(659,496) **4.1**[e]	−.0328 (−.0409, −.0246), .0041	<.0001[e]
Hookah				
Ever use by follow-up	288(596,626) **3.1**[e]	378(1,630,828) **9.8**[e]	−.067 (−.0802, −.0538), .0067	<.0001[e]
Current use by follow-up	76(157,343) **.8**[e]	193(834,126) **5.0**[e]	−.042 (−.0509, −.0332), .0044	<.0001[e]

CI = confidence interval; PATH = Population Assessment of Tobacco and Health Study.

[a] Any tobacco product use includes cigarettes, e-cigarettes, cigars, and hookah.

[b] Youth ages 12 to <17 at wave 1 and ages 13 to <18 at wave 2.

[c] Young adults ages 18–24 at wave 1 and ages 19–25 at wave 2.

[d] Each subset of never users for a tobacco product for youth was appended to the same subset of never users for the same tobacco product among the adults for the purpose of the comparison.

[e] PATH restricted file received disclosure to publish: November 21, 2017. United States Department of Health and Human Services. National Institutes of Health. National Institute on Drug Abuse, and United States Department of Health and Human Services. Food and Drug Administration. Center for Tobacco Products. Population Assessment of Tobacco and Health (PATH) Study [United States] Restricted-Use Files. ICPSR36231-v13. Ann Arbor, MI: Interuniversity Consortium for Political and Social Research [distributor], June 19, 2017. https://doi.org/10.3886/ICPSR36231.v13.

Table 4
Comparing the prevalence of tobacco use at one-year follow-up among PATH youth and young adults with TATAMS youth among wave 1 never users

	PATH youth[b] (Ages 12 to <17)	PATH young Adults[c] (Ages 18–24)	TATAMS youth[d] (Ages 11 to <17)	
Of wave 1 never users of:	n(N) **% users** at wave 2	n(N) **% users** at wave 2	n	**% users** by wave 3 (95% CI) adjusted and standardized[e,f]
Any tobacco product[a]				
Ever use by follow-up	829(1,703,309) **10.5**[g]	215(1,369,565) **13.9**[g]	2,164	**6.3** (4.3–9.1)
Current use by follow-up	276(567,314) **3.5**[g]	125(774,671) **7.9**[g]	2,164	**1.6** (.7–3.3)
Cigarettes				
Ever use by follow-up	333(683,138) **3.8**[g]	215(945,559) **6.8**[g]	2,472	**3.6** (2.6–5.0)
Current use by follow-up	137(280,898) **1.6**[g]	146(625,208) **4.5**[g]	2,472	**.4** (.2–1.2)
E-cigarettes				
Ever use by follow-up	808(1,675,248) **9.2**[g]	740(2,947,552) **14.6**[g]	2,258	**5.1** (3.3–7.7)
Current use by follow-up	217(457,997) **2.5**[g]	227(901,931) **4.5**[g]	2,258	**2.0** (1.1–3.7)
Cigars				
Ever use by follow-up	267(566,752) **3.1**[g]	290(1,172,870) **7.4**[g]	2,568	**2.9** (2.0–4.3)
Current use by follow-up	78(159,062) **.9**[g]	183(659,496) **4.1**[g]	2,568	**.4** (.2–1.2)
Hookah				
Ever use by follow-up	288(596,626) **3.1**[g]	378(1,630,828) **9.8**[g]	2,579	**1.3** (.7–2.5)
Current use by follow-up	76(157,343) **.8**[g]	193(834,126) **5.0**[g]	2,579	**.3** (.1–1.3)

CI = confidence interval; PATH = Population Assessment of Tobacco and Health Study; TATAMS = Texas Adolescent Tobacco and Marketing Surveillance System.
[a] Any tobacco product use includes cigarettes, e-cigarettes, cigars, and hookah.
[b] Youth ages 12 to <17 at wave 1 and ages 13 to <18 at wave 2.
[c] Young adults ages 18–24 at wave 1 and ages 19–25 at wave 2.
[d] Youth ages 11 to <17 at wave 1 and ages 12 to <18 at wave 3.
[e] Adjusted for study design (point-of-sale proximity), gender, and race/ethnicity.
[f] TATAMS ages 11–16 at baseline standardized by gender and ethnicity (Hispanic vs. non-Hispanic). Results are standardized to corresponding U.S. population of 11–16 years old in 2014.
[g] PATH restricted file received disclosure to publish: November 21, 2007. United States Department of Health and Human Services. National Institutes of Health. National Institute on Drug Abuse, and United States Department of Health and Human Services. Food and Drug Administration. Center for Tobacco Products. Population Assessment of Tobacco and Health (PATH) Study [United States] Restricted-Use Files. ICPSR36231-v13. Ann Arbor, MI: Interuniversity Consortium for Political and Social Research [distributor], June 19, 2017. https://doi.org/10.3886/ICPSR36231.v13.

adults, and a marked shift from the 1990s [28]. Marketing methods currently involve point-of-sale at retail establishments, price discounts, samples, adult public entertainment, digital media, and magazines [29]. Price discounts accounted for 80% of cigarette marketing dollars in 2014 [30], and is a key strategy for tobacco companies to make cigarettes less expensive for price-sensitive populations, such as youth and young adults. Several marketing methods were regulated during the Master Settlement Agreement, so that there would be less exposure to appealing marketing for youth (under age 18) [16]. Importantly, although youth have been exposed to marketing via point-of-sale, there is high compliance with the Synar Amendment that mandated that all states prohibit

Table 5
Comparing the prevalence of tobacco use at one-Year follow-up among PATH youth and young adults with M-PACT young adults among wave 1 never users

	PATH youth[b] (ages 12 to <17)	PATH young adults[c] (ages 18–24)	M-PACT young adults[d] (ages 18–24)	
Of wave 1 never users of:	n(N) **% users** at wave 2	n(N) **% users** at wave 2	n	**% users** by wave 3 (95% CI) adjusted and standardized[f,g]
Any tobacco product[a]				
Ever use by follow-up	829(1,703,309) **10.5**[e]	215(13,69,565) **13.9**[e]	1,411	**17.6** (14.3–22.7)
Current use by follow-up	276(567,314) **3.5**[e]	125(774,671) **7.9**[e]	1,411	**7.9** (5.2–13.2)
Cigarettes				
Ever use by follow-up	333(683,138) **3.8**[e]	215(945,559) **6.8**[e]	2,209	**9.6** (7.4–12.6)
Current use by follow-up	137(280,898) **1.6**[e]	146(625,208) **4.5**[e]	2,209	**4.1** (2.6–6.8)
E-cigarettes				
Ever use by follow-up	808(1,675,248) **9.2**[e]	740(2,947,552) **14.6**[e]	2,125	**15.0** (13.0–17.5)
Current use by follow-up	217(457,997) **2.5**[e]	227(901,931) **4.5**[e]	2,125	**5.2** (3.8–7.2)
Cigars				
Ever use by follow-up	267(566,752) **3.1**[e]	290(1,172,870) **7.4**[e]	2,641	**15.2** (13.2–17.7)
Current use by follow-up	78(159,062) **.9**[e]	183(659,496) **4.1**[e]	2,641	**5.1** (3.5–7.5)
Hookah				
Ever use by follow-up	288(596,626) **3.1**[e]	378(1,630,828) **9.8**[e]	1,874	**19.9** (17.0–23.5)
Current use by follow-up	76(157,343) **.8**[e]	193(834,126) **5.0**[e]	1,874	**5.6** (4.4–7.6)

CI = confidence interval; M-PACT = Marketing and Promotions Across Colleges in Texas; PATH = Population Assessment of Tobacco and Health Study.
[a] Any tobacco product use includes cigarettes, e-cigarettes, cigars, and hookah.
[b] Youth ages 12 to <17 at wave 1 and ages 13 to <18 at wave 2.
[c] Young adults ages 18–24 at wave 1 and ages 19–25 at wave 2.
[d] Young adults ages 18–24 at wave 1 and ages 19–25 at wave 3.
[e] PATH restricted file received disclosure to publish: November 21, 2017. U. S. Department of Health and Human Services. National Institutes of Health. National Institute on Drug Abuse, and United States Department of Health and Human Services. Food and Drug Administration. Center for Tobacco Products. Population Assessment of Tobacco and Health (PATH) Study [United States] Restricted-Use Files. ICPSR36231-v13. Ann Arbor, MI: Interuniversity Consortium for Political and Social Research [distributor], June 19, 2017. https://doi.org/10.3886/ICPSR36231.v13.
[f] Adjusted for institution type (two- or four-year), college attended, gender, race/ethnicity, and age at wave 1.
[g] Standardized by gender and ethnicity (Hispanic vs. non-Hispanic) for ages 18–24 at baseline. Results are standardized to corresponding U.S. population of 18–24 years old in 2014.

the sale of tobacco to minors by 1995. Data on compliance show that while 60% of tobacco retail outlets in the United States were compliant in 1997; this has increased to over 90% by 2012 [31]. Thus, while price discounts are appealing to youth and young adults, compliance with age-of-sale laws may have made these discounts less directly relevant to youth. In all, efforts to reduce the appeal and exposure to the marketing of cigarettes to youth have likely been impactful [1], while few prevention programs or policies have directly focused on young adults.

A second factor to consider is that many of the behaviors associated with adolescence also may be shifting to young adulthood. For example, in 2000, 50% of 12th graders in the Monitoring the Future Study reported drinking alcohol in the past 30 days; this decreased to 33% of 12th graders by 2016 [32]. Also, 8th, 10th, and 12th graders are much *less* likely to engage in traditional activities of adolescents, such as hanging out with friends (without their parents), wanting to get their driver's licenses, or going on a date in 2016, than they were in 2010 [33]. Since these behaviors covary with tobacco use, the reduction of tobacco use onset among youth may be part of an overall trend to extend or delay this constellation of risk behaviors.

In addition, traditional young adult behaviors, such as starting a career, getting married, or having children, also are delayed, and so the entire developmental trajectory from adolescence to adulthood may be increasing in duration [34]. For example, age of first marriage is now 28 years old, compared with 24–25 in 1990 [35]. In addition, young adults are more likely to be living with their parents than previous generations [36]. Thus, there may be a trend for young adults to initiate behaviors that were previously started in adolescence, while they (young adults) delay their own traditional developmental tasks until their late 20s or 30s.

While young adults from PATH or M-PACT were more likely to initiate all forms of tobacco use than youth in PATH or TATAMS, from 2014–2016 using three separate comparisons, the TATAMS youth were generally initiating at lower rates than PATH youth. This may be due to the sampling method of recruiting by grade, so that the overall age of the TATAMS cohort was younger, even though the data were controlled by age and nationally standardized. Interestingly, the M-PACT young adults had similar rates of onset of current use compared with their national counterpart. However, M-PACT young adults were more likely to initiate tobacco use (ever use, except e-cigarettes) than their PATH counterparts, even if they were not current users. This difference was not expected, given that college students generally have lower tobacco use than noncollege students [37]. It may be that Texas college students have been exposed to more tobacco industry advertising, given that Texas is the #1 state in spending by the tobacco industry for marketing [38]. Alternatively, Texas college students may be more likely to exhibit characteristics of "emerging adults" including behaviors that are associated with identity development, such as tobacco use [39]. However, these reasons are speculative and they do not alter the primary findings of the substantial differences found in onset rates between youth and young adults at regional and national levels. The above comparisons, though, do reinforce demographic and regional similarities and differences in the prevalence of tobacco products and the need to continue to monitor youth and young adult use at the regional level [40].

There are limitations to our study. The most important is the lower prevalence of tobacco use among youth (vs. young adults) at wave 1. This suggests that for the young adults in our samples, some *may* have first used tobacco products while they were youth. The restriction of the analyses to never-users of each tobacco product and especially the finding that many of these never-users became current users over one year during young adulthood, strengthens the conclusion that young adults are now at risk of onset of tobacco use—contrary to prior conclusions [1,2]. However, continuing longitudinal analyses from adolescence to young adulthood will be needed to definitively confirm that most onset occurs from age 18 and older, and to identify which subgroups are at highest risk for initiation including specific gender and racial/ethnic groups.

This study reveals that initiation across multiple tobacco products among never-using young adults at both the national and regional (Texas) levels is now greater than among youth. This recent and unprecedented change in the age of onset is likely to have many causes, such as successful policies, programs, and communications concerning tobacco use and youth since the late 1990s [40]. These efforts have been implemented in the context of changes in the social environments of youth that reinforce social monitoring (via social media) and a decline in other risky covarying behaviors. These data clearly point to greater attention and action needed to prevent onset with young adults—to prevent long-term adult tobacco use and associated health consequences.

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News Hub

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ATLANTA–Users of e-cigarettes and other electronic nicotine delivery systems (ENDS) in the United States are no more likely to quit smoking cigarettes than people who don't use such devices, according to a study by a group of tobacco researchers at the School of Public Health at Georgia State University.

The researchers found "no evidence" that ENDS as they have been marketed and used in the U.S. are effective at helping smokers quit at a population level, despite anecdotal reports that some smokers have found them useful.

"Absent any meaningful changes, ENDS use among adult smokers is unlikely to be a sufficient solution to obtaining a meaningful increase in population quit rates," the authors wrote in a newly released article in the journal *PLOS ONE*. "We observed no instance where ENDS users were more likely to quit (smoking cigarettes) than non-ENDS users."

At the end of the one-year study, the researchers found 90 percent of "dual users" (people who used ENDS and traditional cigarettes at the start of the study) were still smoking. Among the dual users, nearly 54 percent were smoking cigarettes as well as using ENDS after a year, and more than 37 percent were still smoking cigarettes but had stopped using ENDS.

The researchers also found that users of e-cigarettes and related products were more likely to try to quit smoking, but those attempts did not translate into greater success. Even study participants who said they were using ENDS to help them stop smoking (a majority of ENDS users) were less likely to manage to quit than those who did not use the devices.

Results of the study are published in an article titled "Are Electronic Nicotine Delivery Systems Helping Cigarette Smokers Quit? Evidence from a Prospective Cohort Study of U.S. Adult Smokers, 2015-2016." Dr. Scott Weaver, assistant professor of epidemiology & biostatistics, is the lead author."

"Many smokers are using ENDS in their smoking quit attempts, but these devices may not be providing a sufficiently satisfying nicotine delivery and overall user experience to completely supplant their smoking," Weaver said. "Coordinated regulation aimed at improving the appeal and satisfaction of ENDS available to smokers, while reducing the

nicotine levels in combustible tobacco products to non-addictive levels may be necessary for ENDS to have a meaningful role in reducing the staggering public health burden of smoking."

The study analyzed the responses of 858 smokers who participated in an initial survey in late 2015 and a follow-up a year later as part of a national, online panel conducted by marketing research institute GfK.

The authors recommend additional research to monitor the rapidly changing ENDS market and usage patterns.

The study's co-authors are Dr. Jidong Huang, associate professor of health management & policy; Dr. Terry Pechacek, professor of health management & policy; John Wesley Heath, data administrator; Dr. David Ashley, professor of environmental health; and Dean Michael Eriksen, all of the School of Public Health at Georgia State.

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Featured Researcher

Scott Weaver
Assistant Professor
Epidemiology & Biostatistics

Identifying primarily as a prevention scientist and quantitative methodologist, Dr. Weaver has over a decade of experience conducting research on minority and immigrant health and health disparities; substance use and risky youth behaviors; social and cultural determinants of health; systems interventions for promoting positive youth and family outcomes; and global urban health.

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Are electronic nicotine delivery systems helping cigarette smokers quit? Evidence from a prospective cohort study of U.S. adult smokers, 2015–2016

Scott R. Weaver , Jidong Huang, Terry F. Pechacek, John Wesley Heath, David L. Ashley, Michael P. Eriksen

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Abstract

Background

The potential of electronic nicotine delivery systems (ENDS) to reduce the cardiovascular and other disease risks of smoking is of great interest. While many smokers report using ENDS for cessation, their impact under real-world use patterns and conditions on adult smokers' quitting behavior is uncertain. The objective of this study was to generate more recent and comprehensive evidence on the effect of "real world" ENDS use on the population quit rates of adult smokers while taking account of frequency and duration of use, device type, e-liquid flavor, and reasons for use.

