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Subject: Ecigs not successful to reduce smoking prevalence - It is noticeable that Robert West was part of this study

[redacted]

Subject: Ecigs not successful to reduce smoking prevalence - It is noticeable that Robert West was part of this study

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.

Attachments:
e016046.full.pdf

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.

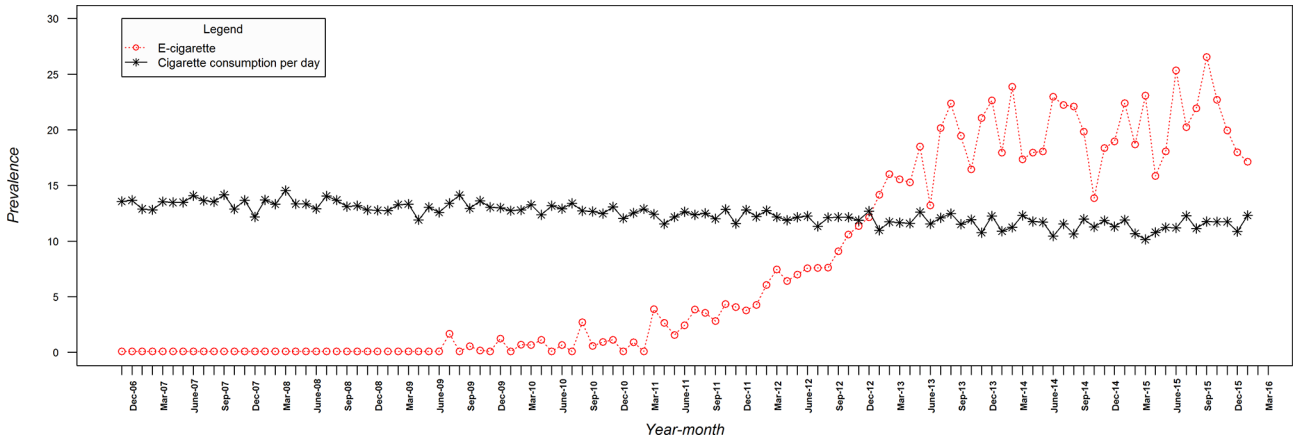

Figure 1 Monthly prevalence of cigarette consumption and e-cigarettes for harm reduction among smokers.

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.

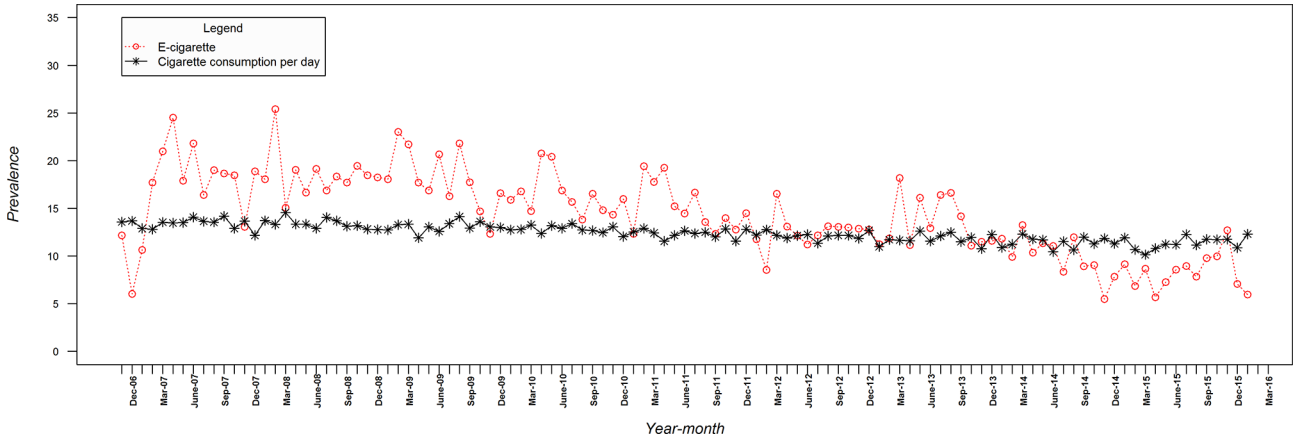

Figure 2 Monthly prevalence of cigarette consumption and nicotine replacement therapy use for harm reduction among smokers.

