RESEARCH REPORT

ADDICTION   SSA

Association of quarterly prevalence of e-cigarette use with ever regular smoking among young adults in England: a time–series analysis between 2007 and 2018

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Abstract

Aims: To assess how changes in the prevalence of e-cigarette use among young adults have been associated with changes in the uptake of smoking in England between 2007 and 2018.

Design: Time–series analysis of population trends with autoregressive integrated moving average with exogeneous input (ARIMAX models).

Setting: England.

Participants: Data were aggregated quarterly on young adults aged 16–24 years (n = 37 105) taking part in the Smoking Toolkit Study.

Measures: In the primary analysis, prevalence of e-cigarette use was used to predict prevalence of ever regular smoking among those aged 16–24. Sensitivity analyses stratified the sample into those aged 16–17 and 18–24. Bayes' factors and robustness regions were calculated for non-significant findings [effect size beta coefficient (B) = 3.1].

Findings: There was evidence for no association between the prevalence of e-cigarette use and ever regular smoking among those aged 16–24 [B = –0.015, 95% confidence interval (CI) = –0.046 to 0.016; P = 0.341; Bayes factor (BF) = 0.002]. Evidence for no association was also found in the stratified analysis among those aged 16–17 (B = 0.070, 95% CI –0.014 to 0.155, P = 0.102; BF = 0.015) and 18–24 (B = –0.021, 95% CI –0.053 to 0.011; P = 0.205; BF = 0.003). These findings were able to rule out percentage point increases or decreases in ever regular smoking prevalence greater than 0.31% or less than –0.03% for 16–17-year-olds and 0.01 or –0.08% for 18–24-year-olds for every 1%-point increase in e-cigarette prevalence.

Conclusion: Prevalence of e-cigarette use among the youth population in England does not appear to be associated with substantial increases or decreases in the prevalence of smoking uptake. Small associations cannot be ruled out.

KEYWORDS
ARIMAX, e-cigarettes, England, smoking, Smoking Toolkit Study, time–series

INTRODUCTION

Policymakers have cited a gateway from e-cigarette use to cigarette smoking as a key motivation for various regulations to heavily restrict e-cigarettes. For example, India announced an executive order in 2019 to ban the production, import and sale of electronic cigarettes, in part due to the argument that 'when used by never smokers, these devices can be a gateway for cigarette smoking and other drug use' [1]. The US Food and Drug Administration (FDA) announced a ban on non-tobacco-flavoured products saying that 'we will not stand idly by as [e-cigarettes] become an on-ramp to combustible cigarettes' [2]. However, there remains academic debate on whether there is good evidence that e-cigarettes act as a gateway into smoking [3–5].

Longitudinal observational studies show that there is a strong association between initiation of e-cigarette use and later use of cigarettes, including among people who have never smoked [6–8]. However, these findings may reflect a common liability whereby people with characteristics or a social environment that make them susceptible to use e-cigarettes are also more likely to smoke cigarettes later [9].

One way to rule out this self-selection bias is with a randomized controlled trial. However, it is unethical and impracticable to allocate never smokers to e-cigarette or no e-cigarette use. Population time–series data offer an alternative option. These can rule out such selection bias, as analyses are at the population rather than individual level [10–12]. Time–series analysis can assess the gateway effect by looking at the association between the prevalence of e-cigarette use among young adults with uptake of smoking generally and among never smokers in particular. If gateway effects existed, we would expect that an increase in e-cigarette prevalence would be associated with an increase in the prevalence of smoking uptake. Time–series models are particularly suited to address this question. First, time–series models go beyond simple correlation and assess the extent to which the past prevalence of a series (e.g. e-cigarette use) can forecast the future prevalence of another series (e.g. smoking uptake) [13, 14]. Secondly, population-level time–series analysis has the advantage of estimating directly the net population-level effect of e-cigarettes. For example, a gateway could act through e-cigarette use by an individual leading them to start smoking, but could also occur if the promotion and presence of e-cigarettes on the UK market re-normalizes smoking. This effect could only be detected at a population level. The recent increases in the use of e-cigarettes by young people provides a useful natural experiment [15].