Methods and findings

We conducted a population-based, prospective cohort study of a random probability sample of 1284 U.S. adult smokers recruited in August/September 2015 and re-contacted one-year later (September 2016) from GfK's KnowledgePanel, a national, probability-based web-panel designed to be representative of non-institutionalized U.S. adults. Among the 1081 baseline smokers who remained members of KnowledgePanel, 858 completed the follow-up survey. The primary outcome was smoking abstinence for at least 30 days prior to follow-up. Secondary outcomes were making a quit attempt during the 12-month study period and number of cigarettes smoked per day at follow-up. The adjusted odds of quitting smoking were lower for those that used ENDS at baseline (9.4%, 95% CI = 5.22%-16.38%; AOR = 0.30, 95% CI = 0.13–0.72) compared to smokers who did not use at ENDS (18.9%, 95% CI = 14.24%-24.68%). Smokers who used ENDS daily at some point during the study period were also less likely to quit smoking than nonusers (AOR = 0.17; 95% CI = 0.04–0.82). Limited ability to draw causal inferences from the observational design and a lack of biochemical verification of quitting smoking or ENDS use are limitations of this study.

Conclusions

We found no evidence that ENDS use, within context of the 2015–2016 US regulatory and tobacco/vaping market landscape, helped adult smokers quit at rates higher than smokers who did not use these products. Absent any meaningful changes, ENDS use among adult smokers is unlikely to be a sufficient solution to obtaining a meaningful increase in population quit rates. Additional research is needed to reconcile the divergent literature and monitor the impact of ENDS in an environment of rapidly evolving markets and regulatory policies.

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Introduction

Electronic nicotine delivery systems (ENDS) have generated significant interest for their potential cardiovascular effects, as well as their potential to reduce the cardiovascular disease and other health risks of smoking [1–8]. Whereas several tobacco control experts have expressed support for the harm reduction potential of ENDS [9–20], a spirited debate has ensued [21–25]. Two of the central pillars on which the harm reduction argument rests are: (a) use of ENDS is substantially less harmful than smoking cigarettes and (b) their use leads to higher population-level smoking quit rates [6,13,26–30]. Although more research is necessary before the full extent of the risks from ENDS use are known [31,32], the extant research suggests that use of ENDS is likely substantially less harmful than smoking combustible cigarettes [25,33–37], with most debate focusing on how much less harmful [28]. Reduced risk, however, is insufficient for achieving population-level harm reduction without effecting switching from a higher risk to a lower risk product. Nearly one-half of smokers reported having ever tried and approximately one in six currently using ENDS in 2014 [38], with more recent data suggesting these numbers increased in 2015 [39]. Quitting and/or reducing the harms of smoking are cited as the main reasons smokers use ENDS [40], and some smokers have credited ENDS with helping them to successfully quit smoking [41,42]. Two randomized controlled trials (RCTs), conducted in New Zealand and Italy, found limited support for their efficacy in smoking cessation [43,44]. Whereas the effects of ENDS with nicotine compared to placebo (non-nicotine) ENDS were non-significant in these two studies, the pooled effect was statistically significant [45]. One of these studies also found higher cessation, though not statistically significant, for ENDS compared to the nicotine patch; however, participants' access to products differed in the two conditions [44]. A recent naturalistic RCT found that, whereas ENDS were associated with reduced smoking, the numerically positive effect on quit attempts and abstinence was not significant [46]. In contrast, two meta-analyses of primarily longitudinal cohort studies found lower odds of quitting among ENDS users, casting doubt on the claim that observed declines in U.S. adult population smoking rates can be attributed to ENDS [47,48]. Reflecting the conflicted and nuanced scientific literature, two other meta-analytic studies with different study-eligibility criteria found either no significant effect [49] or a positive effect of ENDS use on quitting [50]. However, the quality of extant evidence has been rated very low in several reviews [45,48,49,51], prompting the US Preventive Services Task Force to conclude the evidence insufficient to recommend ENDS for smoking cessation [52]. More recently, a National Academies of Science committee concluded that there "is limited evidence that e-cigarettes may be effective aids to promote smoking cessation," but "there is moderate evidence from observation studies that more frequent use of e-cigarettes is associated with an increased likelihood of cessation" [37].

Well-controlled RCTs can provide critical evidence of the potential of ENDS for effecting smoking cessation, whereas well-designed longitudinal cohort studies can offer unique and important insights on the population-level effectiveness of ENDS under "real world" use and conditions [37,47,53,54]. However, insights gleaned from past longitudinal cohort studies have been clouded by methodological limitations [21,48,51,53], specifically insufficient attention to the motivations and intentions for using ENDS, characteristics of the ENDS device related to the delivery of nicotine, overall user satisfaction, and frequency of use [37,53]. Smokers note many different reasons for using ENDS [55,56], and accounting for whether they use ENDS primarily to quit smoking or for other reasons (e.g., to use in situations where smoking is not permitted) is important [56,57]. Even when the primary reason for using ENDS is to quit smoking, certain device types and patterns of use may be more conducive to quitting than others [36,53,58]. ENDS with nicotine delivery profiles comparable to the combusted cigarette may better alleviate smokers' nicotine cravings and serve as a more acceptable alternative for cigarettes. In contrast to disposables and many rechargeable/cartridge-based ENDS, newer and later generation ENDS that are predominantly open-systems with more powerful batteries have produced nicotine delivery profiles more comparable to combusted cigarettes [59,60]. However, the few studies that have examined the effect of device type on quitting smoking have yielded mixed results [56,61]. Smoking behavior may also be affected by e-liquid flavor, though this research remains limited [62–65]. To our knowledge, no RCTs and only one prospective cohort studies of ENDS and smoking have considered the effect of e-liquid flavor despite important implications for regulatory policy [66]. Results from multiple cross-sectional survey studies using large, nationally representative samples have provided compelling evidence that frequent use (daily or at least >5 times in the last month) is associated with recent former smoker status [67–69]. Two cohort studies have found limited evidence in support of a positive association between daily ENDS use with subsequent substantial reduction in cigarettes smoked, cessation attempts, and, for one of these studies, increased quitting if using a tank system, compared to non-users [61,70]. However, other research has found either no effect of frequency (or device type) on smoking abstinence [56] or an association of more frequent ENDS use with subsequent greater quantity and frequency of smoking [71]. Another study found no difference in smoking abstinence at follow-up between daily ENDS users and non-users; whereas non-daily users were less likely to be abstinent compared to non-users [72].

In summary, the research on the impact of ENDS use on adult smokers' quitting remains inconsistent and methodologically limited. Further, due to the rapid evolution in technology and marketing of ENDS, along with population shifts in patterns of use [36,57], results of older studies may not apply to the present [37]. Therefore, the objective of this national, prospective cohort study is to generate more recent and comprehensive evidence on the effect of "real world" ENDS use on the population quit rates of adult smokers while addressing key limitations of prior studies, specifically by taking account of frequency of use, device type, e-liquid flavor, and reasons for use. We hypothesized that ENDS use among smokers would be prospectively associated with quitting outcomes after adjusting for baseline differences in potential confounding factors, and this association would depend on device, use patterns, and intensions for use.

Methods

Study design and participants

Participants were recruited from GfK's KnowledgePanel, a national, probability-based web-panel designed to be representative of non-institutionalized U.S. adults. For this prospective cohort study, a sample of 1284 current, established smokers at baseline was identified among respondents to the 2015 (August-September) Tobacco Products and Risk Perceptions Survey (TPRPS) for a 12-month follow-up study on their smoking and ENDS use. A study completion rate of 76.0% was obtained for the baseline survey. In August-October 2016, 1018 baseline current smokers who had remained members of GfK KnowledgePanel were invited to complete the follow-up survey, which yielded 858 respondents (66.8% of the baseline smokers; 84% of those invited for the follow-up survey). The institutional review board of the Georgia State University approved this study with a waiver of informed consent.

Outcome variables

The primary outcome variable was smoking abstinence for at least 30 days at follow-up measured by responding (a) "not at all" to "Do you now smoke cigarettes every day, some days, or not at all?" and (b) "no" to "In the past 30 days, have you smoked a cigarette, even one or two puffs?" Secondary outcome variables were (a) making at least one attempt to quit smoking completely since the baseline survey, including successful quit attempts, and (b) among those smoking at follow-up, the average number of cigarettes smoked per day (CPD). Detailed information about these measures can be found in S1 Table.

Primary ENDS exposure variables

All survey participants were shown preamble text with pictures describing ENDS and their different features. When answering questions about their ENDS use, participants were instructed to "think only about use of these products without marijuana, marijuana concentrates, marijuana waxes, THC, or hash oils." Current ENDS use at baseline was then assessed by "Do you now use electronic vapor products every day, some days, rarely, or not at all?" Smokers who reported using ENDS "every day," "some days," or "rarely" were defined as baseline ENDS users (n = 248), whereas those reporting "not at all," or, on prior questions never use or no awareness of ENDS were defined as baseline nonusers (n = 606). In addition, we separately classified smokers by whether they used ENDS during the study period spanning from baseline survey to follow-up. Participants who reported current use of ENDS at baseline and/or follow-up, any past 30-day use of ENDS at follow-up, or any use of ENDS since the baseline survey were classified as any ENDS users (n = 347), whereas those who reported no current use at baseline and at follow-up and no use in between baseline and follow-up were classified as nonusers during the study period (n = 507). Those who reported any ENDS use during the 12-month study period were further subdivided as follows: (a) ENDS use at both baseline and follow-up (n = 129), (b) ENDS use during the study period but not at baseline (n = 53), or (c) ENDS use at or after baseline but not at follow-up (n = 165). Frequency of ENDS use, importance of quitting smoking as reason for using ENDS, and ENDS product characteristics (flavor and device type) were assessed as potential effect modifiers of ENDS use on quitting smoking. We operationalized each as follows (see S1 Table for more details regarding their measurement):

1. Smokers who used ENDS were classified as daily ENDS users if they reported daily use of ENDS or using ≥25 days during the past 30 days at either baseline or follow-up (n = 53).
2. To assess whether smokers were using ENDS for quitting or for other reasons, they were asked to indicate how important ENDS were to help them "quit smoking regular cigarettes" on a 7-point scale (0 = Not at all important to 6 = Very important). Quitting smoking was considered an important reason for using ENDS if a smoker responded 3 or higher (0 = not at all important to 6 = very important) (n = 248).
3. At both baseline and follow-up, ENDS users were asked to indicate among a list of 10 flavor categories, including "tobacco flavor," which flavors they usually used (or "last used" if they were no longer using ENDS at follow-up). They were coded as (a) tobacco flavor or unflavored user if they selected only tobacco flavor or unflavored at baseline and follow-up (n = 96); (b) a menthol/wintergreen/mint flavor user if they indicated they selected this flavor at baseline or follow-up, but no other flavor other than tobacco flavor or unflavored (n = 57); (c) other flavor user if they selected any flavor other than tobacco or menthol/wintergreen/mint at baseline or follow-up (n = 174).
4. ENDS users were asked at baseline and follow-up if the device they used most of the time was (a) rechargeable, (b) used cartridges (if rechargeable), or (c) used a tank system (if rechargeable but did not use cartridges). If they reported using a tank system, they were classified as a tank user (n = 87); if they reported using a cartridge system but no tank system, they were classified as a cartridge user (n = 113); else if were coded as a disposable/other ENDS user (n = 48).

Adjustment variables

Sociodemographic variables, smoking history and intensity, quit intentions and history, other combustible tobacco use, physical health, prior mental health treatment, and alcohol use were identified as potential confounders and measured at baseline. Smoking dependence was measured separately by (a) intensity of smoking (i.e., average number of cigarettes per day), (b) perceived addiction to smoking, and (c) strength of cravings to smoke cigarettes. Length of smoking was measured by number of years smoked. Motivation to quit smoking was measured separately by (a) reported intentions to quit smoking, (b) number of past-year quit attempts, (c) prior use of FDA-approved pharmacological treatments for smoking cessation, and (d) regret having started smoking. Dual/poly combustible tobacco use was measured by items assessing concurrent use of traditional cigars, little cigars and cigarillos, or hookah. Other respondent characteristics were measured by questions from profile surveys pre-administered by GfK to all KnowledgePanel members assessing: (a) physical health (self-reported physical health status and whether they have been diagnosed with asthma, chronic bronchitis or COPD); (b) prior mental health treatment (having ever seen a psychiatrist, psychologist, or social worker for counseling or therapy); (c) past month consumption of alcohol; and (d) sociodemographic characteristics (e.g., age, gender, race/ethnicity, sexual orientation, education, income). To address potential panel conditioning bias, the number of smoking-related studies completed by the respondent in the past year was computed by GfK and controlled for in the analysis. Detailed information about these measures can be found in S1 Table.

Measures of methods used to quit smoking

In order to better interpret results of primary results regressing smoking outcomes on ENDS exposure variables, we also assessed the methods and resources smokers used in their attempts, either successful or unsuccessful, to quit smoking. If a participant reported they had completely quit smoking for good, they were asked "When you quit smoking for good, did you do any of the following?": responding *yes*/*no* to (a) "gave up cigarettes all at once?" (cold turkey); (b) "gradually cut back on cigarettes?"; (c) "switched completely to electronic vapor products, such as…?"; (d) "substituted some of my regular cigarettes with electronic vapor products, such as…?"; (e) "used nicotine replacements like the nicotine patch, nicotine gum, nicotine lozenges, nicotine nasal spray, or nicotine inhaler?"; (f) "used medications like Wellbutrin, Zyban, buproprion, Chantix, or varenicline?"; (g) got counseling, help from a telephone help or quit line, a website such as Smokefree.gov, books, pamphlets, videos, a quit tobacco clinic, class, or support group, or an internet or web-based program, or from a doctor or other health professional?"; (h) "used little cigars, filtered cigars or cigarillos to quit smoking cigarettes?"; (i) "used any of the following: traditional cigars, snus, chewing tobacco, dip or snuff, dissolvables, hookah, or 'heat-not-burn' to quit smoking cigarettes?; and (j) "relied on the support of friends and family to help you quit smoking cigarettes?" If the participant was still smoking at the follow-up survey, they were asked to report the methods or resources they had used to try to quit smoking since the baseline survey. Detailed information about these measures can be found in S1 Table.

Statistical analysis

We first calculated proportions and their 95% confidence intervals for ENDS use at baseline and for smoking and ENDS use at follow-up among baseline dual users. We then used weighted logistic regression or weighted general linear models to assess whether ENDS users were more likely to be smoke daily at baseline and whether they differed on study covariates. For our primary analyses, associations between ENDS use and binary outcomes (i.e., making a smoking quit attempt and 30-day smoking abstinence), controlling for potential confounders, were estimated by adjusted odds ratios and 95% confidence intervals from weighted logistic regression models. Weighted general linear models were used to estimate the association between ENDS use and CPD among those participants still smoking at follow-up, controlling for potential confounders. For all primary analyses, models were estimated separately for each operational definition of ENDS exposure (viz., baseline ENDS use vs. nonuse at baseline; any ENDS use and sub-pattems of any ENDS use vs. no use during the study; by frequency of ENDS use; by importance of ENDS use for quitting; by flavor use; and by device type). When the ENDS exposure variable had more than two levels, exploratory pairwise tests were conducted. Furthermore, all primary analyses were repeated while restricting the sample to participants who were daily smokers at baseline. Finally, among smokers who reported a quit attempt during the study, either successful or unsuccessful, we estimated weighted proportions and associated 95% confidence intervals for each assessed method or resource used during their quit attempt(s), stratified by their use of ENDS and whether they were 30-day

abstinent from smoking at the follow-up survey.