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	NA	NA
Seasonal MA p value	NA	NA	NA	NA	NA	NA
R^2	0.65	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	NA	NA
Seasonal MA p values	NA	NA	NA	NA	NA	NA
R^2	0.64	0.64	0.65	0.64	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.

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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).

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Subject: Ecig use in Scottish cohort

[redacted]

Conclusions Young never smokers are more likely to experiment with cigarettes if they have tried an e-cigarette. Causality cannot be inferred, but continued close monitoring of e-cigarette use in young people is warranted.

Attachments:
tobaccocontrol-2017-053691.full.pdf

Relationship between trying an electronic cigarette and subsequent cigarette experimentation in Scottish adolescents: a cohort study

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ABSTRACT

Background This study examines whether young never smokers in Scotland, UK, who have tried an e-cigarette are more likely than those who have not, to try a cigarette during the following year.

Methods Prospective cohort survey conducted in four high schools in Scotland, UK during February/March 2015 (n=3807) with follow-up 1 year later. All pupils (age 11–18) were surveyed. Response rates were high in both years (87% in 2015) and 2680/3807 (70.4%) of the original cohort completed the follow-up survey. Analysis was restricted to baseline 'never smokers' (n=3001/3807), 2125 of whom were available to follow-up (70.8%).

Results At baseline, 183 of 2125 (8.6%) never smokers had tried an e-cigarette and 1942 had not. Of the young people who had not tried an e-cigarette at baseline, 249 (12.8%) went on to try smoking a cigarette by follow-up. This compares with 74 (40.4%) of those who had tried an e-cigarette at baseline. This effect remained significant in a logistic regression model adjusted for smoking susceptibility, having friends who smoke, family members' smoking status, age, sex, family affluence score, ethnic group and school (adjusted OR 2.42 (95% CI 1.63 to 3.60)). There was a significant interaction between e-cigarette use and smoking susceptibility and between e-cigarette use and smoking within the friendship group.

Conclusions Young never smokers are more likely to experiment with cigarettes if they have tried an e-cigarette. Causality cannot be inferred, but continued close monitoring of e-cigarette use in young people is warranted.

INTRODUCTION

In the UK and many other countries, e-cigarette use among young people is largely confined to those who have already tried tobacco and is mostly experimental in nature.[1 2] That is, most young people who have never tried tobacco smoking, hereon referred to as never-smokers, do not engage in regular e-cigarette use that is sustained over time. Nevertheless, there remains concern that trying an e-cigarette could ease the pathway to experimentation with tobacco smoking for young never-smokers.

Eight longitudinal studies, all conducted in the USA with follow-up after 6[3 4] and/or 12 months,[5–10] have explored the relationship between e-cigarette use and smoking initiation in young never-smokers. They found that young people who had ever used an e-cigarette at baseline were more likely to have tried a cigarette by follow-up.

Most of the evidence from prospective cohort studies of young never smokers, e-cigarette use and smoking initiation has come from the USA. It is important this evidence can be compared with studies from different countries because varied national contexts, such as different tobacco control regulations, historical and cultural factors around tobacco use, availability and supply of products, ethnic composition of the population and investment in advertising of products, make it difficult to generalise findings across national boundaries. For example, in Poland 27.4% of adolescents report using an e-cigarette in the past month.[11] Poland is a major European tobacco and e-cigarette producer. Recently smoking rates have increased among Polish female adolescents although they are stable in men[12–14] and by late adolescence most Polish e-cigarette users are dual users (tobacco and e-cigarette use). A recent study found 21.8% of students (16–18 years) were dual users and this was not associated with reduced cigarette consumption compared with tobacco-only users.[15] The case of Poland highlights the potential role of national factors such as tobacco production and industry involvement in affecting levels of use in young people.

In Scotland, the prevalence of cigarette smoking among young people has steadily fallen over the last two decades. In 2015, only 2% of 13 year olds and 7% of 15 year olds were regular smokers.[16] However, current smoking among young people aged 16–24 years in Scotland is significantly higher at 21%.[17] This disparity suggests that smoking initiation may now be delayed until early adulthood. Therefore early risk factors for later smoking initiation require further investigation.