This study used time–series analysis to assess if a gateway effect exists at a population level by determining if there is any association between the prevalence of current use of e-cigarettes with prevalence of ever regular smoking (as a measure of uptake) among those aged 16–24 years in England. To our knowledge, this is the first study to use a time–series methodology to address this question and follows a call for methodological triangulation to draw causal inference regarding gateway effects [16].

METHODS

Sample size

The sample size of this study meets previous requirements of at least 50 time–points and at least 2 years of data collection to account for seasonality [17]. We have shown previously, using power simulations, that the Smoking Toolkit Study (STS) data set in England has 80% power to detect a 0.1% in smoking behaviour as a consequence of a 1% change in e-cigarette prevalence [18].

Design

Data on the explanatory and outcome variables come from the STS. The STS is a monthly survey of a representative sample of the population in England aged 16+ [19]. The STS was established in 2006 and involves monthly household surveys using a form of random location sampling, with initial random selection of grouped output areas (containing $\sim$ 300 households), stratified by socio-demographic characteristic and region. Interviewers then select houses within these areas that are most likely to fulfil quotas and conduct face-to-face computer-assisted interviews with one member per household. The quotas are tailored to the output area and the probability of certain groups being at home. Participants from the STS appear to be representative of the population in England, having similar socio-demographic composition as other large national surveys, such as the Health Survey for England, and comparisons with sales data suggest representative estimates of cigarette consumption [20]. Data on the covariate mass media expenditure were obtained from Public Health England and the affordability index calculated using data from the Office for National Statistics and the STS [21].

Measures

Output variable: prevalence of ever regular smoking among 16–24-year-olds

Ever regular smoking among 16–24-year-olds is a widely used indicator of uptake [22–25]. While the ever-smoking rate in young adults in a given quarter does not provide a direct and absolute measure of uptake in that quarter, changes in this figure quarter on quarter provide a population-level indication of changes in uptake. Uptake after the age of 24 is rare, so ever regular smoking up to this age should capture almost all uptake [22, 26]. The prevalence of ever regular smoking was calculated as the proportion of all participants aged 16–24 who reported that they smoked cigarettes (including hand-rolled) every day; that they smoked cigarettes (including hand-rolled), but not every day; that they did not smoke cigarettes at all, but smoked tobacco of some kind (e.g. cigar); that they have stopped smoking completely in the last year; or that they had stopped smoking completely more than a year ago. Those counted as never smokers responded: 'I have never been a smoker (i.e. smoked for a year or more)'.

Input variable: prevalence of e-cigarette use among 16–24-year-olds

Participants who reported that they smoked cigarettes were then asked the following questions, with one of the response options being e-cigarettes:

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?'

Current smokers and those who had stopped smoking in the last year (past-year smokers) were also asked:

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 other participants (non-smokers) were asked:

4. 'Can I check, are you using any of the following?'

Prevalence of use of e-cigarettes was obtained for each quarter by counting the number of respondents who answered 'electronic cigarette' in response to any of the four questions above, divided by the total sample size in that quarter. As a sensitivity analysis, we also include the prevalence of e-cigarette use among never smokers as an input variable. This was obtained for each quarter by counting the number never smokers who answered 'electronic cigarettes', divided by the total sample size in that quarter of never smokers.

Data on covariates

A number of tobacco control policies were adjusted for in the analyses using a composite score, coded as 0 when no policies were present and 1 for the quarter when policies were present (reflecting a pulse effect). These include the move in commissioning of stop smoking services to local authorities in April 2013 [27], introduction of a smoking ban in July 2007 [28], licensing of nicotine replacement therapy (NRT) for harm reduction in December 2009 [29], change in the minimum age of sale of cigarettes October 2007 [30] and the tobacco products directive/plain packaging in May 2016 [31]. An affordability index was derived using a modified formula published by the Office for National Statistics [21, 32]: $\frac{adjusted\ real\ households'\ disposable\ income\ index}{weekly\ tobacco\ expenditure\ index} \times 100$.

An affordability index greater than 100 in a given quarter signifies that cigarettes were more affordable than in the first quarter of 2007 [33].