For all analyses, a study-specific post-stratification weight, based on demographic and geographic benchmarks from the March 2015 Current Population Survey, was used to adjust all analyses for sources of sampling and non-sampling error. Missing data were handled using two different approaches. The first approach involved a complete-case analysis whereby participants missing data on one or more variables in a model were excluded from that analysis. A post-stratification weight variable that adjusts for attrition bias was used with this approach. For the second approach, we used the Mplus statistical package (v. 8) to generate 50 imputed datasets based on Bayesian Monte Carlo Markov Chain (MCMC) estimation of an unrestricted mean and variance covariance model, which included all analysis variables and additional variables from the baseline survey that were predictive of missingness. The fraction of missing information ranged .20 to .52 for parameter estimates of key interest to this study. As the general pattern of results were similar between the two approaches, results from the complete-case analysis with weight adjustment for missingness are presented in this paper, and results from the multiple-imputation approach are presented in S2–S6 Tables. The few instances where differences in patterns of statistical significance were observed between the two approaches are noted in text. A two-tailed $\alpha = .05$ was set *a priori* for all analyses, which were conducted using the Survey package (v. 3.31.5) for the R statistical program (v. 3.4.0) [73,74].

Results

Descriptive data

Among smokers who completed the follow-up survey, 27.1% (95% CI: 22.6%, 32.0%) reported using ENDS at baseline. One year later, 90% of dual users were still smoking. Over half (53.5%, 95% CI = 43.5%, 63.1%) continued to smoke and use ENDS, and 37.4% (95% CI = 28.6%, 47.1%) were still smoking but had discontinued ENDS. Only 9.2% (95% CI: 5.1%, 15.8%) reported having quit smoking at follow-up (Table 1).

	n	wt. %	95% CI
Quit Smoking and Quit ENDS	17	6.67	3.23, 13.24
Quit Smoking, Using ENDS	9	2.49	1.02, 5.98
Current Smoker, Quit ENDS	102	37.37	28.60, 47.06
Dual User (Current Smoker and Using ENDS)	120	53.47	43.56, 63.11

ENDS = electronic nicotine delivery systems. wt. = weighted. CI = confidence interval.

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Table 1. Smoking and ENDS use at one year follow-up for baseline dual users (Smoker + ENDS user) (N = 248).
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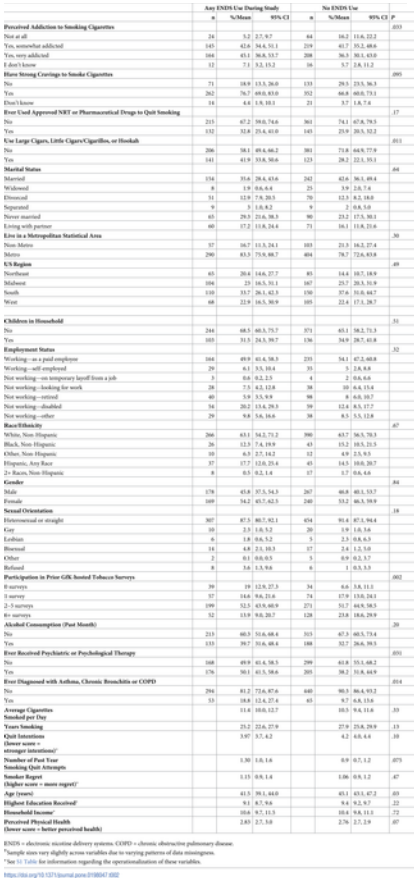
We also examined whether those who used ENDS were more likely than non-users to be daily smokers at baseline. Among smokers who did not use ENDS at baseline, 73.5% (95% CI: 66.8, 81.2%) smoked daily compared 70.5% (95% CI: 60.6, 78.7%) among those who were using ENDS at baseline ($p = .56$). Similarly, there was no statistically significant difference in the proportion of daily smokers among those who used ENDS at any point during the study and those that did not: 74.7% (95% CI: 66.8, 81.2%) and 71.4% (64.8, 77.2%), respectively ($p = .50$).

Covariate distributions for those that used ENDS at any point during the study and for non-users are reported in Table 2. Compared to smokers who did not use ENDS, smokers who used ENDS during the 12-month study were younger (41.5 vs. 45.1 years) and were more likely to perceive they were addicted to smoking cigarettes (87.7% vs. 78.0% perceived being somewhat or very addicted); to report a history of psychiatric/psychological therapy (50.1% vs. 38.2%); to use little cigars, cigarillos, or hookah (41.9% vs. 28.2%); to report having a prior diagnosis of asthma, chronic bronchitis or chronic obstructive pulmonary disease (18.8% vs. 9.7%); and to report participating in zero tobacco-related surveys hosted by GfK during the past year. Interestingly, less than one-third of ENDS users and of non-ENDs users (32.8% and 25.9%, respectively; $p = .17$) reported ever using an approved nicotine replacement therapy or pharmaceutical drugs to quit smoking. No statistically significant differences were observed at baseline for quit intentions, number of smoking quit attempts in the past year, smoker regret, number of years smoking, cigarettes per day smoked, having strong cravings to smoke, or socio-demographic variables other than age.



	Any ENDS Use During Study			No ENDS Use			
	n	%/Mean	95% CI	n	%/Mean	95% CI	P
Perceived Addiction to Smoking Cigarettes							.033
Not at all	24	5.2	2.7, 9.7	64	16.2	11.6, 22.2	
Yes, somewhat addicted	145	42.6	34.4, 51.1	219	41.7	35.2, 48.6	
Yes, very addicted	164	45.1	36.8, 53.7	208	36.3	30.1, 43.0	
I don't know	12	7.1	3.2, 15.2	16	5.7	2.8, 11.2	
Have Strong Cravings to Smoke Cigarettes							.095
No	71	18.9	13.3, 26.0	133	29.5	23.5, 36.3	
Yes	262	76.7	69.0, 83.0	352	66.8	60.0, 73.1	
Don't know	16	4.4	1.9, 10.1	21	3.7	1.8, 7.4	
Ever Used Approved NRT or Pharmaceutical Drugs to Quit Smoking							.17
No	215	67.2	59.0, 74.6	301	74.1	67.8, 79.5	
Yes	132	32.8	25.4, 41.0	143	25.9	20.5, 32.2	
Use Large Cigars, Little Cigars/Cigarillos, or Hookah							.011
No	206	58.1	49.4, 66.2	301	71.8	64.9, 77.9	
Yes	141	41.9	33.8, 50.6	123	28.2	22.1, 35.1	
Marital Status							.64
Married	134	35.6	28.4, 43.6	242	62.6	56.1, 69.4	
Widowed	8	1.9	0.6, 6.4	25	3.9	2.0, 7.4	
Divorced	51	12.9	7.9, 20.5	70	12.3	8.2, 18.0	
Separated	9	3	1.0, 8.2	9	2	0.8, 5.0	
Never married	65	29.5	21.6, 38.5	90	23.2	17.5, 30.1	
Living with partner	60	17.2	11.8, 24.4	71	16.1	11.8, 21.6	
Live in a Metropolitan Statistical Area							.30
Non-Metro	57	16.7	11.3, 24.1	103	21.3	16.2, 27.4	
Metro	290	83.3	75.9, 88.7	404	78.7	72.6, 83.8	
US Region							.49
Northeast	65	20.4	14.6, 27.7	85	14.4	10.7, 18.9	
Midwest	104	25	16.5, 31.1	167	25.7	20.3, 31.9	
South	110	33.7	26.1, 42.3	150	37.6	31.0, 44.7	
West	68	22.9	16.5, 30.9	105	22.4	17.1, 28.7	
Children in Household							.51
No	244	68.5	60.3, 75.7	371	65.1	58.2, 71.3	
Yes	103	31.5	24.3, 39.7	136	34.9	28.7, 41.8	
Employment Status							.32
Working—as a paid employee	104	49.9	41.4, 58.3	235	54.1	47.2, 60.8	
Working—self-employed	29	6.1	3.5, 10.4	35	5	2.8, 8.8	
Not working—on temporary layoff from a job	5	0.6	0.2, 2.3	4	2	0.6, 6.6	
Not working—looking for work	28	7.5	4.2, 12.8	38	10	6.4, 15.4	
Not working—retired	40	3.9	3.5, 9.9	98	8	6.0, 10.7	
Not working—disabled	34	20.2	13.4, 29.3	59	12.4	8.5, 17.7	
Not working—other	29	9.8	5.6, 16.6	38	8.5	5.5, 12.8	
Race/Ethnicity							.67
White, Non-Hispanic	266	63.1	54.2, 71.2	390	63.7	56.5, 70.3	
Black, Non-Hispanic	26	12.3	7.4, 19.9	43	15.2	10.5, 21.5	
Other, Non-Hispanic	10	6.3	2.7, 14.2	12	4.9	2.5, 9.5	
Hispanic, Any Race	37	17.7	12.0, 25.4	43	14.5	10.0, 20.7	
2+ Races, Non-Hispanic	8	0.5	0.2, 1.4	17	1.7	0.6, 4.6	
Gender							.84
Male	178	45.8	37.5, 54.3	267	46.8	40.1, 53.7	
Female	169	54.2	45.7, 62.5	240	53.2	46.3, 59.9	
Sexual Orientation							.18
Heterosexual or straight	307	87.3	80.7, 92.1	454	91.4	87.1, 94.4	
Gay	10	2.3	1.0, 5.2	20	1.9	1.0, 3.6	
Lesbian	6	1.8	0.6, 5.2	5	2.3	0.8, 6.3	
Bisexual	16	6.8	2.3, 18.3	17	2.4	1.2, 5.0	
Other	2	0.1	0.0, 0.5	5	0.9	0.2, 3.7	
Refused	8	3.6	1.3, 9.6	6	1	0.3, 3.3	
Participation in Prior GfK-hosted Tobacco Surveys							.002
0 surveys	39	19	12.9, 27.3	34	6.6	3.8, 11.1	
1 survey	57	14.6	9.6, 21.6	74	17.9	13.0, 24.1	
2–5 surveys	199	52.5	43.9, 60.9	271	51.7	44.9, 58.5	
6+ surveys	52	13.9	9.0, 20.7	128	23.8	18.6, 29.9	
Alcohol Consumption (Past Month)							.20
No	213	60.3	51.6, 68.4	315	67.3	60.5, 73.4	
Yes	133	39.7	31.6, 48.4	188	32.7	26.6, 39.5	
Ever Received Psychiatric or Psychological Therapy							.031
No	168	49.9	41.4, 58.5	299	61.8	55.1, 68.2	
Yes	176	50.1	41.5, 58.6	205	38.2	31.8, 44.9	
Ever Diagnosed with Asthma, Chronic Bronchitis or COPD							.014
No	294	81.2	72.6, 87.6	440	90.3	86.4, 93.2	
Yes	53	18.8	12.4, 27.4	63	9.7	6.8, 13.6	
Average Cigarettes Smoked per Day			11.4	10.0, 12.7		10.3	9.4, 11.6	.33
Years Smoking			25.2	22.6, 27.9		27.9	25.8, 29.9	.13
Quit Intentions (lower score = stronger intentions)[c]			3.97	3.7, 4.2		4.2	4.0, 4.4	.10
Number of Past Year Smoking Quit Attempts			1.30	1.0, 1.6		0.9	0.7, 1.2	.075
Smoker Regret (higher score = more regret)[c]			1.15	0.9, 1.4		1.06	0.9, 1.2	.47
Age (years)			41.5	39.1, 44.0		45.1	43.1, 47.2	.03
Highest Education Received[c]			9.1	8.7, 9.6		9.4	9.2, 9.7	.22
Household Income[c]			10.6	9.7, 11.5		10.4	9.8, 11.1	.72
Perceived Physical Health (lower score = better perceived health)			2.83	2.7, 3.0		2.76	2.7, 2.9	.07

ENDS = electronic nicotine delivery systems; COPD = chronic obstructive pulmonary disease.
[a]Sample sizes vary slightly across variables due to varying patterns of data missingness.
[b]See S1 Table for information regarding the operationalization of these variables.

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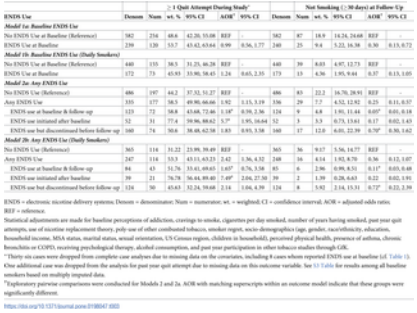
Table 2. Proportions/Means of covariates measures at baseline by ENDS use[†].
https://doi.org/10.1371/journal.pone.0198047.t002

Associations between ENDS use and quitting outcomes

While baseline ENDS users did not differ from baseline non-users in their adjusted odds of making a subsequent smoking quit attempt over the next 12 months (53.7% vs. 48.6%; AOR = 0.99, 95% CI = 0.56–1.77) (Table 3, Model 1a), smokers who reported ENDS use at any time during the study period had nearly twice the adjusted odds of making a quit attempt as those who did not use ENDS at all during the same period (58.5% vs. 44.4%; AOR = 1.92, 95% CI = 1.15–3.19) (Model 2a). This latter association was not statistically significant in analysis of multiply imputed data (see S3 Table, Model 2).



		≥ 1 Quit Attempt During Study[a]				Not Smoking (≥ 30 days) at Follow-Up				
ENDS Use	**Denom**	**Num**	**wt. %**	**95% CI**	**AOR[b]**	**95% CI**	**Denom**	**Num**	**wt. %**	**95% CI**	**AOR[b]**	**95% CI**
Model 1a: Baseline ENDS Use												
No ENDS Use at Baseline (Reference)	582	254	48.6	42.20, 55.08	REF	-	582	87	18.9	14.24, 24.68	REF	-
ENDS Use at Baseline	239	120	53.7	43.42, 63.64	0.99	0.56, 1.77	240	25	9.4	5.22, 16.38	0.30	0.13, 0.72
Model 1b: Baseline ENDS Use (Daily Smokers)												
No ENDS Use at Baseline (Reference)	440	155	38.5	31.23, 46.28	REF	-	440	39	8.03	4.97, 12.73	REF	-
ENDS Use at Baseline	172	73	45.93	33.90, 58.45	1.24	0.63, 2.35	173	13	4.36	1.95, 9.44	0.37	0.13, 1.05
Model 2a: Any ENDS Use												
No ENDS Use (Reference)	486	197	44.2	37.32, 51.27	REF	-	486	83	22.2	16.70, 28.91	REF	-
Any ENDS Use	335	177	58.5	49.80, 66.66	1.92	1.15, 3.19	336	29	7.7	4.52, 12.92	0.25	0.11, 0.57
ENDS use at baseline & follow-up	123	72	58.8	43.68, 72.46	1.18[c]	0.59, 2.36	124	9	6.8	1.91, 11.44	0.05[c]	0.01, 0.18
ENDS use initiated after baseline	52	31	77.4	59.96, 88.62	3.7[c]	1.95, 16.04	52	3	3.3	0.73, 13.61	0.17	0.02, 1.43
ENDS use but discontinued before follow-up	160	74	50.6	38.48, 62.58	1.83	0.93, 3.58	160	17	12.0	6.01, 22.39	0.70[c]	0.30, 1.62
Model 2b: Any ENDS Use (Daily Smokers)												
No ENDS Use (Reference)	365	114	31.22	23.99, 39.49	REF	-	365	36	9.17	5.56, 14.77	REF	-
Any ENDS Use	247	114	53.3	43.13, 63.23	2.42	1.36, 4.32	248	16	4.14	1.92, 8.70	0.36	0.12, 1.07
ENDS use at baseline & follow-up	84	43	51.76	33.41, 69.65	1.65[c]	0.76, 3.58	85	6	2.96	0.99, 8.51	0.11[c]	0.03, 0.48
ENDS use initiated after baseline	39	21	76.78	56.44, 89.40	7.49[c]	2.04, 27.50	39	2	1.39	0.28, 6.63	0.22	0.02, 1.91
ENDS use but discontinued before follow-up	124	50	45.63	32.24, 59.68	2.14	1.04, 4.39	124	8	5.92	2.14, 15.31	0.73[c]	0.22, 2.39