Previous cross-sectional research has shown a positive association between e-cigarette use and weakened intentions not to smoke in children aged 10–11 years in Wales.[1] Recently the ever use of e-cigarettes among young non-smokers has increased in Scotland with 10% of non-smoking 15 year olds having tried them in 2013 and 24% in 2015.[16] Levels of regular e-cigarette use among young people in Wales have also increased with 2.7% of young people aged 11–18 years reporting using them at least once a week in 2015.[18] These increases were preceded by a marked growth in the

Table 1 Number of 'never smoking' respondents by school and year group

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
School 1 Accessible small town/medium–low deprivation	207 24.1%	184 21.5%	193 22.5%	129 15.0%	93 10.8%	52 6.1%	858 100%
School 2Urban/medium–low deprivation	147 19.9%	175 23.7%	136 18.4%	134 18.2%	85 11.5%	61 8.3%	738 100%
School 3 Other urban/high deprivation	177 26.3%	160 23.8%	106 15.8%	125 18.6%	62 9.2%	42 6.3%	672 100%
School 4 Urban/high deprivation	151 20.6%	197 26.9%	122 16.6%	126 17.2%	94 12.8%	43 5.9%	733 100%
Total	682	716	557	513	333	197	3001
Mean age (SD)	12.5 (0.34)	13.5 (0.34)	14.6 (0.34)	15.6 (0.35)	16.6 (0.36)	17.6 (0.32)	14.4 (1.58)

retail availability of e-cigarettes with the proportion of retailers with displays of e-cigarettes doubling between 2013 and 2014.[19] When this study was conducted, within store advertising and promotion of e-cigarettes was not regulated and there was no age restriction on the legal purchase of e-cigarettes in the UK. This study is one of the first to examine e-cigarette use and cigarette experimentation in a UK longitudinal sample.

METHODS

The data presented here are drawn from the Determining the Impact of Smoking Point-of-Sale Legislation Among Youth (DISPLAY) study.[20] The DISPLAY study is a 5-year multimodal study designed to measure the impact of UK legislation to ban point-of-sale displays of tobacco products on the smoking attitudes and behaviours of young people. One element of the DISPLAY study is an annual school survey conducted in four Scottish secondary schools located in communities that differ in terms of their socioeconomic and urban–rural profiles. The data presented here are from the 2015 and 2016 surveys which included all pupils (aged 11–18) in the four schools. All four schools had pupils across the age range 11–18 years and a breakdown of participant numbers by school and by year group is given in table 1. The survey was administered by class teachers under exam conditions and took on average 40 min to complete. Pupils who were absent on the day of the survey were given opportunity during the following 2 weeks to complete the survey.

Ethical approval was obtained from the University of St Andrews, University Teaching and Research Ethics Committee (UTREC). Parental opt-out consent was obtained prior to pupils completing the survey. Pupils also provided active consent by completing the survey.

Derivation of variables

Smoking status

Respondents were asked "Have you ever smoked cigarettes or hand-rolled cigarettes (roll-ups), even if it is just one or two puffs?" to which they could respond 'yes' or 'no'. Young people who responded 'no' were deemed to be never-smokers at that point.

E-cigarette use

Respondents were asked whether or not they had heard of e-cigarettes. Pupils who answered that they had not heard of e-cigarettes were routed past further questions on e-cigarettes. Pupils that had heard of e-cigarettes were then asked "Which ONE of the following is closest to describing your experience of e-cigarettes/vapourisers/shisha pens?" with response options of 'I have never used them', 'I have tried them once or twice', 'I use them sometimes (more than once a month)' or 'I use them often (more than once a week)'. Young people who responded that they had never heard of e-cigarettes were coded as having 'never used them'.

For the logistic regression analysis, due to low frequencies in the categories reflecting regular use, participants were divided into those who had never tried e-cigarettes versus those who had tried e-cigarettes.

Susceptibility to smoking

Susceptibility to smoking was assessed through two questions "If one of your friends offered you a cigarette or hand-rolled cigarettes (roll-ups), would you smoke it?" and "Do you think you will smoke a cigarette or hand-rolled cigarettes (roll-ups) at any time during the next year?". The response option for these questions was 'definitely yes', 'probably yes', 'probably not' and 'definitely not'. If respondents answered anything other than 'definitely not' to either of these questions then they were coded as being susceptible to smoking. These measures of smoking susceptibility have been used in related studies[6] and are based on validated measures.[21]

Number of friends and family who smoke

Respondents were asked "How many of your friends smoke cigarettes or hand-rolled cigarettes (roll-ups)?" and could respond 'most of them', 'about half of them', 'some of them', 'none of them' or 'don't know'. 'Don't know' responses were coded as missing and then a binary variable was generated distinguishing those who responded 'none of them' versus any other response.