Monthly tobacco mass media expenditure (in £million) was also adjusted for and was obtained from Public Health England. Total spending on campaigns was calculated for each quarter and included spending on 'Smokefree' campaigns, Stoptober campaigns and Health Harms campaigns. Spend included TV, radio, print, cinema and on-line advertisements.

Missing data

Prevalence of e-cigarette use among never and long-term ex-smokers was only available from October 2013. As use in these groups was extremely rare immediately after October 2013, it was assumed that use before October 2013 was zero.

Data were also only available on the prevalence of use of e-cigarettes among smokers from April 2011. Prevalence of e-cigarette use between January 2007 and April 2011 was assumed to be 0.1% of smokers based on other surveys [34]. Two waves of data were collected in March 2007; these were combined. No data were collected in December 2008. Variables during this period were calculated as an average of the quarter before and the quarter after. Data on e-cigarette use among past-year smokers were not recorded for 6 months (May 2012, July 2012, September 2012, November 2012, January 2013, March 2013). Quarters covering these months were estimated instead based on available months.

Analysis

The analysis plan (see on-line Supporting information) and data set were pre-registered on the Open Science Framework (https://osf.io/8b7pr). One major amendment was the exclusion of affordability as a covariate due to evidence of high multi-collinearity and model instability when it was included in the models. Results including affordability can be found in the Supporting information for affordability. In Supporting information, Table S1a a lag of one is used for mass media, and in Supporting information, Table S1b no lag is used. Comparison of transfer functions using the Aikaike information criterion (AIC) showed that a lag of one provided the best model fit. Supporting information, Table S2 shows that including affordability did not increase model fit substantially. The analysis plan also stated that we would use data from November 2006 when the STS was established, but this was changed to January 2007 when data on mass media spend first became available. All data were analysed in R and aggregated quarterly. Strengthening the reporting of observational studies in epidemiology (STROBE) guidelines were followed [35]. All analyses were two-tailed, reflecting the null hypothesis that the association between e-cigarette use and smoking behaviour could be positive or negative.

Primary analysis

The primary analysis focused upon the association between e-cigarette prevalence and ever regular smoking prevalence among those aged 16–24 years, with an additional stratified analysis with those aged 16–17 and 18–24. Autoregressive integrated moving

average with exogeneous input (ARIMAX) analysis was used to assess the association between changes in the prevalence of e-cigarette use and prevalence of ever regular smoking as a measure of uptake. Standard recommended procedures were followed. This included assessing the series for outlying values and the presence of exogeneity using the Granger causality test. Unit root tests, the cross-correlation function and the autocorrelation function were used to identify the level of differencing, specification of the transfer function (lags between the series) and the presence of autoregressive and moving average autocorrelation.

Bayes factors were calculated for non-significant findings. Bayes factors help to determine if there is evidence for the null hypothesis of no difference or if the data are insensitive to detect an effect. This approach requires the specification of an expected effect size (i.e. a plausible range of predicted values based on previous studies, judgement or clinical significance), the published effect size (e.g. risk difference) and standard error of this parameter. It assumes that the sampling distribution of the parameter estimate is Gaussian. The expected effect size used in the Bayes factor calculation was derived from a recent meta-analysis of seven cohort studies in youths (B = 3.1) [8]. A Gaussian distribution was specified where the population parameter values close to the mean are assumed to be more plausible than others. A default standard deviation of mean/2 is often used. Bayes factors are interpreted based on Jeffreys' cut-offs, which indicate the strength of evidence for or against the null hypothesis [36]. We also calculated a robustness region for each Bayes factor.

Sensitivity analysis: robustness of data assumptions

We conducted several sensitivity analyses to test the robustness of two different data assumptions. In the primary analysis, we assumed that e-cigarette use among respondents who were never smokers and long-term ex-smokers was zero before October 2013. In the first sensitivity analysis, we adjusted the ARIMAX model for a step level change in October 2013. Next, we used a ratio of use among long-term ex-smokers and never smokers versus past-year smokers for the first year of assessment to adjust the prevalence prior to October 2013. Another assumption for the primary analysis was that prevalence of e-cigarette use between January 2007 and April 2011 was 0.1%, when questions on e-cigarettes were not asked of anyone. In sensitivity analyses we instead (a) assumed a linear function starting at close to zero from 2007 and (b) used Kalman smoothing for univariate time–series to impute the values.