ENDS = electronic nicotine delivery systems; Denom = denominator; Num = numerator; wt. = weighted; CI = confidence interval; AOR = adjusted odds ratio; REF = reference.
Statistical adjustments are made for baseline perceptions of addiction, cravings to smoke, cigarettes per day smoked, number of years having smoked, past year quit attempts, use of nicotine replacement therapy, poly-use of other combusted tobacco, smoker regret, socio-demographics (age, gender, race/ethnicity, education, household income, MSA status, marital status, sexual orientation, US Census region, children in household), perceived physical health, presence of asthma, chronic bronchitis or COPD, receiving psychological therapy, alcohol consumption, and past year participation in other tobacco studies through GfK.
[a]Thirty-six cases were dropped from complete-case analyses due to missing data on the covariates, including 8 cases whom reported ENDS use at baseline (cf. Table 1). One additional case was dropped from the analysis for past year quit attempt due to missing data on this outcome variable. See S3 Table for results among all baseline smokers based on multiply imputed data.
[b]Exploratory pairwise comparisons were conducted for Models 2 and 2a. AOR with matching superscripts within an outcome model indicate that these groups were significantly different.

https://doi.org/10.1371/journal.pone.0198047.t003

Table 3. Making a quit attempt and quitting smoking for ≥ 30 days by ENDS use among all baseline smokers (N = 822[*]) and baseline daily smokers (N = 613[*]).
https://doi.org/10.1371/journal.pone.0198047.t003

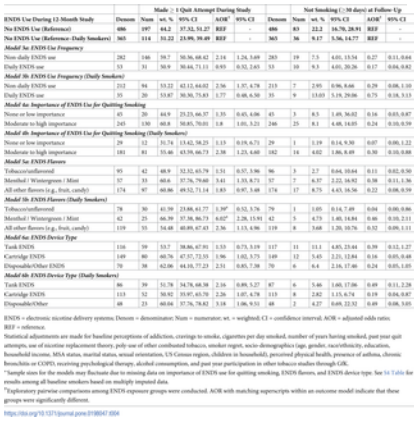
The higher likelihood of making at least one quit attempt did not correspond to greater success in quitting smoking (past 30-day abstinence) by follow-up: baseline ENDS users had 70% lower adjusted odds of quitting smoking than baseline non-users (Model 1a: 9.4% vs. 18.9%; AOR = 0.30, 95% CI = 0.13–0.72) and those smokers who reported any ENDS use during the 12-month study had 75% lower odds of quitting smoking than non ENDS-users (Model 2a: 7.7% vs. 22.2%; AOR = 0.25, 95% CI = 0.11–0.57). Those who reported using ENDS throughout the study (i.e., at baseline and follow-up) had the lowest adjusted odds of quitting compared to nonusers (4.8%; AOR = 0.05, 95% CI = 0.01–0.18), as well as those who used ENDS during the study but had discontinued using them before the

follow-up survey ($p < .05$). Sensitivity analyses were conducted where we either dropped the minimum abstinence period criterion of 30 days or increased it to six months; the general pattern of results remained consistent.

Turning to analyses of baseline daily smokers, we found no statistically significant association between ENDS use *at baseline* and making at least one subsequent smoking quit attempt (Model 1b), although we did find that those who used ENDS *at any point* during the study period did have 2.4 (95% CI: 1.4, 4.3) times the odds of making a subsequent quit attempt compared to their non-using counterparts (Model 2b). The proportion that reported quitting smoking at follow-up was considerably lower, regardless of ENDS use, for daily smokers compared to the full sample of daily and nondaily smokers. Similar to the full sample, baseline daily smokers who reported using ENDS throughout the study (i.e., at baseline and follow-up) reported significantly lower adjusted odds of quitting smoking at follow-up compared to those who did not use ENDS during the study (3.0% vs. 9.2%; AOR = 0.11, 95% CI = 0.03–0.48) and to those who reported using ENDS during the study but not at follow-up ($p < .05$). Although the adjusted odds of quitting did not differ significantly for other temporal patterns of ENDS use compared to non-use, similar to the overall smoker sample, we observed no instance where ENDS users were more likely to quit than non-ENDS users.

ENDS use frequency (Model 3).

Considering the frequency of ENDS use, intentions for using ENDS to quit smoking, use of flavored ENDS, or use of a tank-system ENDS did not substantially change the aforementioned pattern of results (Table 4). Only 19.2% (95% CI = 12.6–28.0) of ENDS users reported any daily use during the study period. Whereas non-daily ENDS users (though not daily users) had higher adjusted odds of making a quit attempt than non-users (59.7% vs. 44.2%; AOR = 2.14, 95% CI = 1.24–3.69), both non-daily (7.5%; AOR = 0.27, 95% CI = 0.11–0.64) and daily (9.3%; AOR = 0.17, 95% CI = 0.04–0.82) ENDS users had lower odds of quitting smoking. In analysis of multiply imputed data, the effects of frequency of ENDS use on making a quit attempt were smaller and statistically non-significant (see S4 Table, Model 3).



ENDS Use During 12-Month Study	Denom	Made ≥ 1 Quit Attempt During Study				Not Smoking (≥ 30 days) at Follow Up				
		Num	wt. %	95% CI	AOR[1]	95% CI	Denom	Num	wt. %	95% CI	AOR[1]	95% CI
No ENDS Use (Reference)	**486**	**197**	**44.2**	**37.32, 51.27**	**REF**	-	**486**	**83**	**22.2**	**16.70, 28.91**	**REF**	-
No ENDS Use (Reference - Daily Smokers)	**365**	**114**	**31.22**	**23.99, 39.49**	**REF**	-	**365**	**36**	**9.17**	**5.56, 14.77**	**REF**	-
Model 1a: ENDS Use Frequency												
Non-daily ENDS use	282	146	59.7	50.56, 68.42	2.14	1.24, 3.69	283	19	7.5	4.01, 13.54	0.27	0.11, 0.64
Daily ENDS use	53	31	50.9	30.44, 71.11	0.93	0.32, 2.65	53	10	9.3	4.01, 20.26	0.17	0.04, 0.82
Model 1b: ENDS Use Frequency (Daily Smokers)												
Non-daily ENDS use	212	94	53.22	42.12, 64.02	2.56	1.57, 4.78	213	7	2.95	0.96, 8.66	0.29	0.08, 1.10
Daily ENDS use	35	20	53.87	30.30, 75.83	1.77	0.48, 6.50	35	9	13.03	5.19, 29.06	0.75	0.18, 3.13
Model 4a: Importance of ENDS Use for Quitting Smoking												
None or low importance	45	20	44.9	25.23, 66.37	1.35	0.45, 4.06	45	3	8.3	1.49, 36.02	0.16	0.03, 0.87
Moderate to high importance	245	130	60.8	50.85, 70.01	1.8	1.01, 3.21	246	25	8.1	4.48, 14.05	0.24	0.10, 0.59
Model 4b: Importance of ENDS Use for Quitting Smoking (Daily Smokers)												
None or low importance	29	12	31.74	13.42, 58.25	1.13	0.19, 6.71	29	1	1.19	0.14, 9.30	0.07	0.00, 1.22
Moderate to high importance	181	81	55.46	43.39, 66.73	2.38	1.23, 4.60	182	14	4.02	1.86, 8.49	0.30	0.10, 0.88
Model 5a: ENDS Flavors												
Tobacco/unflavored	95	42	48.9	32.32, 65.79	1.51	0.57, 3.96	96	3	2.7	0.64, 10.64	0.11	0.02, 0.50
Menthol / Wintergreen / Mint	57	33	60.6	37.76, 79.60	3.41	1.33, 8.73	57	7	6.37	2.22, 16.92	0.38	0.11, 1.36
All other flavors (e.g., fruit, candy)	174	97	60.86	49.32, 71.14	1.83	0.97, 3.48	174	17	8.75	4.43, 16.56	0.22	0.08, 0.59
Model 5b: ENDS Flavors (Daily Smokers)												
Tobacco/unflavored	78	30	41.39	23.88, 61.77	1.39*	0.52, 3.76	79	1	1.05	0.14, 7.49	0.04	0.00, 0.86
Menthol / Wintergreen / Mint	42	25	66.39	37.38, 86.73	6.02*	2.28, 15.91	42	5	4.73	1.40, 14.84	0.46	0.10, 2.11
All other flavors (e.g., fruit, candy)	119	55	54.48	40.89, 67.43	2.36	1.13, 4.96	119	8	3.68	1.20, 10.76	0.32	0.09, 1.11
Model 6a: ENDS Device Type												
Tank ENDS	116	59	53.7	38.86, 67.91	2.33	0.73, 3.19	117	11	11.1	4.93, 23.44	0.39	0.12, 1.27
Cartridge ENDS	149	80	60.76	47.57, 72.55	1.96	1.02, 3.75	149	12	5.45	2.21, 12.84	0.16	0.05, 0.48
Disposable/Other ENDS	70	38	62.06	44.10, 77.23	2.51	0.85, 7.38	70	6	6.4	2.16, 17.46	0.24	0.05, 1.05
Model 6b: ENDS Device Type (Daily Smokers)												
Tank ENDS	86	39	51.78	34.78, 68.38	2.16	0.89, 5.27	87	6	5.46	1.60, 17.06	0.49	0.11, 2.28
Cartridge ENDS	113	52	50.92	35.97, 65.78	2.26	1.07, 4.78	113	8	2.82	1.15, 6.74	0.19	0.04, 0.87
Disposable/Other	68	23	60.04	37.76, 78.82	3.18	1.06, 9.51	68	2	4.27	0.69, 22.52	0.49	0.08, 3.05

ENDS = electronic nicotine delivery systems; Denom = denominator; Num = numerator; wt. = weighted; CI = confidence interval; AOR = adjusted odds ratio; REF = reference.

Statistical adjustments are made for baseline perceptions of addiction, cravings to smoke, cigarettes per day smoked, number of years having smoked, past year quit attempts, use of nicotine replacement therapy, poly-use of other combusted tobacco, smoker regret, socio-demographics (age, gender, race/ethnicity, education, household income, MSA status, marital status, sexual orientation, US Census region, children in household), perceived physical health, presence of asthma, chronic bronchitis or COPD, receiving psychological therapy, alcohol consumption, and past year participation in other tobacco studies through GfK.

[1]Sample sizes for the models may fluctuate due to missing data on importance of ENDS use for quitting smoking, ENDS flavors, and ENDS device type. See S4 Table for results among all baseline smokers based on multiply imputed data.

[2]Exploratory pairwise comparisons among ENDS exposure groups were conducted. AOR with matching superscripts within an outcome model indicate that these groups were significantly different.

https://doi.org/10.1371/journal.pone.0198047.t004

Table 4. Making a quit attempt and quitting smoking for ≥ 30 days by ENDS use and characteristics of ends use among all baseline smokers (N = 822) and baseline daily smokers (N = 613[*]).

https://doi.org/10.1371/journal.pone.0198047.t004

Among those who were daily smokers at baseline (Model 3b), 53.8% of daily ENDS users and 53.2% of non-daily ENDS users reported a quit attempt; however, only non-daily ENDS users were significantly more likely to than non-users of ENDS to report a quit attempt (31.2%; AOR = 2.56, 95% CI: 1.2, 3.7). While a greater proportion (13.0%; 95% CI: 5.2%, 29.1%) of baseline daily smokers who used ENDS daily had quit smoking compared to their counterparts who did not use ENDS (9.2%; 95% CI: 5.6%, 14.8%), after adjusting for covariates, the odds of quitting was lower, albeit not statistically significantly lower, for daily ENDS users compared to nonusers.

Importance of ENDS use for quitting smoking (Model 4).

Similarly, whereas smokers who indicated that quitting smoking was an important reason for their use of ENDS (the majority) were more likely to report at least one quit attempt (60.8%; AOR = 1.80, 95% CI = 1.01–3.21), odds of quitting smoking were lower for ENDS users regardless of level of importance (important: 8.1%; AOR = 0.24, 95% CI = 0.10–0.59) (Model 4a). Importance of using ENDS for quitting smoking was not associated with making a quit attempt, and the adjusted odds for none or low importance in predicting quitting smoking was not statistically significant in analysis of multiply imputed data (see S4 Table, Model 4).

Similar to the overall smoker sample, daily smokers at baseline who indicated that quitting smoking was an important reason for their use of ENDS were more likely to report at least one quit attempt than their counterparts who did not use ENDS (Model 4b: 55.5% vs. 31.2%; AOR = 2.38, 95% CI = 1.23–4.60). However, they were less likely to have quit smoking a year later (4.0%; AOR = 0.30, 95% CI = 0.10–0.88).

ENDS flavors (Model 5).

There was limited evidence that e-liquid flavor might influence quitting rates. Tobacco-flavored or unflavored ENDS users (2.7%; AOR = 0.11, 95% CI = 0.02–0.50) and users of other flavors (e.g., fruit, dessert, spice; 8.8%; AOR = 0.22, 95% CI = 0.08–0.59) had significantly lower adjusted odds of quitting than non-users (Model 5a). In the multiple imputation analysis, only users of other flavors had significantly lower odds of quitting smoking see S4 Table, Model 5). The comparison with non-users' adjusted odds of quitting was not statistically significant for menthol/wintergreen/mint users. Although the estimated odds of quitting for menthol/mint /wintergreen and other flavor users were more than twice (AOR = 3.4 and 2.0; 95% CI = 0.48–24.1 and 0.38–10.2; respectively) the estimated odds for tobacco/unflavored users, these differences were not statistically significant, possibly due to insufficient statistical power.

Among baseline daily smokers (Model 5b), both menthol/wintergreen/mint users and other flavor users were more likely to report a quit attempt (AORs = 6.0 and 2.4, respectively) than nonusers of ENDS, and menthol/wintergreen/mint users were more likely to report a quit attempt than tobacco/unflavored users ($p < .05$). Only daily smokers who used tobacco/unflavored ENDS were significantly less likely to report quitting smoking (AOR = 0.04) compared to their counterparts who did not use ENDS.

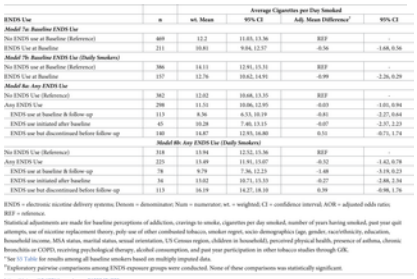
ENDS device type (Model 6).

While cartridge ENDS users were significantly more likely to report a subsequent quit attempt (60.1%; AOR = 1.96, 95% CI: 1.02,3.8), they had significantly lower adjusted odds of quitting (5.5%; AOR = 0.16, 95% CI = 0.05–0.48) compared to non-users. The comparisons were similar in direction but not statistically significant for disposable or tank system users (Model 6a). In analysis of multiply imputed data, tank users also had significantly lower rates of quitting (see S4 Table, Model 6). While the odds of quitting for users of tank systems were more than twice the odds of quitting for disposable ENDS users, this difference was nonsignificant (AOR = 2.5, 95% CI = 0.60–10.2).

Among baseline daily smokers, both cartridge and disposable/other ENDS users were more likely to report a subsequent quit attempt (AORs = 2.3 and 3.2, 95% CIs: 1.07, 4.78 and 1.06, 9.51, respectively) compared to their ENDS non-using counterparts. Similar to the full smoker sample, only daily smokers who used cartridge ENDS were significantly less likely to report quitting smoking (AOR = 0.19, 95% CI: 0.04, 0.87).

ENDS use and smoking intensity among non-quitters

Among participants who were still smoking at follow-up, there were no significant differences observed in the average number of cigarettes per day (CPD) smoked between ENDS users and non-users, regardless of whether we considered ENDS use status only at baseline (Model 7a: Mean CPD = 10.8 vs. 12.2 for baseline ENDS use and non-use, respectively; adj. M_{diff} = -0.56, 95% CI = -1.68–0.56) or at any time during the study (Model 8a: Mean CPD = 11.5 vs. 12.0 for any ENDS use and non-use, respectively; adj. M_{diff} = -0.03, 95% CI = -1.01–0.94) or if analysis is limited to baseline daily smokers (Models 7a and 8a) (Table 5).