Respondents were asked "which if any of the following people smoke cigarettes or hand rolled cigarettes (roll-ups)?". Options included their mother or female carer, father or male carer, brother (eldest if more than one) and sister (eldest if more than one). A binary variable was created splitting participants who had responded that any of these family members smoked versus those that reported no smokers in their immediate family.

Demographic variables

Respondents were asked their gender, ethnic group and date of birth. Individual family material well-being was assessed through the Family Affluence Scale (FAS).[22] The FAS consists of four questions (own bedroom, number of family cars, number of computers and number of family holidays abroad per year). The FAS raw scores were transformed though categorical principal component analysis into single-dimensional scores that were then divided into tertiles of high, medium and low FAS.

Analysis

Analysis was conducted in Stata V.14 (StataCorp).

Never smokers were divided into those who had tried an e-cigarette at baseline and those who had not and these groups were compared in terms of the proportion of participants that reported having experimented with cigarettes by follow-up. Tobacco experimentation in this study was defined as any cigarette use, even just one or two puffs.

Multivariate logistic regression was used to control for potential confounding factors—sex, age, ethnicity, family affluence, smoking within the family, smoking by friends and susceptibility to smoking. The model was built in three blocks, first with only e-cigarette use and smoking-related variables as independent variables and in the second block demographic variables were added and an indicator for school was included in the model. Including school as a covariate makes explicit the effect of school as school-level smoking norms are an important influence on smoking behaviour.[23] In the third block interactions between e-cigarette use, smoking susceptibility and smoking within friendship group were included. The risk ratio (RR) for the unadjusted model was obtained from a binomial log-linear regression and for the adjusted models a Poisson regression model with a robust variance estimator.[24]

To test the effect of missing data on the parameter estimates, we used multiple imputation by chained equations (Stata V.14: mi impute chained). Further information on the imputation procedure is given in the online supplementary materials.

RESULTS

Sample characteristics

In 2015, there were 3001 never smokers in our sample, of these 9.4% had tried an e-cigarette. Twenty-six per cent were coded as susceptible to smoking, 32.8% had a family member who smoked and 23.8% reported having at least one friend who smoked.

Our final sample included 2125 young people for whom we had data on e-cigarette use and smoking status at baseline and follow-up. Of these, 183 (8.6%) had tried an e-cigarette at baseline and 1942 (91.4%) had not. Table 1 shows the year group distribution of the sample by school.

Relationship between baseline e-cigarette use and smoking status at follow-up in baseline never smokers

Of the young people who had tried an e-cigarette at baseline (n=183), 74 (40.4%) went on to initiate smoking cigarettes by follow-up. This compares with 249 (12.8%) of those who reported never having used an e-cigarette at baseline (n=1942) and went on to initiate smoking cigarettes by follow-up. Table 2 shows the bivariate relationship between e-cigarette use in 2015 and smoking status in 2016.

Logistic regression on 'experimented with cigarettes by follow-up'

Baseline e-cigarette use is a significant predictor of experimentation with cigarettes. In an unadjusted model, the OR for ever-smoking at follow-up in ever e-cigarette users versus never e-cigarette users was 4.62 (95% CI 3.34 to 6.38), giving a RR of 3.15 (95% CI 2.55 to 3.89). Table 3 below shows the ORs, p values and 95% CIs for the OR for each of the models. All the models below were adjusted for sex, age centred on the mean (ie, individual age minus the mean age of the sample) FAS, ethnic group and school.

Model 1 RR for e-cigarette use is 1.72 (95% CI 1.31 to 2.26), model 2 RR for e-cigarette use is 4.09 (95% CI 2.57 to 6.52), RR for e-cigarette*susceptibility interaction is 0.43 (95% CI 0.25 to 0.72), RR for e-cigarette*friend smokes interaction 0.62 (95% CI 0.39 to 0.99), model 3 RR for e-cigarette use is 4.22 (95% CI 2.83 to 6.36), RR for e-cigarette*susceptibility interaction is 0.41 (95% CI 0.26 to 0.64) and RR for e-cigarette*friend smokes interaction 0.65 (95% CI 0.44 to 0.97).