Sensitivity analysis: prevalence among never smokers and ever regular smoking

The next sensitivity analysis involved restricting the input variable to e-cigarette prevalence among never smokers to provide a more stringent test of the on-ramp gateway hypothesis.

Sensitivity analysis: feedback from prevalence of ever regular smoking

Due to evidence of violation of the assumption of weak exogeneity for affordability, and it being theoretically plausible that ever regular smoking may affect prevalence of e-cigarette use, additional structural time–series models known as structural vector autoregression (SVAR) were run.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research directly to study participants or any specific patient community.

Ethical approval

Ethical approval for the STS was granted by the UCL ethics committee (ID 0498/001). Ethical approval was not required for use of data from stop smoking services, as the data are publicly available. Data sets are available on the Open Science Framework (https://osf.io/8b7pr).

RESULTS

Data were collected on 37 105 participants aged 16–24 between January 2007 and December 2018. Of these, 30.5% [95% confidence interval (CI) = 30.0–31.0] were ever regular smokers and 27.4% (95% CI = 27.0–27.9) were past-year smokers. Table 1 and Fig. 1 show the descriptive statistics for the time–series.

Primary analysis

There was evidence of no association between the prevalence of e-cigarette use and ever regular smoking among those aged 16–24 in both the unadjusted (B = −0.013, 95% CI = −0.046 to 0.021, P = 0.461; BF = 0.022) and adjusted models B = −0.015, 95% CI = −0.046 to 0.016, P = 0.341; BF 0.002) (see Tables 2 and 3). Bayes factor robustness regions suggest that the null hypothesis was more likely than, on average, a 1% percentage point increase in the prevalence of e-cigarette use being associated with more than a 0.014 percentage point increase in ever regular smoking among 16–24-year-olds. Conversely, negative associations less than −0.058 could be ruled out.

After stratifying the results for those aged 16–17 and 18–24, there was no association in the unadjusted and adjusted sensitivity analysis between prevalence of e-cigarette use and ever regular

TABLE 1 Mean, standard deviation (SD), 95% confidence interval (CI) start and end values of the time–series (per quarter) for prevalence of e-cigarette use and ever regular smoking prevalence

Time–series	Mean	SD	95% CI Lower	95% CI Upper	Start	End
Primary analysis						
E-cigarette prevalence aged 16–24	2.9	2.7	2.1	3.7	0.1	5.0
Ever regular smoking prevalence aged 16–24	30.5	3.9	29.4	31.6	38.8	24.9
Sensitivity analysis						
E-cigarette prevalence aged 16–17	1.8	2.2	1.2	2.4	0.1	3.6
Ever regular smoking prevalence aged 16–17	16.9	5.6	15.3	18.5	29.3	15.4
E-cigarette prevalence aged 18–24	3.1	2.8	2.3	3.9	0.1	5.1
Ever regular smoking prevalence aged 18–24	32.9	4.3	31.7	34.1	40.9	25.8
E-cigarette prevalence aged 16–24 with ratio correction for missing data	3.0	2.7	2.2	3.8	0.1	5.0
E-cigarette prevalence aged 16–24 with linear function for missing data	3.0	2.6	2.3	3.7	0.0	5.0
E-cigarette prevalence aged 16–24 with Kalman smoothing for missing data	3.2	2.4	2.5	3.9	0.8	5.0
E-cigarette prevalence aged 16–24 among never smokers	0.2	0.2	0.1	0.3	0.1	1.0
E-cigarette prevalence aged 16–17 among never smokers	0.3	0.7	0.1	0.5	0.1	3.4
E-cigarette prevalence 18–24 among never smokers	0.2	0.2	0.1	0.3	0.1	0.7