ENDS Use	n	Average Cigarettes per Day Smoked			
		wt. Mean	95% CI	Adj. Mean Difference[†]	95% CI
Model 7a: Baseline ENDS Use					
No ENDS use at Baseline (Reference)	469	12.2	11.03, 13.36	REF	-
ENDS Use at Baseline	211	10.81	9.04, 12.57	-0.56	-1.68, 0.56
Model 7b: Baseline ENDS Use (Daily Smokers)					
No ENDS use at Baseline (Reference)	386	14.11	12.91, 15.31	REF	-
ENDS Use at Baseline	157	12.76	10.62, 14.91	-0.99	-2.26, 0.29
Model 8a: Any ENDS Use					
No ENDS Use (Reference)	382	12.02	10.68, 13.35	REF	-
Any ENDS Use	298	11.51	10.06, 12.95	-0.03	-1.01, 0.94
ENDS use at baseline & follow-up	113	8.36	6.53, 10.19	-0.81	-2.27, 0.64
ENDS use initiated after baseline	45	10.28	7.40, 13.15	-0.07	-2.37, 2.23
ENDS use but discontinued before follow-up	140	14.87	12.93, 16.80	0.31	-0.71, 1.74
Model 8b: Any ENDS Use (Daily Smokers)					
No ENDS Use (Reference)	318	13.94	12.52, 15.36	REF	-
Any ENDS Use	225	13.49	11.91, 15.07	-0.52	-1.42, 0.78
ENDS use at baseline & follow-up	78	9.79	7.36, 12.23	-1.48	-3.19, 0.23
ENDS use initiated after baseline	34	13.02	10.71, 15.33	-0.27	-2.88, 2.34
ENDS use but discontinued before follow-up	113	16.19	14.27, 18.10	0.39	-0.98, 1.76

ENDS = electronic nicotine delivery systems; Denom = denominator; Num = numerator; wt. = weighted; CI = confidence interval; AOR = adjusted odds ratio; REF = reference.

Statistical adjustments are made for baseline perceptions of addiction, cravings to smoke, cigarettes per day smoked, number of years having smoked, past year quit attempts, use of nicotine replacement theory, poly-use of other combusted tobacco, smoker regret, socio-demographics (age, gender, race/ethnicity, education, household income, MSA status, marital status, sexual orientation, US Census region, children in household), perceived physical health, presence of asthma, chronic bronchitis or COPD, receiving psychological therapy, alcohol consumption, and past year participation in other tobacco studies through GfK.

*See S3 Table for results among all baseline smokers based on multiply imputed data.

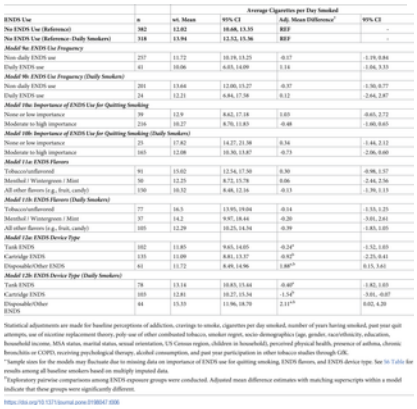
[†]Exploratory pairwise comparisons among ENDS exposure groups were conducted. None of these comparisons was statistically significant.

https://doi.org/10.1371/journal.pone.0198047.t005

Table 5. Average daily cigarette consumption at one-year follow-up by ENDS use among non-quitters for all baseline smokers (N = 680[*]) and baseline daily smokers (N = 543).

https://doi.org/10.1371/journal.pone.0198047.t005

The lack of clinically meaningful or statistically significant difference in smoking intensity between ENDS users and non-users also held regardless of frequency of ENDS use (Models 9a and 9b), importance of quitting smoking as a reason for using ENDS (Models 10a and 10b), or e-liquid flavor (Models 11a and 11b) for both all smokers and baseline daily smokers (Table 6). In contrast, smokers who reported using disposable/other ENDS reported smoking more cigarettes per day at follow-up than both nonusers of ENDS (adj. M_{diff} = 1.88, 95% CI = 0.15–3.61) and tank system users ($p < .05$) (Model 12a). This pattern also held when analyses were restricted to for baseline daily smokers (Model 12b).



ENDS Use	n	Average Cigarettes per Day Smoked			
		wt. Mean	95% CI	Adj. Mean Difference[†]	95% CI
No ENDS Use (Reference)	**382**	**12.02**	**10.68, 13.35**	**REF**	-
No ENDS Use (Reference--Daily Smokers)	**318**	**13.94**	**12.52, 15.36**	**REF**	-
Model 9a: ENDS Use Frequency					
Non-daily ENDS use	257	11.72	10.19, 13.25	-0.17	-1.19, 0.84
Daily ENDS use	41	10.06	6.03, 14.09	1.14	-1.04, 3.33
Model 9b: ENDS Use Frequency (Daily Smokers)					
Non-daily ENDS use	201	13.64	12.00, 15.27	-0.37	-1.50, 0.77
Daily ENDS use	24	12.21	6.84, 17.58	0.12	-2.64, 2.87
Model 10a: Importance of ENDS Use for Quitting Smoking					
None or low importance	39	12.9	8.62, 17.18	1.03	-0.65, 2.72
Moderate to high importance	216	10.27	8.70, 11.83	-0.48	-1.60, 0.65
Model 10b: Importance of ENDS Use for Quitting Smoking (Daily Smokers)					
None or low importance	25	17.82	14.27, 21.38	0.34	-1.44, 2.12
Moderate to high importance	165	12.08	10.30, 13.87	-0.73	-2.06, 0.60
Model 11a: ENDS Flavors					
Tobacco/unflavored	91	13.02	12.54, 17.50	0.30	-0.98, 1.57
Menthol / Wintergreen / Mint	50	12.25	8.72, 15.78	0.06	-2.44, 2.56
All other flavors (e.g., fruit, candy)	150	10.32	8.48, 12.16	-0.13	-1.39, 1.13
Model 11b: ENDS Flavors (Daily Smokers)					
Tobacco/unflavored	77	16.3	13.95, 19.04	-0.14	-1.53, 1.25
Menthol / Wintergreen / Mint	37	14.2	9.97, 18.44	-0.20	-3.01, 2.61
All other flavors (e.g., fruit, candy)	105	12.29	10.25, 14.34	-0.39	-1.83, 1.05
Model 12a: ENDS Device Type					
Tank ENDS	102	11.85	9.65, 14.05	-0.24[a]	-1.52, 1.03
Cartridge ENDS	135	11.09	8.81, 13.37	-0.92[b]	-2.25, 0.41
Disposable/Other ENDS	61	11.72	8.49, 14.96	1.88[a,b]	0.15, 3.61
Model 12b: ENDS Device Type (Daily Smokers)					
Tank ENDS	78	13.14	10.83, 15.44	-0.40[a]	-1.82, 1.03
Cartridge ENDS	103	12.81	10.27, 15.34	-1.54[b]	-3.01, -0.07
Disposable/Other ENDS	61	15.33	11.96, 18.70	2.14[a,b]	0.02, 4.26

Statistical adjustments are made for baseline perceptions of addiction, cravings to smoke, cigarettes per day smoked, number of years having smoked, past year quit attempts, use of nicotine replacement theory, poly-use of other combusted tobacco, smoker regret, socio-demographics (age, gender, race/ethnicity, education, household income, MSA status, marital status, sexual orientation, US Census region, children in household), perceived physical health, presence of asthma, chronic bronchitis or COPD, receiving psychological therapy, alcohol consumption, and past year participation in other tobacco studies through GfK.

*Sample sizes for the models may fluctuate due to missing data on importance of ENDS use for quitting smoking, ENDS flavors, and ENDS device type. See S6 Table for results among all baseline smokers based on multiply imputed data.

[†]Exploratory pairwise comparisons among ENDS exposure groups were conducted. Adjusted mean difference estimates with matching superscripts within a model indicate that these groups were significantly different.

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Table 6. Average daily cigarette consumption at one-year follow-up by ENDS use and ends use characteristics among non-quitters for all baseline smokers (N = 680[*]) and baseline daily smokers (N = 543[*]).

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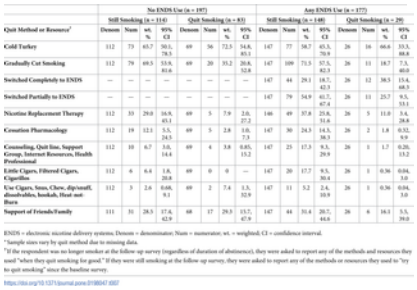
Methods used to quit smoking

Table 7 shows the quit methods and resources reported by smokers whom made a quit attempt, either successful or unsuccessful, during the study. Among those who did not use ENDS but had quit smoking, the majority (72.5%) reported quitting by giving up cigarettes all at once (i.e., "cold turkey"). Approximately one-third cut back gradually (35.1%) and relied on the support of friends and family (29.3%). Those who did not use ENDS and were still smoking had similar rates of trying to

quit cigarettes all at once (65.7%) as those who had successfully quit, but were more likely to report quitting by gradually cutting back on cigarettes (69.5%). Among those who used ENDS during the study and had quit smoking, a majority reported quitting cigarettes all at once (66.6%), 38.5% reported they had switched completely to ENDS, and 25.7% reported switching partially to ENDS. However, as the sample size for this group is very small (n = 29, of whom 26 reported the method(s) they used to quit smoking), caution is warranted. Among those who used ENDS and were still smoking at the follow-up survey, most reported gradually cutting back on cigarettes in order to quit (71.5%), trying to quit cigarettes all at once (58.7%), and switching partially to ENDS (54.9%).



	No ENDS Use (n = 197)						Any ENDS Use (n = 177)					
	Still Smoking (n = 114)			Quit Smoking (n = 83)			Still Smoking (n = 148)			Quit Smoking (n = 29)		
Quit Method or Resource[†]	Denom	Num	wt. %	95% CI	Denom	Num	wt. %	95% CI	Denom	Num	wt. %	95% CI	Denom	Num	wt. %	95% CI
Cold Turkey	112	73	65.7	50.1, 78.5	69	56	72.5	54.8, 85.1	147	77	58.7	45.3, 70.9	26	16	66.6	33.5, 88.8
Gradually Cut Smoking	112	79	69.5	53.9, 81.6	69	20	35.2	20.8, 52.8	147	109	71.5	57.5, 82.3	26	11	38.7	7.3, 80.0
Switched Completely to ENDS	—	—	—	—	—	—	—	—	147	44	29.1	18.7, 42.3	26	12	38.5	15.4, 68.3
Switched Partially to ENDS	—	—	—	—	—	—	—	—	147	79	54.9	41.7, 67.4	26	11	25.7	9.5, 53.1
Nicotine Replacement Therapy	112	33	29.0	16.9, 43.1	69	5	7.9	2.0, 27.2	146	49	37.8	25.6, 51.6	26	5	11.0	3.4, 28.8
Counties Pharmacology	112	19	12.1	5.5, 24.5	69	5	2.8	1.0, 7.3	147	30	24.3	14.3, 38.3	26	2	1.8	0.32, 9.9
Counseling, Quit line, Support Group, Internet Resources, Health Professional	112	10	6.7	3.0, 14.4	69	4	3.8	0.85, 15.2	147	25	17.3	9.3, 29.9	26	1	1.7	0.20, 15.2
Little Cigars, Filtered Cigars, Cigarillos	112	6	6.4	1.8, 20.8	69	0	0	—	147	20	17.7	9.5, 30.4	26	1	0.36	0.04, 3.0
Use Cigars, Snus, Chew, dip/snuff, dissolvables, hookah, Heat-not-Burn	112	3	2.6	0.68, 9.1	69	2	7.4	1.3, 32.9	147	11	5.2	2.4, 10.9	26	1	0.36	0.04, 3.0
Support of Friends/Family	111	31	28.5	17.4, 42.9	68	17	29.3	15.7, 47.9	147	44	31.4	20.7, 44.6	26	6	16.1	5.5, 39.0

ENDS = electronic nicotine delivery systems; Denom = denominator; Num = numerator; wt. = weighted; CI = confidence interval.

[*] Sample sizes vary by quit method due to missing data.

[†] If the respondent was no longer smoker at the follow-up survey (regardless of duration of abstinence), they were asked to report any of the methods and resources they used "when they quit smoking for good." If they were still smoking at the follow-up survey, they were asked to report any of the methods or resources they used to "try to quit smoking" since the baseline survey.

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Table 7. Methods used to quit smoking by ENDS use and smoking status at follow-up (N = 374[*]).
https://doi.org/10.1371/journal.pone.0198047.t007

Discussion

The decline of U.S adult smoking rates has accelerated in recent years [75]. In this study, 16% of smokers in 2015 had stopped smoking a year later. However, we found no evidence that ENDS, at least within the context of the US regulatory and tobacco/vaping market landscape during 2015–2016, were helping adult smokers quit at a higher rate than smokers who did not use these products, despite ENDS users being more likely to make a quit attempt. Our findings indicate that, at the time of this study, ENDS under "real world" use and conditions may have suppressed or delayed quitting among some adult smokers, though interpretation of negative effects of ENDS use should consider the high rate of quitting (18%-22%) among non-ENDS users in this study. While this quit rate is higher than a PATH Study estimate for adult smokers, ages 25+ years, who did not use ENDS at wave 1 (11.3%), it is comparable to the quit rate among the PATH younger adult smokers, 18–24 years, 21.3% [76]. Furthermore, among those who had not quit smoking by follow-up, our study did not find evidence that ENDS use was associated with a reduction in cigarette consumption after adjusting for covariates. While aligned with several prior studies [47,71,77–81], these findings diverge from other studies that have found positive associations of ENDS use with quitting smoking [45,61,82,83]. Inconsistencies within the literature have been attributed to the failure of nearly all studies, save the few RCTs, to satisfy six proposed quality standards [53]. Our study may be the only longitudinal cohort study to include the consideration of ENDS "dose," device type, e-liquid flavors, and whether they are being used for quitting or other purposes. Our results are robust and consistent even after taking into account these factors: regardless of frequency or duration of ENDS use, device type, quitting as reason for use, or e-liquid flavor, ENDS users quit at a lower rate than non-ENDS users. While the few, limited RCT studies indicate the potential of ENDS to help at least some smokers quit, our study, along with a number of population cohort studies, strongly suggest that the potential of ENDS as a disruptive technology capable of helping smokers quit combustibles is not being realized. There are several potential explanations for these findings. First, the effectiveness of ENDS for promoting cessation may be greater for early-adopters (before 2015) [82] compared to later adopters (in 2015–2016), despite the early market dominance of disposable and cig-a-like devices with poorer nicotine delivery. Later adopters of ENDS may differ from early adopters in important yet unidentified ways. Patterns and characteristics of ENDS use may also explain the findings. Many smokers were neither using ENDS daily nor using tank systems despite past research suggesting daily use of advanced systems that offer better nicotine delivery to be predictors of quitting success [61,69,82]. Whereas a recently published analysis of the PATH study found that daily ENDS and tank system users were more likely to have quit smoking cigarettes or reduced their smoking compared to nonusers [84]; another recent, well-designed study of smokers found that few of the smokers that used ENDS post-discharge used them regularly, and that this was associated with lower rates of cessation at 6-months post discharge from the hospital compared to nonusers [85]. Although neither daily use nor use of tank-system ENDS improved quitting over non-ENDS use in this study, this study may have been underpowered to detect higher quitting among tank-system users compared to disposable or cartridge users, and to detect higher quitting among daily users compared to non-daily users. ENDS vary considerably in their features and nicotine delivery across and within subtype and though nicotine delivery among some systems may be comparable to cigarettes, many systems are less efficient in this regard [60,86–91]. Tank systems also may not adequately mimic the experience of smoking a cigarette. Recent innovation and advancements in ENDS engineering, including cartridge-systems (e.g., JUUL), or other nicotine-delivery systems (e.g., heat-not-burn) may offer more appealing and satisfying options to facilitate complete switching for smokers [92,93]. Third, many dual users may use ENDS as a complement, rather than a substitute, to cigarettes [94,95]. In times/places when/where smoking is either prohibited, discouraged or inconvenient, smokers may use ENDS as a way to cope with their cravings in those situations. This type of dual use pattern is unlikely to result in higher quit rates compared to non-ENDS users and is concerning as smoking even one cigarette per day is associated with a substantially higher risk of coronary heart disease and stroke [96]. Lastly, a significant portion of smokers inaccurately believes that ENDS pose higher or similar risks to health as combustible cigarettes [97]. Misinformation and uncertainty about the risks of ENDS relative to smoking may have discouraged complete switching from combustibles to ENDS for many smokers.