Figure 1 shows that the impact of having tried an e-cigarette at baseline on probability of tobacco experimentation at follow-up is much greater for young people who were non-susceptible to smoking at baseline. The contrast of predicted probabilities is significant ($\chi^2=53.93, p<0.001$).

Figure 2 shows that the impact of having tried an e-cigarette at baseline on probability of tobacco experimentation at follow-up is much greater for young people who have no friends who smoke. The contrast of predicted probabilities is significant ($\chi^2=4.91$, $p=0.042$).

Further information on characteristics of missing cases is given in online supplementary materials. To test the effect of missing data on our parameter estimates we used multiple imputation by chained equations. Model 3 shows the estimates from an imputed model (m=100). The model estimates are stable under complete case analysis and imputation.

DISCUSSION

This study found that young 'never-smokers' who had tried an e-cigarette were more likely to try a cigarette during the following year than young never-smokers who had not tried an e-cigarette. This is consistent with the results of all previous

Table 2 Baseline e-cigarette use in 2015 and follow-up smoking status in 2016

		Have you ever smoked cigarettes or roll-ups, even if it is just one or two puffs? (2016)		
		No	Yes	Total
E-cigarette use (2015)	I have never used an e-cigarette	1693	249	1942
		87.2%	12.8%	100%
	I have only used them once or twice	104	65	169
		61.5%	38.5%	100%
	I use them sometimes (monthly)	3	5	8
		37.5%	62.5%	100%
	I use them often (weekly)	2	4	6
		33.3%	66.7%	100%
Total		1802	323	2125
		84.9%	15.2%	100%

Table 3 Multivariate logistic regressions on 'ever smoked a cigarette' in 2016

Variable	Model 1—adjusted main effects model (n=1806)			Model 2—adjusted model including interactions (n=1806)			Model 3—imputed model with interactions (n=2520)		
	OR	CI	p	OR	CI	p	OR	CI	p
E-cigarette ever use 2015	2.42	1.63 to 3.60	<0.001	5.97	3.12 to 11.40	<0.001	6.64	3.60 to 12.26	<0.001
Susceptibility to smoking 2015	3.65	2.70 to 4.94	<0.001	4.13	2.98 to 5.72	<0.001	5.19	3.74 to 7.21	<0.001
Any family member smokes 2015	1.89	1.40 to 2.56	<0.001	1.93	1.43 to 2.61	<0.001	1.83	1.37 to 2.44	<0.001
'At least some' friends smoke 2015	1.33	0.95 to 1.85	0.094	1.56	1.09 to 2.25	0.016	1.51	1.07 to 2.14	0.020
Interaction between e-cigarette and susceptibility				0.42	0.19 to 0.94	0.036	0.42	0.20 to 0.88	0.021
Interaction between e-cigarette and friends smoking				0.49	0.23 to 1.07	0.072	0.52	0.25 to 1.09	0.082

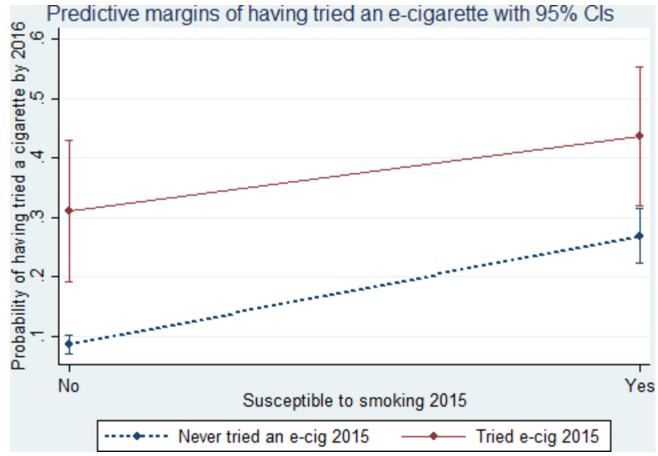

Figure 1 Marginal probabilities of cigarette experimentation by e-cigarette use and smoking susceptibility. e-cig, e-cigarette.

published longitudinal studies of the relationship between e-cigarettes and tobacco experimentation in young people from the USA,[3–9] providing further confirmation in a non-US context.