FIGURE 1 Prevalence of ever regular smoking and e-cigarette use over the study period among those aged 16–24 years
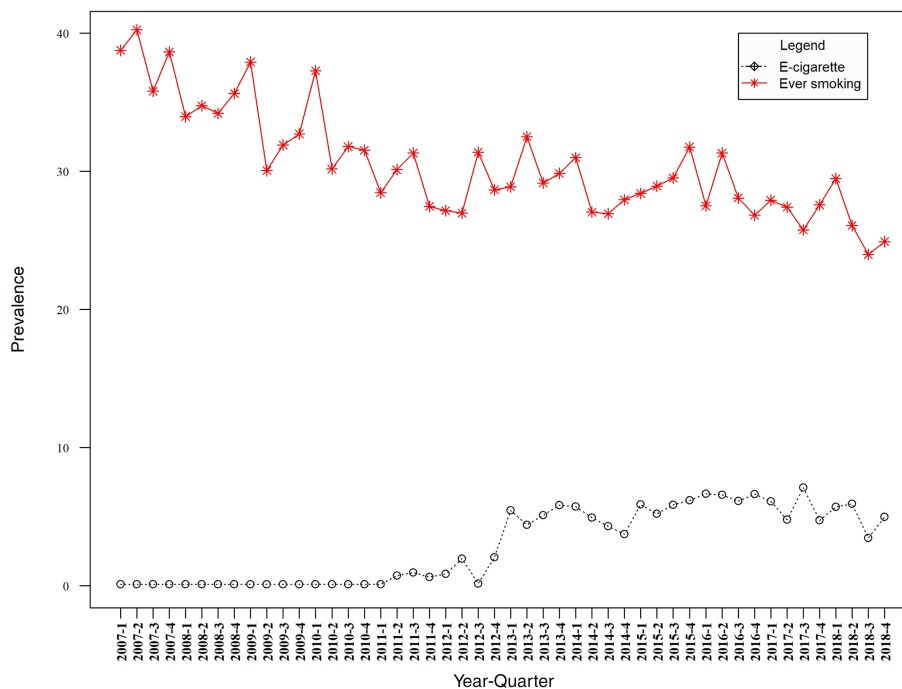
smoking among these (see Tables 2 and 3). Bayes factor robustness regions suggest that the null hypothesis was more likely than, on average, a 1% increase in the prevalence of e-cigarette use being associated with more than a 0.310 percentage point increase in ever regular smoking among 16–17-year-olds and a 0.013 percentage point increase in ever regular smoking among 18–24-year-olds. Conversely, respective negative associations less than −0.028 and −0.080 percentage points could also be ruled out.

Sensitivity analysis: testing the robustness of data assumptions

Similar findings were found for the association between e-cigarette prevalence among 16–24-year-olds and ever regular smoking prevalence when additionally adjusting for a step level change in October 2013 ($B_{adjusted}$ = −0.010, 95% CI= −0.035 to 0.014; P = 0.411). Using a ratio of use among long-term ex-smokers and

TABLE 2 Primary analysis—unadjusted estimated percentage point changes in ever regular smoking prevalence as a function of e-cigarette prevalence, based on autoregressive integrated moving average with exogeneous input (ARIMAX)

	Unadjusted								
	Prevalence of ever regular smoking, aged 16–24			Prevalence of ever regular smoking, aged 16–17			Prevalence of ever regular smoking, aged 18–24		
	Percentage change per 1% change in the exposure	95% CI	P-value	Percentage change per 1% change in the exposure	95% CI	P-value	Percentage change per 1% change in the exposure	95% CI	P-value
Prevalence of current e-cigarette use aged 16–24	−0.013	−0.046 to 0.021	0.461						
Prevalence of current e-cigarette use aged 16–17				0.077	−0.006 to 0.159	0.068			
Prevalence of current e-cigarette use aged 18–24							−0.018	−0.052 to 0.016	0.301
Model	ARIMA (0, 1, 1) (0, 0, 0)$_4$			ARIMA (0, 1, 1) (0, 0, 0)$_4$			ARIMA (0, 1, 1) (0, 0, 0)$_4$		
Adjusted R-squared	0.66			0.37			0.62		
Bayes factor (robustness region)	0.002 (−∞ to −0.052 ∪ 0.018 to ∞)			0.022 (−∞ to −0.025 ∪ 0.400 to ∞)			0.003 (−∞ to −0.065 ∪ 0.015 to ∞)		

CI = confidence interval.

never smokers versus past-year smokers for the first year of assessment to adjust the prevalence prior to October 2013 also did not meaningfully change the findings ($B_{unadjusted}$ = −0.010, 95% CI = −0.048 to 0.027; P = 0.579; $B_{adjusted}$ = −0.014, 95% CI = −0.049 to 0.020; P = 0.415).