Taken together, our results suggest that the current ways that ENDS are used under "real world" conditions may not increase population quit rates and generate meaningful net public health benefits. In the absence of substantial changes in product characteristics that would make ENDS more satisfying and appealing to adult smokers, policies and regulations that incentivize adult smokers to switch to ENDS, and efforts to accurately communicate the risks of ENDS to adult smokers and the general public, a substantial net public health benefit from ENDS in the U.S. seems unlikely. These findings, considered within the context of the current literature, have important regulatory implications. From the perspective of product characteristics, helping smokers quit combustibles will need evidence-based product standards and pre-market reviews that will encourage innovations in products that truly increase population quit rates. For example, the FDA has recently issued an Advance Notice of Proposed Rulemaking (ANPRM) regarding the role of flavors in tobacco product use, including in smokers switching to potentially reduced-harm tobacco products.[98] Much of the research on the impact of flavored ENDS has focused on the toxicity of flavor additives and their appeal to youth, whereas relatively little research has considered their impact on adult smokers. The results of our study suggest whereas the majority of ENDS users reported using flavors other than tobacco or menthol/wintergreen/mint, only the latter were significantly more likely than non-ENDS users to report a subsequent quit attempt, and none of the flavors was associated with greater likelihood of quitting than non-users. In fact, tobacco/unflavored ENDS users, as well as users of fruit, candy, and other flavors (other than menthol or mint) were associated with lower odds of quitting compared to non-ENDS users. Further study of flavors is necessary to better understand how e-liquid flavors influence decisions of smokers to use ENDS and their smoking outcomes.

Moreover, the findings of this and other studies support the notion that focusing on ENDS alone may be insufficient. Regulations and policies that incentivize smokers to switch completely to reduced-harm and reduced-risk products are needed. For example, product standards aimed at reducing the addictiveness of cigarettes may also be required to achieve population harm reduction through switching to lower-harm tobacco products or cessation of all tobacco. This notion is in line with recently announced plans by the FDA to reduce the nicotine within cigarettes while using regulations to promote the availability and acceptability of reduced-harm nicotine and tobacco products (as well as FDA-approved medicinal nicotine products) [99–101]. In addition, education campaigns that accurately communicate the risks of ENDS and other reduced-risk products may also encourage more complete switching from combustibles to ENDS, and in turn boost the potential of ENDS to increase the population quit rate.

Limitations

Interpretation and drawing of conclusions from this study must be tempered by consideration of its methodological limitations. Foremost, the observational design of this study limits the ability to draw causal inferences. Despite adjustment for an extensive list of potential confounders, we cannot adequately test for unmeasured confounders. Observational studies of nicotine replacement therapy (NRT) have also often failed to find a positive effect on long-term smoking cessation, particularly after NRT became available without a prescription [102,103]. Among other explanations, unmeasured confounders have been cited as a possible reason for these studies to replicate the positive effects observed in RCTs [103]. While additional U.S.-based RCTs that improve upon the weaknesses of past RCTs are much needed, RCTs are limited in their capability of assessing population-level effects of ENDS under real-world use patterns and conditions. Related, alternative approaches for handling observed confounding, such as propensity score weighting or entropy balancing adjustment, might have yielded different results. However, studies examining the association between ENDS use and cessation that have used propensity score weighting or entropy-balancing adjustment have obtained similar results as this study [85,104]. Second, whereas the use of a national probability sample is a strength of this study, use of an online panel prohibited biochemical verification of quitting or ENDS use. While the validity of self-reported cigarette smoking has been supported [105], the accuracy of self-report of ENDS use is less known. Third, although the sample size of this study either exceeds or is comparable to that of similar prior cohort studies, it might have been insufficient for conducting adequately powered comparisons of subgroups of ENDS users. Related, while retention of two-thirds of our sample over the one-year follow-up period is comparable or superior to most similar cohort studies, our reliance on statistical weighting adjustments to address attrition may not fully account for all relevant predictors of missingness. Finally, while this cohort study provides more recent data than other published cohort studies, caution is needed in generalizing its findings to the future given the continued rapid changes in the regulatory and market landscape for tobacco products.

Conclusions

Our study suggests that use of current ENDS products in real world conditions do not seem to improve the chances of quitting for smokers, and, under the current landscape, may not be the disruptive technology that increases the population quit rate and reduces the harm of combustibles. Additional steps may be needed to spur innovation to create low-harm and low-risk products that adequately deliver nicotine, address the misperceptions of relative harm of ENDS compared to cigarettes, and encourage cessation and complete switching from combustibles to low-harm and low-risk products among smokers who do not want to quit smoking. While this paper advances the current evidence-base by providing more recent data from the first longitudinal cohort study of a moderately large, nationally representative US sample to address recently proposed quality standards, additional research is needed to reconcile the divergent literature and monitor the impact of ENDS in an environment of rapidly evolving markets and regulatory policies.

Supporting information

S1 Table. Detailed description of measures and variable construction.

https://doi.org/10.1371/journal.pone.0198047.s001
(DOCX)

S2 Table. Smoking and ENDS use at one year follow-up for baseline dual users (multiple imputed).

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(DOCX)

S3 Table. Making a quit attempt and quitting smoking for ≥ 30 days by ENDS use (multiple imputed).

https://doi.org/10.1371/journal.pone.0198047.s003
(DOCX)

S4 Table. Making a quit attempt and quitting smoking for ≥ 30 days by ENDS use and characteristics of ends use (multiple imputed).

https://doi.org/10.1371/journal.pone.0198047.s004
(DOCX)

S5 Table. Average daily cigarette consumption at one-year follow-up by ENDS use among non-quitters (multiple imputed).

https://doi.org/10.1371/journal.pone.0198047.s005
(DOCX)

S6 Table. Average daily cigarette consumption at one-year follow-up by ENDS use and ends use characteristics among non-quitters (multiple imputed).

https://doi.org/10.1371/journal.pone.0198047.s006
(DOCX)

S1 Dataset. Raw data file.

https://doi.org/10.1371/journal.pone.0198047.s007
(CSV)

S1 File. Data dictionary for the raw data file.

https://doi.org/10.1371/journal.pone.0198047.s008
(PDF)

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Is the use of electronic cigarettes while smoking associated with smoking cessation attempts, cessation and reduced cigarette consumption? A survey with a 1-year follow-up

, [1], [1], [2], [2] and [1]

See commentary "Commentary on Brose et al. (2015): Protecting individual and public health by regulating electronic cigarette nicotine delivery" in *Addiction*, volume 110 on page 1169.
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Go to:

Abstract

Go to:

Aims

To use a unique longitudinal data set to assess the association between e-cigarette use while smoking with smoking cessation attempts, cessation and substantial reduction, taking into account frequency of use and key potential confounders.

Go to:

Design

Web-based survey, baseline November/December 2012, 1-year follow-up in December 2013.

Go to:

Setting

Great Britain.

Go to:

Participants

National general population sample of 4064 adult smokers, with 1759 (43%) followed-up.

Go to:

Measurements

Main outcome measures were cessation attempt, cessation and substantial reduction (≥50% from baseline to follow-up) of cigarettes per day (CPD). In logistic regression models, cessation attempt in the last year (analysis $n = 1473$) and smoking status ($n = 1656$) at follow-up were regressed on to baseline e-cigarette use (none, non-daily, daily) while adjusting for baseline socio-demographics, dependence and nicotine replacement (NRT) use. Substantial reduction ($n = 1042$) was regressed on to follow-up e-cigarette use while adjusting for baseline socio-demographics and dependence and follow-up NRT use.

Go to:

Findings

Compared with non-use, daily e-cigarette use at baseline was associated with increased cessation attempts [odds ratio (OR) = 2.11, 95% confidence interval (CI) = 1.24–3.58, $P = 0.006$], but not with cessation at follow-up (OR = 0.62, 95% CI = 0.28–1.37, $P = 0.24$). Non-daily use was not associated with cessation attempts or cessation. Daily e-cigarette use at follow-up was associated with increased odds of substantial reduction (OR = 2.49, 95% CI = 1.14–5.45, $P = 0.02$), non-daily use was not.

Go to:

Conclusions

Daily use of e-cigarettes while smoking appears to be associated with subsequent increases in rates of attempting to stop smoking and reducing smoking, but not with smoking cessation. Non-daily use of e-cigarettes while smoking does not appear to be associated with cessation attempts, cessation or reduced smoking.

Keywords: Electronic cigarettes, electronic nicotine delivery systems, harm reduction, smoking cessation, tobacco, quit attempts

Go to:

Introduction

In electronic cigarettes, a battery-powered heating element heats a solution, usually containing nicotine, to produce a aerosol. The use of e-cigarettes has increased

dramatically in the last few years; users are almost exclusively smokers or former smokers, with fewer than 1% of never-smokers using them regularly 1, 2, 3, 4, 5, 6, 7, 8. The vast majority of e-cigarette users report using them to stop smoking tobacco 6, 9 and in England, for example, smokers attempting to stop smoking now use e-cigarettes more often than any other aid, including nicotine replacement therapy (NRT) 10. Smoking prevalence in England has been declining from 20% in 2012 to 18.4% in 2014 (up to October), and in 2014 smoking cessation rates were the highest since at least 2008 10, 11. This simultaneous increase in e-cigarette use and cessation may be coincidental, and it is therefore vitally important for longitudinal studies to be conducted to assess the impact of e-cigarette usage on quitting behaviour.

Evidence on NRT supports the possibility of a link between using e-cigarettes that deliver nicotine and attempts to stop smoking. Use of NRT while smoking is associated with a small reduction in cigarette consumption and a significant increase in the likelihood of subsequent smoking cessation even in smokers without intentions to stop smoking 12, 13. Very little evidence is available to evaluate whether a similar pattern is observed with use of e-cigarettes by smokers and only a handful of studies have used any longitudinal data on e-cigarette use and smoking behaviour. A trial in smokers not intending to quit compared e-cigarettes with no nicotine with e-cigarettes with two different nicotine strengths and found that all led to significant reduction in tobacco consumption, and that significantly more smokers using the e-cigarettes with nicotine quit smoking 14. In a web-based survey of a national sample of current smokers in the United States who were followed-up 1 year later, e-cigarette use at baseline did not predict smoking cessation 1 year later 15. Data from two waves of the International Tobacco Control survey showed that smokers who were using e-cigarettes at follow-up were more likely to have reduced their cigarette consumption than non-users, but cessation did not differ 9. Among a cohort of young adults in the United States, those who had used e-cigarettes at least once in the month before baseline had a similar likelihood of quitting smoking 1 year later to those who had never used e-cigarettes 16. Unfortunately, none of these analyses distinguished frequency of use and many defined any trial or experimentation, even if just once, as use, so it is unclear what proportion were actually using e-cigarettes with any regularity. Regular use is likely to have a stronger effect on smoking behaviour than trial or infrequent use. When separating regular from intermittent use, respondents who had used e-cigarettes daily for at least a month were far more likely to have quit smoking than those who had not used them, whereas there was no such association of quitting with intermittent e-cigarette use 17. This highlights the importance of disentangling use from trial; however, the intensity of e-cigarette use had to be determined retrospectively. Because use is more common in smokers making quit attempts and all those who had quit must have made a quit attempt, this method confounds e-cigarette use with quit attempts.

To address the question as to whether use of e-cigarettes by smokers is associated with smoking behaviour change, this study used a web-based national sample from the general population in Great Britain with a 1-year follow-up.

We used the two waves of survey data to assess the association of:

1. daily, non-daily and non-use of e-cigarettes in smokers at baseline with smoking cessation attempts during follow-up (quit attempt analysis);

2. daily, non-daily and non-use of e-cigarettes in smokers at baseline with smoking cessation at follow-up (cessation analysis); and

3. daily, non-daily and non-use of e-cigarette use at follow-up with substantial reduction in tobacco cigarette consumption from baseline to follow-up. First (primary reduction analysis), we excluded those using e-cigarettes at baseline because, if use of e-cigarettes is associated with reduction in tobacco consumption, respondents may already have reduced their consumption at baseline, making detection of reduction from baseline to follow-up less likely. As it could also be argued that e-cigarette using smokers should be reducing further, we then also included smokers using e-cigarettes at both time-points (secondary reduction analysis).

Go to:

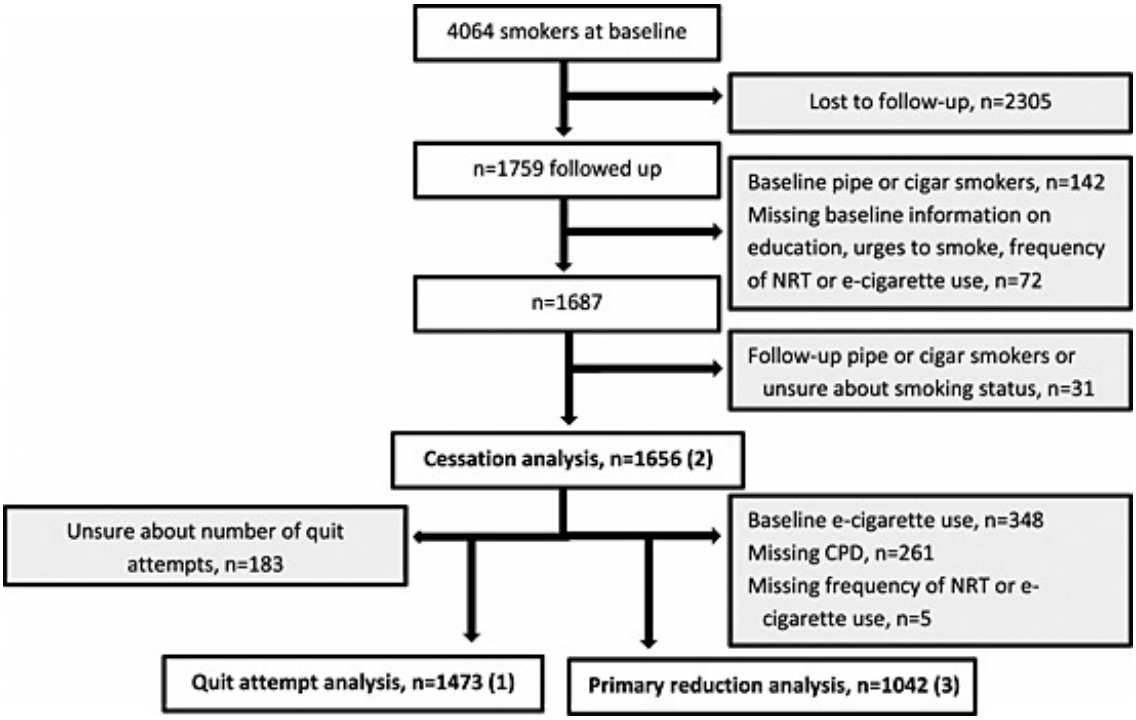
Methods

Design

This was a web-based longitudinal survey, with baseline data collected in November/December 2012 and follow-up in December 2013. University College London ethics committee confirmed that specific approval was not required. Data were anonymized before being passed to the research team.

Sample

The study sample was recruited from an online panel managed by Ipsos MORI. Ipsos MORI is the second largest market research organization in the United Kingdom. Members were invited by e-mail to participate in an online study about smoking. By completing the survey respondents would earn points which could be redeemed against high street vouchers or used to enter a prize draw. Each respondent logged into their Ipsos MORI online account and was asked a screening question about their past-year smoking status. Between November and December 2012, a total of 23 785 respondents were asked the screening question of whom 25.9% ($n = 6165$) had smoked in the past year. This proportion was similar to that identified by a face-to-face survey of representative samples of the population in England during 2012 10. Five thousand respondents completed the survey (4064 current smokers). They were re-contacted 1 year later for follow-up. Follow-up achieved a response rate of 43.6% overall ($n = 2182$) and of 43.3% among baseline smokers ($n = 1759$). Figure shows the selection of analyses samples for the three main outcomes.