It is possible that the relationship between e-cigarettes and tobacco experimentation may not be causal if young never-smokers who try an e-cigarette would have gone on to initiate smoking anyway due to being already favourably disposed towards tobacco use. In other words, it is possible that e-cigarette use and tobacco experimentation have common liability[25] and the former is incidental to tobacco experimentation. To address this possibility, we controlled for factors associated with transition to smoking such as smoking susceptibility[26] and smoking among friends and family[27] in the analysis. However, even when these items were included in the model e-cigarette use remained a significant predictor of cigarette experimentation. Importantly, there was also an interaction between smoking susceptibility and e-cigarette use and between e-cigarette use and having friends who smoked. These data indicate that e-cigarette use had a greater effect on the odds of cigarette experimentation in young people not traditionally thought to be high risk, that is, those with a firm intention not to smoke and/or those with no smokers in their friendship group.

There is some evidence from other studies that young people who try e-cigarettes before tobacco have different characteristics to those who go straight to smoking. Wills and colleagues[28] found

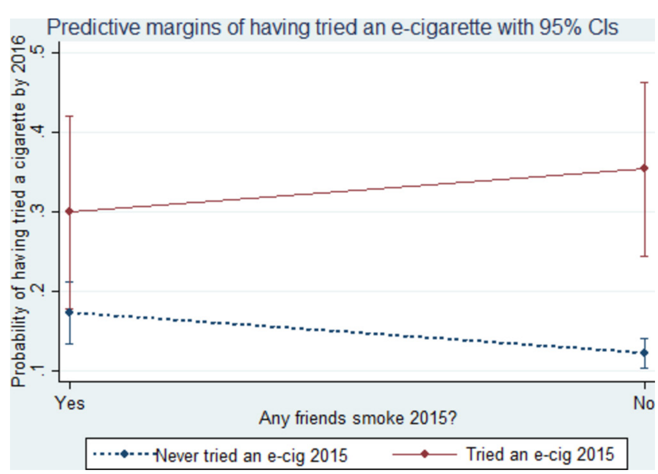

Figure 2 Marginal probabilities of cigarette experimentation by e-cigarette use and smokers within friendship. e-cig, e-cigarette.

that those who used an e-cigarette first were less rebellious and more likely to receive social support from their parents. Miech and colleagues[10] found that young never-smokers who had tried e-cigarettes were more likely to move away from the perception that cigarettes were a 'great risk' over the following year. Wills and colleagues[29] also found that young never smokers who used e-cigarettes were also more likely to increase their positive smoking expectancies (such as beliefs that smoking would make them more confident, help them relax and reduce boredom) and were more likely to become friends with smokers and subsequently try smoking. However, with only 1-year follow-up these studies were not able to determine whether changes in expectancies or affiliations preceded smoking. Further research on this topic is required over longer follow-up periods.

Schneider and Diehl have outlined a 'catalyst model' of e-cigarette influence on smoking uptake in adolescence.[30] This is intended as an alternative to 'gateway theory'[31 32] as an explanation of the relationship between e-cigarette and tobacco use. They break the process down into two stages: factors influencing transition from 'no use' to 'e-cigarette use' and then the factors influencing the second stage of transition from 'e-cigarette use' to 'tobacco use'. The first-stage mechanisms include easing the process of initial trial, for example, with sweet flavours. The second-stage mechanisms include increased accessibility and learning of smoking rituals. Thus, there are a number of paths within the catalyst model whereby e-cigarette use, even single trial, might facilitate smoking uptake. There are also pathways by which e-cigarettes could mitigate against a transition to regular smoking. For those young people who are curious to try the performative aspects of smoking (the hand to mouth action and inhalation process), the act of trying e-cigarettes may result in lower motivation to try tobacco smoking.

Levy and colleagues have modelled the public health impacts of e-cigarettes and estimate that under a range of conditions, e-cigarettes may have a positive net impact on public health at a population level because of the greater benefits conferred on smokers relative to the potential harm to young people.[33] Further studies could usefully examine e-cigarette use, smoking and smoking-related attitudes over longer time periods to determine the conditions under which e-cigarettes enhance adult quit rates without facilitating uptake in young people.