Similar estimates were found using different assumptions for missing data between January 2009 and April 2011. When assuming a linear function, there was no significant association between prevalence of e-cigarettes and prevalence of ever regular smoking among those aged 16–24 ($B_{unadjusted}$ = −0.016, 95% CI = −0.041 to 0.009; P = 0.203; $B_{adjusted}$ = −0.017, 95% CI = −0.041 to 0.006; P = 0.143). The same was true when Kalman smoothing was used to impute values ($B_{unadjusted}$ = −0.012, 95% CI = −0.055 to 0.032; P = 0.597; $B_{adjusted}$ = −0.013, 95% CI = −0.054 to 0.027; P = 0.515).

Sensitivity analysis: e-cigarette prevalence among never smokers and ever regular smoking

There was no significant association between prevalence of e-cigarette use and ever regular smoking among those aged 16–24 when e-cigarette use was restricted to never smokers ($B_{unadjusted}$ = −0.017, 95% CI = −0.057 to 0.0023; P = 0.394; $B_{adjusted}$ = −0.019, 95% CI = −0.057 to 0.019; P = 0.321). Prevalence of e-cigarette use among never smokers was also not associated with prevalence of ever regular smoking either among those aged 16–17 ($B_{unadjusted}$ = 0.052, 95% CI = −0.044 to 0.147; P = 0.288; $B_{adjusted}$ = 0.055, 95% CI = −0.041 to 0.151; P = 0.262) or those aged 18–24 ($B_{unadjusted}$ = −0.034, 95% CI = −0.081 to 0.013; P = 0.155; $B_{adjusted}$ = −0.036, 95% CI = −0.081 to 0.009; P = 0.116).

Sensitivity analysis: accounting for feedback from prevalence of ever regular smoking

In the unadjusted and adjusted SVAR models (see Table 4 and Supporting information, Table S3), there was an immediate effect (short-term impact) of the prevalence of e-cigarette use among those aged 16–17 on ever regular smoking prevalence in the same age group. The impulse response function (IRF) can be interpreted as a 1% increase in the prevalence of e-cigarette use being associated with an immediate 0.097 percentage point increase in the prevalence of ever regular smoking. There were no significant associations between prevalence of e-cigarettes and ever regular smoking for those aged 16–24 and 18–24.

The results of running SVAR models on the data over a 4-quarter period (1 year) for those aged 16–17 are presented in eFigs 1 and 2 in the Supporting information and illustrate both the contemporaneous and cumulative impacts for the unadjusted and adjusted models, respectively.

TABLE 3 Primary analysis—adjusted estimated percentage point changes in ever regular smoking prevalence as a function of e-cigarette prevalence, based on autoregressive integrated moving average with exogeneous input (ARIMAX)

Adjusted									
	Prevalence of ever regular smoking aged 16–24			Prevalence of ever regular smoking aged 16–17			Prevalence of ever regular smoking aged 18–24		
	Percentage change per 1% change in the exposure	95% CI	P-value	Percentage change per 1% change in the exposure	95% CI	P-value	Percentage change per 1% change in the exposure	95% CI	P-value
Prevalence of current e-cigarette use aged 16–24	-0.015	-0.046 to 0.016	0.341						
Prevalence of current e-cigarette use aged 16–17				0.070	-0.014 to 0.155	0.102			
Prevalence of current e-cigarette use aged 18–24							-0.021	-0.053 to 0.011	0.205
Tobacco control mass media spend	0.018	-0.001 to 0.038	0.069	-0.004	-0.084 to 0.077	0.930	0.020	-0.002 to 0.042	0.080
	Total change due to the exposure	95% CI	P-value	Total change due to the exposure	95% CI	P-value	Total change due to the exposure	95% CI	P-value
Tobacco control policies	0.061	0.001 to 0.121	0.047	0.086	-0.171 to 0.343	0.512	0.054	-0.015 to 0.123	0.122
Model	ARIMA (0, 1, 1) (0, 0, 0)$_4$			ARIMA (0, 1, 1) (0, 0, 0)$_4$			ARIMA (0, 1, 1) (0, 0, 0)$_4$		
Adjusted R-squared	0.70			0.38			0.65		
Bayes factor (robustness region)	0.022 (−∞ to −0.058 ∪ 0.014 to ∞)			0.015 (−∞ to −0.028 ∪ 0.310 to ∞)			0.003 (−∞ to −0.080 ∪ 0.013 to ∞)		