Sample flowchart. Grey boxes indicate exclusions. Bold numbers in brackets indicate the three different outcomes. CPD = cigarettes per day

The secondary reduction analysis included smokers using e-cigarettes at both time-points (*n* = 1005).

Measures

Baseline and follow-up surveys included a range of questions on socio-demographic and smoking characteristics, nicotine use, quit attempts and health status. The current analyses included the following measures, fully presented in the Supporting information, Appendix.

Outcome measures

1. Quit attempts: smokers and recent ex-smokers were asked about the number of attempts to stop they had made in the previous year. Those reporting at least one attempt and 37 respondents who did not report an attempt but had stopped smoking between baseline and follow-up were coded as having made an attempt.

Cessation: smoking status was assessed at baseline and follow-up in all respondents. Change from being a smoker at baseline to being an ex-smoker at follow-up was coded as cessation.

3

Substantial reduction: smoking characteristics included the number of cigarettes smoked per day (CPD) for daily smokers and the number of cigarettes per week for non-daily smokers. Number of cigarettes per week were divided by seven to calculate CPD. Substantial reduction was defined as a reduction by at least 50% from baseline CPD to follow-up CPD 13.

Socio-demographic characteristics, dependence and nicotine use

All characteristics were measured at baseline and follow-up; the Analysis section explains which time-points were used in each analysis. Respondents provided their age, gender and highest level of formal education (see Supporting information, Appendix for questions and response options). Level of education was collapsed into those with any university education (including 'some university') and those without university education.

Strength of urges to smoke (SUTS) can be used as a measure of dependence and is a strong predictor of successful cessation in population samples 18, 19. The SUTS was included rather than the Fagerstrom Test of Nicotine Dependence (FTND 20) or the subset of FTND questions used for the Heaviness of Smoking Index (HSI 21) for two reasons. One reason was that the SUTS has outperformed the FTND in predicting failure of quit attempts 18; the second was that we hypothesized e-cigarette use to have an effect on smoking behaviour, specifically on the number of cigarettes smoked, one of the two components of the HSI, which would limit the comparability of scores across users and non-users of e-cigarettes.

Smokers and recent ex-smokers also reported if they were using NRT for any reason (not necessarily for a quit attempt), and how frequently they used NRT products. Respondents who had heard of e-cigarettes were asked whether they had ever tried one and, if they had, how often they were currently using an e-cigarette. For the main analyses, frequency of use of NRT and e-cigarettes were each collapsed into daily, non-daily and none.

Analysis

Respondents who completed the follow-up were compared with those who did not respond to the invitation in terms of socio-demographic characteristics, nicotine use and dependence using *t*-tests or analyses of variance (ANOVAs) for continuous data and χ^2 statistics for categorical data.

In the main logistic regression models, reports of at least one quit attempt in the last year and smoking status at follow-up were regressed onto baseline e-cigarette use (none, non-daily, daily) while adjusting for baseline age, gender, education, dependence (SUTS) and NRT use. Similar logistic regression models were used to analyse substantial reduction in CPD, but using NRT and e-cigarette use at follow-up, not baseline. Because only a small number of respondents overall had reduced substantially and 26.1% ($n = 322$) of the sample for the primary reduction analysis had increased consumption, the quantitative change in CPD was analysed using multiple linear regression, adjusting for the same characteristics as in the logistic regressions but dummy-coding NRT and e-cigarette use.

As sensitivity analyses, we collapsed daily and non-daily e-cigarette use categories and conducted logistic regressions using the collapsed variable while adjusting as in the main models.

SPSS version 21 was used for all analyses.

Go to:

Results

Prevalence and characteristics of users of e-cigarettes in the baseline survey have been reported previously 22. In brief, more than 90% of current smokers and recent ex-smokers were aware of e-cigarettes, approximately a third had ever used e-cigarettes and a fifth was currently using them. Daily use was more common in recent ex-smokers (46% of current users) than in current smokers (23%). Age and gender split did not differ between users and non-users. Among smokers, e-cigarette users had a higher socio-economic status than non-users and were more likely to have made a quit attempt in the past year. Users reported higher tobacco cigarette consumption than non-users 22.

Follow-up respondents differed from respondents lost to follow-up on some baseline characteristics. Those lost to follow-up were younger and women were more likely to be lost to follow-up than men. Frequency of NRT use differed; those who used NRT less than daily were more probably lost to follow-up (Supporting information, Table S1). Education, dependence and frequency of e-cigarette use did not differ.

A range of e-cigarettes were used and will be reported in a separate publication23; briefly, a majority used ‘first generation’ e-cigarettes that were cigarette-like in appearance (‘cigalikes’).

Quit attempts

Overall, 46.2% ($n = 680$) of respondents in the analysis made a quit attempt; 43.7% ($n = 508$) of non-users of e-cigarettes, 52.5% ($n = 124$) of non-daily e-cigarette users and 64.9% ($n = 48$) of daily users. Sample characteristics are presented in Table . In unadjusted analysis, both daily [odds ratio (OR) = 2.38, 95% confidence interval (CI) = 1.46–3.89, $P = 0.001$] and non-daily e-cigarette use (OR = 1.43, 95% CI = 1.08–1.89, $P = 0.013$) were associated with increased likelihood of quit attempts compared with non-use.

Table 1

Logistic regression analyses of association of baseline socio-demographics, dependence [strength of urges to smoke (SUTS)] and non-cigarette nicotine intake with quit attempts and smoking cessation during follow-up.

		Quit attempt (n = 1473, of whom n = 680 made attempt)				***Cessation (n = 1656, of whom n = 200 stopped smoking)***			
		n(%)/mean (SD)	***OR***	***95% CI***	***P***	***n(%)/mean (SD)***	***OR***	***95% CI***	***P***
Age[a]		46.6 (15.2)	0.83	0.77–0.90	<0.001	45.7 (15.3)	0.88	0.79–0.97	0.009
Gender	Female	642 (43.6)	1			720 (43.5)	1		
	Male	831 (56.4)	0.84	0.67–1.05	0.12	936 (56.5)	0.86	0.64–1.16	0.32
Level of education	No HE	958 (65.0)	1			1074 (64.9)	1		
	Some HE	515 (35.0)	0.83	0.66–1.05	0.12	582 (35.1)	0.76	0.55–1.05	0.099

		Quit attempt (n = 1473, of whom n = 680 made attempt)				*Cessation (n = 1656, of whom n = 200 stopped smoking)*			
		n(%)/mean (SD)	*OR*	*95% CI*	*P*	*n(%)/mean (SD)*	*OR*	*95% CI*	*P*
SUTS[b]		2.2 (1.1)	1.06	0.96–1.18	0.25	2.2 (1.1)	0.74	0.64–0.86	<0.001
NRT use	None	1212 (82.3)	1			1339 (80.9)	1		
	Non-daily	161 (10.9)	4.21	2.89–6.14	<0.001	193 (11.7)	1.39	0.88–2.21	0.16
	Daily	100 (6.8)	9.43	5.17–17.23	<0.001	124 (7.5)	1.67	0.98–2.84	0.062
E-cig use	None	1163 (79.0)	1			1307 (78.9)	1		
	Non-daily	236 (16.0)	1.18	0.87–1.60	0.29	263 (15.9)	0.77	0.49–1.21	0.25
	Daily	74 (5.0)	2.11	1.24–3.58	0.006	86 (5.2)	0.62	0.28–1.37	0.24

While adjusting for socio-demographic characteristics, dependence and NRT use, daily e-cigarette use at baseline was associated with increased odds of making an attempt to stop smoking compared with non-use. Non-daily e-cigarette users did not differ significantly from non-users (Table). There was a strong association of quit attempts with daily and non-daily NRT use. In the sensitivity analysis that collapsed daily and non-daily use, e-cigarette use remained associated with quit attempts (OR = 1.35, 95% CI = 1.03–1.77, *P* = 0.03).

Smoking cessation

Among smokers not using e-cigarettes at baseline, 168 (12.9%) quit smoking, compared with 25 non-daily users (9.5%) and seven daily users (8.1%). Sample characteristics are presented in Table . Unadjusted results showed no significant association with cessation for daily (OR = 0.60, 95% CI = 0.27–1.32, *P* = 0.21) or non-daily e-cigarette use (OR = 0.71, 95% CI = 0.46–1.11, *P* = 0.13) compared with non-use.

While adjusting for baseline characteristics, neither daily nor non-daily use of e-cigarette at baseline was associated with cessation at follow-up and nor was NRT use (Table). Considering any e-cigarette use (daily and non-daily), we found non-significantly reduced cessation (adjusted OR = 0.73, 95% CI = 0.48–1.09, *P* = 0.13).

Reduction in tobacco cigarette consumption

Overall, 6.2% (*n* = 65) of respondents reduced their consumption substantially. Forty-four (5.7%) smokers not using e-cigarettes at follow-up, 11 (5.5%) non-daily e-cigarette users and 10 (13.9%) daily users reduced substantially. Sample characteristics are included in Table . In unadjusted analysis of substantial reduction, daily use of e-cigarettes at follow-up compared with non-use was associated with increased likelihood of reduction (OR = 2.66, 95% CI = 1.28–5.54, *P* = 0.009); non-daily use was not associated with substantial reduction (OR = 0.96, 95% CI = 0.48–1.89, *P* = 0.90).

Table 2

Logistic regression analyses of association of socio-demographics, dependence (SUTS) and non-cigarette nicotine intake at follow-up with substantial reduction in cigarettes per day (CPD).

		Reduction (n = 1042, of whom n = 65 reduced CPD by ≥50% of baseline)			
		n(%) /mean (SD)	***OR***	***95% CI***	***P***
Baseline age[a]		46.7 (15.3)	0.99	0.78 to 1.08	0.30
Gender	Female	455 (43.7)	1		
	Male	587 (56.3)	0.51	0.30 to 0.86	0.012
Baseline level of education	No HE	706 (67.8)	1		
	Some HE	336 (32.3)	0.90	0.52 to 1.57	0.71
Baseline SUTS[b]		2.1 (1.1)	0.76	0.59 to 0.98	0.031
Follow-up NRT use	None	909 (87.2)	1		
	Non-daily	83 (8.0)	1.50	0.61 to 3.70	0.38
	Daily	50 (4.8)	1.66	0.58 to 4.70	0.34
Follow-up e-cig use	None	769 (73.8)	1		
	Non-daily	201 (19.3)	0.85	0.43 to 1.71	0.66
	Daily	72 (6.9)	2.49	1.14 to 5.45	0.022

In the primary reduction analysis and while adjusting for other relevant characteristics, daily use of e-cigarettes remained associated with increased likelihood of reduction while non-daily use was not associated significantly with substantial reduction (Table). Neither daily nor non-daily NRT use was associated with substantial reduction (Table).

When daily and non-daily e-cigarette use were collapsed, this was not significantly different from non-use (OR = 1.23, 95% CI = 0.70–2.15, $P = 0.48$). Secondary analysis in those using e-cigarettes at both time-points, adjusted for the same variables as the primary analysis, showed that compared with non-use at follow-up ($n = 769$), daily e-cigarette use ($n = 79$) was again associated with substantial reduction (OR = 4.19, 95% CI = 2.13–8.24, $P < 0.001$), while non-daily use ($n = 157$) was not (OR = 1.02, 95% CI = 0.48–2.19, $P = 0.96$).

Linear regression on quantitative change in CPD indicated that the difference in change between those using e-cigarettes daily and those not using them at follow-up (Table) was significant while adjusting for baseline age, gender, education, dependence and follow-up NRT use {[B [standard error (SE)] = –1.55 (0.65), β = –0.08, $P = 0.02$}. The difference in change between non-daily users and non-users was not significant [B (SE) = 0.28 (0.41), β = 0.02, $P = 0.50$] Secondary analysis in those using e-cigarettes at both time-points suggested a larger difference between changes for daily users and non-users [Table , B

(SE) = –2.58 (0.61), β = –0.14, $P < 0.001$, adjusted as before], whereas the difference in change between non-daily users and non-users remained small [B (SE) = –0.08 (0.44), β = –0.01, $P = 0.85$].

Table 3

Cigarettes per day by frequency of e-cigarette use.

	Mean (SD) cigarettes per day		
Follow-up e-cigarette use	***Baseline***	***Follow-up***	***Change***
None	13.3 (8.9)	13.5 (8.9)	0.2 (4.7)
Primary analysis, use initiated after baseline			
Non-daily	13.5 (7.9)	13.9 (8.9)	0.4 (5.9)
Daily	14.3 (9.8)	13.0 (9.4)	–1.4 (6.8)
Secondary analysis, some use at baseline			
Non-daily	14.9 (8.9)	15.0 (8.0)	0.09 (5.4)
Daily	14.1 (7.9)	11.5 (7.2)	–2.5 (6.1)

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Discussion

In a web-based national sample of smokers from the general population, those using e-cigarettes daily at baseline were more likely to have attempted to stop smoking when followed-up a year later than smokers not using e-cigarettes, but neither non-daily nor daily e-cigarette use was associated with smoking cessation during follow-up. Smokers using e-cigarettes daily when followed-up were more likely to have achieved at least 50% reduction in tobacco cigarette consumption from baseline. Less frequent e-cigarette use did not have a significant effect on consumption. Using e-cigarettes every day while smoking increased the prevalence of substantial reduction in tobacco consumption, and this was not restricted to smokers who had recently taken up e-cigarettes, suggesting that persistent users continue to reduce consumption over time. Reduction in consumption has been reported previously 14. This increase in substantial reduction was reflected in a small overall reduction in the number of cigarettes smoked in daily e-cigarette users. The size of the reduction was similar to that seen in smokers using NRT 12. NRT itself showed a similar size of positive association with subsequent cessation to that found in previous studies 12, but in this case it was not statistically significant using a conventional alpha ($P = 0.067$ two-tailed).

The use of NRT while smoking is supported as a harm reduction approach by national guidance in the United Kingdom 24. It reduces tobacco harm not only by increasing cessation and reducing consumption but also by reducing the amount of nicotine taken in from each cigarette 25, which is likely to be accompanied by a reduction in intake of toxins 26, 27. Although it remains to be tested, it appears possible that the use of e-cigarettes while smoking similarly reduces intake from each cigarette, thus supporting tobacco harm

reduction. Although long-term data on safety of e-cigarettes are not yet available, toxicology testing suggests that they will be considerably safer than tobacco cigarettes 28, although they may be less safe than NRT, which is licensed as medicine.

Smoking cessation rates in England were higher in 2014 than in previous years. Generally, cessation rates in a population can be increased by encouraging as many smokers as possible to make quit attempts and to use the most effective support in each of these attempts. The current data indicate that e-cigarettes were associated with more smokers attempting to stop smoking. We found no evidence that e-cigarette use while smoking increased subsequent smoking cessation. This is in line with previous findings 9, 15, 16, although in one recent study intense long-term use was associated with increased cessation 17. The present analyses extend the evidence by assessing use prospectively, thus avoiding confounding with quit attempts (otherwise e-cigarette use may be mainly a marker of having made a quit attempt) and by assessing quit attempts, cessation and reduction separately. Further research on the link between smoking cessation rates and e-cigarette use is warranted.

Importantly, the current sample used e-cigarettes for any reason, not necessarily to stop smoking, so the results cannot be used to derive statements on their effectiveness as cessation aids. Few studies have looked at e-cigarettes as cessation aids. One randomized controlled trial indicated that the particular e-cigarette used in the trial was of similar effectiveness as nicotine patches in supporting abstinence 29. Use and effects of different devices in the general population are likely to differ from those in controlled trials and samples of dedicated e-cigarette users may differ from other users in the general population. A recent study using a representative population sample found that smokers who used e-cigarettes in an attempt to stop smoking were more likely to report continued abstinence than those using NRT without prescription or no aids 30. Further high-quality longitudinal studies are needed on e-cigarettes as cessation aids. Future research should also evaluate the impact of continued use of e-cigarettes on smoking behaviour, as we were only able to provide snapshots of use at two time-points.