The importance of research findings about the relationship between e-cigarette use and smoking initiation has been debated on the basis that most e-cigarette use among young people is occasional and therefore unlikely to be directly harmful or be sufficient to influence other behaviours. However, some argue that the influence of e-cigarette experimentation may be psychosocial rather than chemical; it has been suggested that e-cigarettes '(convey) to young apprehensive would-be smokers that nicotine is a benign drug and potentially weaken the established message that smoking kills'.[34] E-cigarette advertising has emphasised the commonalities between the products with the message that e-cigarettes can give the psychological and social benefits of smoking without the health or social costs.[35] There are some signs that these messages confuse young people about the harms of smoking. For example, a recent study found that after viewing an e-cigarette advert young people were more likely to rate occasional cigarette smoking as less harmful.[36]

At the time this research was conducted there were no legal restrictions on sales or advertisement of e-cigarettes. However, in the UK e-cigarettes are now banned from sale to people under 18[37 38] and advertising on television, print media and radio is prohibited under the Tobacco Products Directive and associated UK regulations,[39 40] although at present point-of-sale marketing is still permitted. It will be important to ascertain if this legislation is sufficient to prevent or reduce the numbers of young people trying e-cigarettes.

Strengths and limitations

The strengths of this study are its prospective design, large sample and high response and follow-up rates. Importantly, the multiple imputation models indicate that model estimates are not biased by missing data. However, there are a number of limitations. First, most of the young people whom we categorised as having initiated smoking may have only taken one or two puffs of a cigarette during the follow-up period. Therefore, we do not know whether any of these young people will transition to regular smoking. Transition from never-smoker to smoker is often conceptualised as a multistep pathway.[41–43] Recent research suggests that any experimentation with cigarettes is a strong predictor of transition to regular smoking, with experimentation at baseline identifying two-thirds of regular smokers at 2-year follow-up with a false positive rate of only 8%.[44]

Second, participants were drawn from only four schools in Scotland and therefore may not be representative of the Scottish school population. However, comparison of the demographic characteristics of our sample with a nationally representative one does not indicate any significant deviation.[45] Third, the study is based on self-reports and we do not yet know the reliability of young people's self-reported use of e-cigarettes.

The age range of the sample (11–18 years) is broader than in some other research in this area. Therefore, we split our sample in half by age and repeated the analysis on the split samples. The results we obtained were the same and are presented in the online supplementary materials.

Finally, although we have used validated measures of smoking susceptibility, they were developed more than 20 years ago and there may be other aspects of common liability to tobacco and e-cigarette use that are not assessed by existing measures of susceptibility.

CONCLUSIONS

This UK longitudinal study found that young never-smokers who try e-cigarettes are at elevated risk of initiating smoking compared with young never-smokers who do not try e-cigarettes. Further research with longer follow-up is required to discover how many of the full sample of young people, if any, transition to regular smoking and to explore the longitudinal relationship between use of e-cigarettes and changes in attitudes to smoking. Careful and regular monitoring of smoking rates and e-cigarette use among young people is necessary over the

What this paper adds

- Eight prospective studies in the USA have reported a temporal relationship between trying an e-cigarette and subsequent experimentation with cigarettes.
- Consistent with the US studies, this study indicates a positive relationship between e-cigarette use in never smokers and their subsequent first experimentation with cigarettes by follow-up 1 year later.
- This UK study found that e-cigarette use had a greater impact on the odds of cigarette experimentation in young never smokers not traditionally thought to be high risk, that is, those with a firm intention not to smoke and/or no smokers in their friendship group.

coming years. This needs to be set within the context of the rapidly changing landscape of tobacco and nicotine product availability, recent changes in the regulation of advertising and strategies used by industry, particularly the tobacco industry, to promote these products.

Contributors CB conducted the analysis and wrote the first draft of the paper, DC, GO and FH managed the administration of the school survey, data cleaning and analysis and commented on the development of the paper, DE, MS, AMMK, JP, AA, AM and JF were coinvestigators responsible for devising the overall study design and commented on the development of the paper, SH is principal investigator for the DISPLAY study and was involved in devising the overall study, drafting and revising this paper and is its guarantor.

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Tobacco aside, e-cigarette flavorings may harm blood vessels

sciencedaily.com/releases/2018/06/180614095240.htm

Flavor additives used in electronic cigarettes and related tobacco products could impair blood vessel function and may be an early indicator of heart damage, according to new laboratory research in *Arteriosclerosis, Thrombosis and Vascular Biology*, an American Heart Association journal.