CI = confidence interval.

TABLE 4 Unadjusted estimated percentage point changes in ever regular smoking prevalence as a function of e-cigarette prevalence, based on structural vector autoregression (SVAR)

	Prevalence of ever regular smoking aged 16–24			Prevalence of ever regular smoking aged 16–17			Prevalence of ever regular smoking, aged 18–24		
	IRF Percentage change per 1% change in the exposure	95% CI	P-value	IRF Percentage change per 1% change in the exposure	95% CI	P-value	IRF Percentage change per 1% change in the exposure	95% CI	P-value
Unadjusted									
Prevalence of current e-cigarette use aged 16–24	−0.010	−0.044 to 0.049	0.674						
Prevalence of current e-cigarette use aged 16–17				0.092	0.026 to 0.199	0.036			
Prevalence of current e-cigarette use aged 18–24							−0.015	−0.064 to 0.051	0.619
Adjusted									
Prevalence of current e-cigarette use aged 16–24	−0.007	−0.044 to 0.053	0.786						
Prevalence of current e-cigarette use aged 16–17				0.097	0.013 to 0.205	0.048			
Prevalence of current e-cigarette use aged 18–24							−0.010	−0.059 to 0.058	0.746

CI = confidence interval; IRF = impulse response function.

DISCUSSION

Principal findings

The increase in prevalence of e-cigarette use in England among the entire sample does not appear to have been associated with an increase in the uptake of smoking among young adults aged 16–24. In stratified analyses, large positive associations could also be ruled out for those aged 16–17 and 18– 24; however, sensitivity analyses using SVAR models could not rule out small positive associations for the youngest age group.

Strengths and limitations

This study made use of a large and unique long-standing monthly survey of smoking and e-cigarette use in England. We analysed the data set using time–series models, which are particularly well-suited to addressing our research question. We assessed the extent to which the past prevalence of the use of e-cigarettes was able to forecast the future prevalence of a measure of smoking uptake, and established that there was little evidence of reverse causality (smoking uptake forecasting e-cigarette use). By applying a time–series approach to population-level estimates, we were able to directly assess the net population-level effect of e-cigarettes on smoking uptake in England. Our study also had several limitations. First, this study only adjusted for combined pulse effects for the tobacco control policies. This decision was based on previous research evaluating policies which have often been unable to detect sustained prolonged effects, and because there were concerns about over-parameterization of the models. Secondly, the findings might not generalize to other countries. England has a strong tobacco control climate and a relatively liberal attitude towards e-cigarettes. Thirdly, as with all population-level surveys, there are issues with self-report, including forgetting and social desirability. A recent analysis demonstrated that STS data and sales data were closely aligned, with both showing that overall cigarette sales in England have declined by almost a quarter since 2011 [20]. Fourthly, there were differences in the results for the ARIMAX and SVAR models. Although some of this discrepancy lies in the ability of SVAR models to account for feedback from the output series to the input series, there are also important model specification differences. ARIMAX models often provide better adjustment for seasonality, as they use seasonal autocorrelation terms and adjust for autoregressive and moving average autocorrelation when specifying lags [17, 37]. Fifthly, this study attempted to assess the possible evidence for a gateway effect by looking at the association between e-cigarette use and ever regular smoking prevalence as a measure of smoking uptake. These time–series will not be affected by other important causal pathways of interest. For example, quitting smoking with the use of e-cigarettes is not captured by the ever regular smoking variable. This study therefore only assessed gateway effects on uptake, i.e. the extent to which e-cigarettes are associated with more or less people starting to smoke regularly, but does not assess any association with