Further evidence is needed on differences between the numerous types of e-cigarettes, as products vary widely in their appearance, function, content, marketing and nicotine delivery 31, 32, 33, 34, and use and effects on smoking will vary considerably across different types. In this sample, the majority were using cigarette-like products. These have been found to deliver less nicotine than more recently developed products 22, 32, 35, and in a sample of ex-smokers who had quit using e-cigarettes all had used more recently developed products 36, indicating that cigarette-like e-cigarettes may be less helpful.

Several limitations of the study should be noted. Follow-up rate was 43%, resulting in small sample sizes for some analysis. Respondents who were followed-up differed from those not followed-up on some demographic variables, specifically age and gender, potentially reducing the generalizability to younger and female smokers. However, key smoking characteristics and e-cigarette use were not associated with follow-up. The survey did not include questions on the duration of use, so non-daily e-cigarette users will have included people who had just tried e-cigarettes once or twice, as well as occasional users. This also means that we did not assess if respondents continued to use e-cigarettes throughout the follow-up period and not all baseline users may have continued to use them. Also, those

initiating e-cigarette use during the follow-up period were included with baseline non-users. Any short-term use of e-cigarettes around baseline and uptake during follow-up will therefore have led to an underestimation of their effects on quit attempts and cessation. Additionally, the baseline sample including only smokers would have excluded any ex-smokers who had used e-cigarettes and successfully quit, thus potentially biasing the sample in favour of 'treatment failures'. The definition of cessation did not include a minimum time of abstinence, but relied upon respondents' self-report. However, this method avoids recall bias, and in population surveys the risk of misreporting is reduced, as there is no expectation to report cessation 37. The online recruitment method is likely to have led to some selection bias, as internet use is linked to socio-economic status and age; however, the socio-economic divide has narrowed considerably between 2011 and 2013 38. The sample was self-selected in so far as participants had volunteered for a market research company web panel; nevertheless, the overall sample characteristics were broadly similar to those of representative samples from a national household survey 22, 39.

The recruitment method also represents a strength, as in contrast to many early studies of e-cigarettes that recruited from e-cigarette interest groups (e.g. 33, 40), recruitment was not from self-selected populations with decidedly positive attitudes towards the devices. Thus, the association between their use and changes in smoking behaviour found in this study is expected to be more widely generalizable. The present survey has overcome another limitation of the very small number of previous longitudinal studies by separating regular and occasional use. More frequent use showed an effect on smoking behaviour where occasional use did not, and the effect of e-cigarettes on reduction in tobacco consumption disappeared when not differentiating frequency of use, suggesting that previous analyses may have overlooked effects. The current study may have missed important factors associated with quit attempts, cessation or reduction; for example, the use of other aids to stop smoking or mental health status of respondents. However, by adjusting for a range of important characteristics such as age, gender and dependence, it takes into account more potential confounders than previous longitudinal studies 15, 40.

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Conclusions

Daily use of e-cigarette use while smoking at one time-point is associated with subsequent increases in rates of attempting to quit smoking and reducing smoking, but not with increased smoking cessation. These effects persisted after adjusting for a range of socio-demographic characteristics, dependence and other nicotine use. Non-daily use of e-cigarettes while smoking is not associated with quit attempts, cessation or reduced smoking. These findings illustrate the importance of differentiating ever use or very occasional use from regular use in assessing the effects of e-cigarette use on smoking behaviour, a differentiation that has frequently been overlooked in previous research.

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Declaration of interests

J.B. has received an unrestricted grant from Pfizer, R.W. undertakes research and consultancy and receives fees for speaking from companies that develop and manufacture smoking cessation aids (Pfizer, J&J, McNeil, GSK, Nabi, Novartis and Sanofi-Aventis). L.B., S.H. and A.M. have no relationships with companies that might have an interest in the submitted work. There are no other financial relationships with any organizations that might have an interest in the submitted work, particularly electronic cigarette companies, and there are no other relationships or activities that could appear to have influenced the submitted work.

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Supporting information

Appendix S1 Measures

Table A1 Comparison of respondents followed up and lost to follow-up

Supporting info item

Click here for additional data file.(21K, docx)

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Notes

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E-cigarette users in Europe (including England) are less likely to quit smoking conventional cigarettes: Results challenge PHE recommendation that e-cigarettes be used in hospitals

A new paper based on a large sample of smokers across the European Union, *E-cigarettes Associated with Depressed Smoking Cessation: A Cross-sectional Study of 28 European Union Countries* was just published in the *American Journal of Preventive Medicine*. University of California researchers Margarete Kulik, Nadra Lisha and Stanton Glantz found that in the European Union smokers who use e-cigarettes are less, not more, likely to quit smoking.

An additional analysis pulling out the data from Great Britain alone showed the same thing: smokers who use e-cigarettes are less likely to quit smoking than smokers who do not use e-cigarettes.

This paper is the first large scale study of the relationship between e-cigarette use and quitting smoking compared to people who do not use e-cigarettes in the EU.

The results based on a cross-sectional survey of 12,608 ever smokers conducted by Eurobarometer are consistent with most other studies of real-world e-cigarette use

This new result particularly calls into question recent suggestions from Public Health England that hospitals in Britain begin selling e-cigarettes and provide patients with vaping lounges. The new study suggests that implementing Public Health England's recommendations will keep most people smoking cigarettes. Results from our study strongly indicate that implementing these policies that promote e-cigarette use will substantially worsen the tobacco epidemic.

In a statement we distributed before the paper was published, my co-author Margarete Kulik observed, "We expect a skeptical response from e-cigarette enthusiasts, especially in England" because study is based on cross-sectional data observed at a single point in time. "Cross-sectional data can only be used to measure associations, not causal links," she continued, "but they are a well-established epidemiological method."

It will be interesting to see how vigorously e-cigarette enthusiasts attack our paper based on the dataset we used and the fact that we did a cross-sectional analysis because these same people heralded a paper using the same Eurobarometer data set in a cross-sectional analysis by Farsalinos et al (Electronic cigarette use in the European Union: analysis of a representative sample of 27460 Europeans from 28 countries. *Addiction*. 2016;111(11):2032–2040. https://doi.org/10.1111/add.13506) that concluded that heavier e-cigarette users quit smoking more often than occasional e-cigarette users. (Our analysis found the same thing.) ***The big problem with the Farsalinos et al study was that they left out the control group, smokers who did not use e-cigarettes.***

Our analysis including ***all*** the smokers, including those who did not use e-cigarettes and compares quitting among all three groups. What we find is that heavy e-cigarette users quit smoking more than intermittent e-cigarette uses, ***but both quit less than people smokers who don't use e-cigarettes.***

We certainly hope that the same e-cigarette enthusiasts who touted the earlier paper will accept ours. The data and methods are the same as the earlier study; we just did a more complete analysis.

But, I expect that they will find some way to continue to love the Farsalinos paper while trashing ours. It will be interesting to see how they do it.

In the meantime, one can only hope that the health authorities in Great Britain will abandon their irresponsible and dangerous policies of promoting e-cigarettes for smoking cessation, especially in hospitals and health facilities.

Here is the abstract:

Introduction: Electronic cigarettes (e-cigarettes) are often promoted to assist with cigarette smoking cessation. In 2016–2017, the relationship between e-cigarette use and having stopped smoking among ever (current and former) smokers was assessed in the European Union and Great Britain by itself.

Methods: Cross-sectional logistic regression of the association between being a former smoker and e-cigarette use was applied to the 2014 Eurobarometer survey of 28 European Union countries controlling for demographics.

Results: Among all ever smokers, any regular ever use of nicotine e-cigarettes was associated with lower odds of being a former smoker (unadjusted OR=0.34, 95% CI=0.26, 0.43, AOR=0.43, 95% CI=0.32, 0.58) compared with smokers who had never used e-cigarettes. In unadjusted models, daily use (OR=0.42, 95% CI=0.31, 0.56); occasional use (OR=0.25, 95% CI=0.18, 0.35); and experimentation (OR=0.24, 95% CI=0.19, 0.30) of nicotine e-cigarettes were associated with lower odds of being a former smoker compared with having never used nicotine-containing e-cigarettes. Comparable results were found in adjusted models. Results were similar in Great Britain alone. Among current smokers, daily cigarette consumption was 15.6 cigarettes/day (95% CI=14.5, 16.7) among those who also used e-cigarettes versus 14.4 cigarettes/day (95% CI=13.4, 15.4) for those who did not use them ($p<0.05$).

Conclusions: These results suggest that e-cigarettes are associated with inhibiting rather than assisting in smoking cessation. On the population level, the net effect of the entry of e-cigarettes into the European Union (and Great Britain) is associated with depressed smoking cessation of conventional cigarettes.

The full citation is: Kulik et al. E-cigarettes Associated With Depressed Smoking Cessation: A Cross-sectional Study of 28 European Union Countries. American Journal of Preventive Medicine. Epub ahead of print 12 Feb 2018 DOI: https://doi.org/10.1016/j.amepre.2017.12.017 . It is available here.

E-cigarettes are expanding nicotine addiction in England, too

One of the arguments coming from Public Health England and the other e-cig cheerleaders there is that youth use is very low.

A new study using data collected in the UK between June 2015 and April 2016 of schoolchildren (mean age 14.1, n=499) shows that, like everywhere else, a substantial number of kids using e-cigarettes have never smoked cigarettes. In fact, at 52.6%, this is the highest fraction of never smokers reported by adolescent e-cig users.

This observation, combined with the substantially stronger gateway effect for smoking McNeill and colleagues reported in their longitudinal study of UK youth, may be another reflection of the likelihood that all the enthusiasm for e-cigs among much (but not all) of the British health establishment is recruiting kids to a lifetime of nicotine addiction.

The new paper is “More than half of adolescent E-Cigarette users had never smoked a cigarette: findings from a study of school children in the UK” by Fulton E, Gokal K, Griffiths S, Wild S (Public Health. 2018 Jun 2;161:33-35. doi: 10.1016/j.puhe.2018.04.014. [Epub ahead of print]).

Here is the abstract:

OBJECTIVES: Electronic cigarettes (ECs) are known for their use as a smoking cessation aid; however, experimental use in adolescence is a growing international concern. The proportion of adolescent EC users who have never used tobacco is rising. EC use is associated with later tobacco initiation in young people. Understanding adolescent beliefs about ECs is needed to inform public health campaigns and school education regarding the EC and the associated risks.

STUDY DESIGN: A cross-sectional questionnaire-based design was used.

METHODS: As part of a larger study, questionnaires to assess beliefs about ECs and current use were distributed to 499 school pupils aged 11-16 years in a county in England, UK.

RESULTS: More than half of EC users had never used tobacco (52.6%), a substantially greater proportion than previously reported in the literature. Adolescents were aware that ECs were less harmful than tobacco but many were unaware that they contain nicotine and the subsequent risk of addiction could lead to later tobacco use.

CONCLUSIONS: Given the possible association of EC use and later smoking initiation, education in schools may warrant greater emphasis on ECs, the role of nicotine and the risk of addiction associated with experimentation. Young people who deem ECs as a 'safe' option, and may otherwise have never experimented with tobacco, could be at risk of later tobacco use.

The paper is available here.

Strong evidence for a huge gateway effect for e-cigs in Britain, even stronger than in USA

Strong evidence for a huge gateway effect for e-cigs in England

Recently researchers from England, led by Ann McNeill and including prominent e-cigarette advocates, published a well-done study showing a huge gateway effect for e-cigarettes leading to cigarette smoking among youth in Great Britain.

The paper, "Association between smoking and electronic cigarette use in a cohort of young people," published in *Journal of Adolescent Health*, showed that youth who initiated product use with e-cigarettes had 12 times the odds of smoking cigarettes 4 months later than kids who did not use e-cigarettes.

Two strengths of the study are that it is longitudinal (follows the kids forward in time) and controls for a wide range of other risk factors for smoking, including susceptibility to smoking. The fact that, controlling for susceptibility e-cigarettes have such a huge effect, indicates that (like other studies) e-cigarettes are attracting kids at low risk of initiating nicotine use with conventional cigarettes.

Another impressive thing about the results is that any use of e-cigarettes predicts subsequent any conventional cigarette smoking (even a puff). While this doesn't sound like much, another recent paper led by Peter Hajek, "What Proportion of People Who Try One Cigarette Become Daily Smokers," shows that about two-thirds of kids who take even a puff on a cigarette go on to become daily smokers.

This result shows that the gateway of e-cigarettes in Great Britain is about four times as powerful in Great Britain, where health authorities have embraced e-cigarettes, more than in the US (where most health authorities have been skeptical of e-cigarettes), where the odds of youth who initiate with e-cigarettes progressing to smoking are "only" tripled.

In the press release on the study minimizing its significance that was issued by ASH UK, ASH pointed out that there is a "two-way association" between e-cigarettes and cigarettes (and there is), but the odds of taking up e-cigarettes after cigarettes were increased by 3.5, a much smaller effect. While it is true, the direction is dominantly from e-cigarettes to cigarettes. (This result is similar to a study done at Yale showing that movement from e-cigarettes to cigarettes dominated movement in the opposite direction.)

The authors also tried to minimze the impact of their findings by stating (in the Discussionn section) that "only 4% of never smokers initiated e-cigarette use (vs. 32% of ever smokers) This suggests that e-cigarettes are attracting few who have never smoked." This is misleading because there are a lot more never smokers (81.2% of their sample) than ever smokers (19.8% of their sample). Thus, the prevalence of e-cigarette use generated from never smokers is .04 x .812 = 3.5% and the prevalence of e-cigarette use generated from ever smokers is .32 x .198 = 6.4%. This means that, of all kids using e-cigarettes,

0.35/(0.35+0.64) = 29% were kids who had never smoked a cigarette. This is about the same as the fraction of never-smoking kids who were using e-cigarettes that have been found in the other studies. These kids represent an expansion of the nicotine addiction market.

Here is the abstract:

PURPOSE: Electronic cigarette (e-cigarette) use is associated with smoking initiation among young people; however, it is also possible that smoking is associated with e-cigarette initiation. This study explores these associations among young people in Great Britain.

METHODS: A longitudinal survey of 1,152 11- to 18-year-olds was conducted with baseline in April 2016 and follow-up between August and October 2016. Logistic regression models and causal mediation analyses assessed whether (1) ever e-cigarette use and escalation were associated with smoking initiation (ever smoking at follow-up) among baseline never smokers (n = 923), and (2) ever smoking and escalation were associated with e-cigarette initiation (ever e-cigarette use at follow-up) among baseline never e-cigarette users (n = 1,020).

RESULTS: At baseline, 19.8% were ever smokers and 11.4% were ever e-cigarette users. Respondents who were ever e-cigarette users (vs. never users, 53% vs. 8%, odds ratio [OR] = 11.89, 95% confidence interval [CI] = 3.56-39.72) and escalated their e-cigarette use (vs. did not, 41% vs. 8%, OR = 7.89, 95% CI = 3.06-20.38) were more likely to initiate smoking. Respondents who were ever smokers (vs. never smokers, 32% vs. 4%, OR = 3.54, 95% CI = 1.68-7.45) and escalated their smoking (vs. did not, 34% vs. 6%, OR = 5.79, 95% CI = 2.55-13.15) were more likely to initiate e-cigarette use. There was a direct effect of ever e-cigarette use on smoking initiation (OR = 1.34, 95% CI = 1.05-1.72), and ever smoking on e-cigarette initiation (OR = 1.08, 95% CI = 1.01-1.17); e-cigarette and smoking escalation, respectively, did not mediate these effects.

CONCLUSIONS: Among young people in Great Britain, ever e-cigarette use is associated with smoking initiation, and ever smoking is associated with e-cigarette initiation.

The citation is: East K, Hitchman S, Bakolis I, Williams S, Cheeseman H, Arnott D, McNeill A. Association Between Smoking and Electronic Cigarette Use in a Cohort of Young People. *J Adolesc Health*. 2018 Feb 21. pii: S1054-139X(17)30903-5. doi: 10.1016/j.jadohealth.2017.11.301. [Epub ahead of print]. It is available here.