The health effects of "combustible" tobacco products including traditional cigarettes and hookah are well-established, but the potential dangers of e-cigarettes have not yet been extensively studied. E-cigarettes are battery-powered devices that heat a liquid -- including tobacco-derived nicotine, flavoring and other additives -- and produce an aerosol that is inhaled.

Nine chemical flavorings -- menthol (mint), acetylpyridine (burnt flavor), vanillin (vanilla), cinnamaldehyde (cinnamon), eugenol (clove), diacetyl (butter), dimethylpyrazine (strawberry), isoamyl acetate (banana) and eucalyptol (spicy cooling) -- which are widely used in e-cigarettes, hookah, little cigars and cigarillos were tested for their short-term effects on endothelial cells, the cells which line the blood vessels and the inside of the heart.

Researchers found all nine flavors were dangerous to cells in the laboratory at the highest levels tested and all the flavorings impaired nitric oxide production in endothelial cells in culture (outside of the body). Several of the flavorings -- menthol, clove, vanillin, cinnamon and burnt flavoring -- resulted in higher levels of an inflammatory marker and lower levels of nitric oxide, a molecule that inhibits inflammation and clotting, and regulates vessels' ability to widen in response to greater blood flow.

"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," said lead study author Jessica L. Fetterman, Ph.D., assistant professor of medicine at Boston University School of Medicine in Massachusetts. "Our findings suggest that these flavoring additives may have serious health consequences."

Endothelial cells were collected from volunteers (nine non-smokers/non-e-cigarette users; six non-menthol and six menthol cigarette smokers) and tested in the lab. Researchers found that both groups of smokers had a similar deficit in nitric oxide production when stimulated by a chemical called A23187. Nonsmokers' cells that were treated with menthol or a clove flavoring also had impaired nitric oxide production, suggesting those flavorings cause damage like that found in active smokers.

The team also exposed commercially-available human aortic endothelial cells to the flavorings. Burnt flavor, vanilla, cinnamon and clove flavors impaired nitric oxide production and boosted an inflammatory chemical called interleukin-6 (IL-6) at all concentrations tested, suggesting the endothelium is particularly sensitive to these flavors.

Menthol applied to the cells increased IL-6 at high concentrations and reduced nitric oxide even at low doses. In smokers, scientists don't see differences in heart disease between menthol and non-menthol users -- probably because cigarette smoke is overwhelmingly toxic, Fetterman said. "But menthol is certainly not a benign player, based upon our work."

At the highest levels tested, all nine chemicals caused cell death, while at lower levels cinnamon, clove, strawberry, banana and spicy cooling flavor did. Dimethylpyrazine/strawberry flavor had that effect even at very low levels, suggesting endothelial cells are especially sensitive to it. Vanillin and eugenol also increased oxidative stress in the cells.

Three flavorings were tested when heated, to mimic what happens in e-cigarettes. Nitric oxide production was impaired with vanillin and eugenol, but not with menthol.

"Our work and prior research have provided evidence that flavorings induce toxicity in the lung and cardiovascular systems. Flavorings are also a driver of youth tobacco use and sustained tobacco use among smokers," Fetterman said.

A key strength of the new research was that it directly tested effects of just the flavorings, at levels likely to be reached in the body. Limitations include the fact that testing did not heat all the flavorings or include other chemicals used in e-cigarettes. Also, the study gauged just the flavorings' short-term effects and captured these with cells outside the body, not inside.

"We still don't know what concentrations of the flavorings make it inside the body," Fetterman said.

Most adult e-cigarette users are current or former combustible cigarette smokers who may use e-cigarettes as an aid in smoking cessation or as a harm-reduction tool. In addition, e-cigarette use by youth is rising rapidly with 37 percent of high schoolers reporting they have had an e-cigarette in 2015. Flavored tobacco products are a major driver of experimentation among youth.

The American Heart Association cautions against the use of e-cigarettes, stating that e-cigarettes containing nicotine are tobacco products that should be subject to all laws that apply to these products. The Association also calls for strong new regulations to prevent access, sales and marketing of e-cigarettes to youth, and for more research into the product's health impact.

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1. 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, Naomi M. Hamburg. **Flavorings in Tobacco Products Induce Endothelial Cell Dysfunction**. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 2018; ATVBAHA.118.311156 DOI: 10.1161/ATVBAHA.118.311156

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