quitting (even if people were stopping successfully with e-cigarettes they would still be reflected in estimates of ever regular smoking). The association with quitting has been assessed previously in another paper, with e-cigarette prevalence associated with an increased prevalence of successful quit attempts [38]. While this analysis shows no negative net public health impact for the promotion of e-cigarettes in this age group on uptake of smoking, it is therefore a conservative estimate of the potential benefits of e-cigarette use. Finally, this study defined ever regular smoking as those using cigarettes either daily or non-daily. This is consistent with other youth surveys in the United Kingdom (e.g. YouGov commissioned by Action on Smoking and Health and the Annual Government Survey). However, internationally there is wide variability and little consensus over the definition of regular smoking [39]. It will be important in future studies to consider the implications of this, perhaps through stratification by daily versus non-daily smoking.

Comparison with other studies and policy implications

The findings from this study contribute to the debate on whether e-cigarettes could act as a gateway into smoking [3–5, 40], and are consistent with a recent population time trend analysis which showed a reduction in smoking initiation during the period of e-cigarettes ascendance in the United States [41]. Although previous longitudinal observational studies show that there is a strong association between initiation of e-cigarette use and later use of cigarettes [6–8], these findings may reflect a common liability whereby people with characteristics or a social environment that make them susceptible to use e-cigarettes are also more likely to smoke cigarettes later [9, 42]. These findings are important, given the contrasting advice given by health bodies and governments in different countries. For example, Public Health England aim to minimize these risks while maximizing the public health opportunity for adult smokers to quit [43]. In contrast, the United States appears primarily focused upon what they judge to be an epidemic of youth e-cigarette use, which threatens to engulf a new generation in nicotine addiction [44]. Research to date supports the argument that e-cigarettes are less harmful than tobacco use, but probably cause some harm relative to never use [4, 15].

If a gateway effect exists, our results suggest that it is likely to be smaller than estimated previously [8]. If there has been a population-level association in England, changes in e-cigarette prevalence by 1% were probably associated with changes of ever regular smoking prevalence of less than 0.310 and 0.013 percentage points for 16–17- and 18–24-year-olds, respectively.

In some of the sensitivity analyses, there was a small positive association between e-cigarette prevalence and ever regular smoking prevalence among 16–17-year-olds. However, findings are not conclusive due to possible model instability, and it remains plausible that a third unmeasured confounding variable may simultaneously be driving up ever regular smoking prevalence and e-cigarette use in the population, creating an artificial association. For example, it may be

that increasing misperceptions around the harms of e-cigarettes are driving users into smoking [45]. Further, the most direct assessment of a gateway effect, i.e. between prevalence of e-cigarette use among never regular smoking adolescents and ever regular smoking, showed no significant association.

Nevertheless, in so far that it was causal, the size of the association (B = 0.097) from the sensitivity analyses, and it being evident only in the youngest age group, would translate to approximately 7200 additional ever regular smokers aged 16–17 in 2018 as a consequence of e-cigarette use. This is on the basis of assuming a prevalence of e-cigarette use of 5% in 2018 which equates to approximately 74 000 e-cigarette users aged 16–17 in the population (population size of those aged 16–17 ∼1490 000 for 2018; i.e. 1 490 000 × 0.05 × 0.097) [46]. This needs to be weighed against the 50 000–70 000 smokers who are estimated to quit smoking each year as a consequence of using e-cigarettes during a quit attempt [21]. These numbers are also much smaller than those proposed by previous evidence for gateway effects, which would have estimated an equivalent of 230 and 768 000 additional ever regular smokers aged 16–17 and 18–24, respectively [8].

CONCLUSION

This time–series analysis suggests that changes in prevalence of e-cigarette use among 16–24-year-olds in England does not appear to be associated with increases in the uptake of smoking in this age group. However, small associations cannot be ruled out, particularly for 16–17-year-olds.

AUTHOR CONTRIBUTIONS

Emma Beard: Conceptualization; formal analysis. **Jamie Brown:** Conceptualization. **Lion Shahab:** Conceptualization.

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