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RESEARCH ARTICLE

REVISED **Further investigation of gateway effects using the PATH study** [version 2; peer review: 1 approved, 2 approved with reservations, 1 not approved]

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Abstract

Background: Interest exists in whether youth e-cigarette use ("vaping") increases risk of initiating cigarette smoking. Using Waves 1 and 2 of the US PATH study we previously reported adjustment for vaping propensity using Wave 1 variables explained about 80% of the unadjusted relationship. Here data from Waves 1 to 3 are used to avoid over-adjustment if Wave 1 vaping affected variables recorded then.

Methods: Main analyses M1 and M2 concerned Wave 2 never smokers who never vaped by Wave 1, linking Wave 2 vaping to Wave 3 smoking initiation, adjusting for predictors of vaping based on Wave 1 data using differing propensity indices. M3 was similar but derived the index from Wave 2 data. Sensitivity analyses excluded Wave 1 other tobacco product users, included other product use as another predictor, or considered propensity for smoking or any tobacco use, not vaping. Alternative analyses used exact age (not previously available) as a confounder not grouped age, attempted residual confounding adjustment by modifying predictor values using data recorded later, or considered interactions with age.

Results: In M1, adjustment removed about half the excess OR (i.e. OR–1), the unadjusted OR, 5.60 (95% CI 4.52-6.93), becoming 3.37 (2.65-4.28), 3.11 (2.47-3.92) or 3.27 (2.57-4.16), depending whether adjustment was for propensity as a continuous variable, as quintiles, or the variables making up the propensity score. Many factors had little effect: using grouped or exact age; considering other products; including interactions; or using predictors of smoking or tobacco use rather than vaping. The clearest conclusion was that analyses avoiding over-adjustment explained about half the excess OR, whereas analyses subject to over-adjustment explained about 80%.

Conclusions: Although much of the unadjusted gateway effect results from confounding, we provide stronger evidence than previously of some causal effect of vaping, though doubts still remain about the

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Any reports and responses or comments on the article can be found at the end of the article.

completeness of adjustment.

Keywords

Cigarettes, Confounding, Over-adjustment, E-cigarettes, Gateway effects, Modelling, Propensity score

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REVISED **Amendments from Version 1**

Following comments made by the reviewers we have amended the original version of the paper in a number of ways. In the order of their appearance in the revised paper, the main changes can be summarized as follows:

- The methods section of the abstract now makes clearer the purpose of our Main Analyses.

- In the introduction, when discussing our first paper relating to the gateway effect, we show how many published papers we considered, and also refer to a recent meta-analysis by Khouja *et al.*

- At the end of the introduction we make the objectives of our work clearer.

- In the methods section, more detail is added to show how the analyses presented in the current paper relate to our earlier analyses based only on data from Waves 1 and 2 of the PATH study.

- In the discussion we have added a new paragraph starting "Other issues are possible biases…" comparing the youths considered in Main analysis M1 (Table 2) with those for whom no data on cigarettes were available at Wave 3 (mainly due to their not being followed-up), and with those who were followed up at Wave 3 but had missing data for some of the predictors. We also discuss why we did not consider more interactions of predictor variables than those we had considered originally.

- Later in the discussion a new paragraph starting "There have, by now…" comments on a number of other papers on the gateway effect based on the PATH study that have been published since the original version of our paper.

- Another new paragraph in the discussion starting "A question of interest…" estimates the extent to which an estimated gateway effect could affect the number of youths taking up cigarette smoking.

Any further responses from the reviewers can be found at the end of the article

Abbreviations

CI, confidence interval; OR, odds ratio; PATH, Population Assessment of Tobacco and Health.

Introduction

In youths, use of e-cigarettes ("vaping") has increased considerably in recent years in many countries (e.g. (Barrington-Trimis *et al.*, 2016; Best *et al.*, 2016; Miech *et al.*, 2019)). It is generally recognized that vaping significantly reduces exposure to harmful constituents compared to smoking (National Academies of Sciences Engineering and Medicine, 2018), so one might expect risks from vaping to be much lower (Nutt *et al.*, 2014). However, there are concerns about the rise in vaping. The concern of interest here is the possibility that vaping may encourage some individuals to start smoking who would otherwise not havedone so, often referred to as the "gateway" effect. The concern that vaping may act as a gateway into smoking was originally brought sharply into focus by a 2017 meta-analysis (Soneji *et al.*, 2017) which combined data from nine cohort studies in young people in the US which related previous vaping to later smoking initiation. It reported that, among never-smokers at

baseline, ever vaping at baseline strongly predicted initiating smoking in the next 6 to 18 months, with an odds ratio (OR) of 3.62 (95% confidence interval (CI) 2.42-5.41) after adjusting for various factors predictive of initiation. Similarly past 30-day vaping at baseline also predicted later 30-day cigarette use (OR 4.25, 95% CI 2.52-7.37).

We have previously published two papers relating to the gateway effect. Our first paper (Lee *et al.*, 2018) considered various general issues, including a detailed examination of cohort studies that have reported unadjusted and adjusted estimates of the effect, the nine considered in the 2017 meta-analysis (Soneji *et al.*, 2017), and six additional studies. It made a number of relevant points:

- The studies that reported that vaping significantly predicts initiation of smoking after adjusting for various other predictors used sets of predictors that were generally quite incomplete.

- Residual confounding arising from the predictors being inaccurately measured was not taken account of in any of the studies.

- Adjusting more precisely may have reduced the association substantially.

- Any true gateway effect would only alter smoking prevalence modestly.

- In youths in the US and UK in 2014–2016 smoking prevalence declined more rapidly than the preceding trend would predict, contrary to what might expect if any large gateway effect existed.

- Even given the existence of some gateway effect, the introduction of e-cigarettes would still likely reduce smoking-related mortality.

We note that a recent meta-analysis (Khouja *et al.*, 2020) based on 17 studies, 13 considered in our first paper (Lee *et al.*, 2018) and four more recent studies also pointed to weaknesses in the data, including "reliance on self-report measures of smoking history without biochemical verification", and noted that the findings did not provide evidence that the "strong consistent association … between e-cigarette use among non-smokers and later smoking" was not due "to shared common causes of both e-cigarette use and smoking".

Our second paper (Lee & Fry, 2019) described results of our own analyses, based on data from Waves 1 and 2 of the Population Assessment of Tobacco and Health (PATH) study, a nationally representative longitudinal cohort study in the United States of tobacco use and how it affects the health of people. Wave 1 was conducted from 12 September 2013 to 15 December 2014, with Wave 2 the first annual follow-up. For each Wave, data are available separately for Youths (aged 12–17 years) and Adults (aged 18+ years), the Youth data including some information from the parents. Publicly available data files include extensive information on use of various types of tobacco products and on a range of variables linked to initiation of tobacco. Note that where youths become

18 between successive Waves of the survey, their data will be available in the Adult data rather than the Youth data. Also, additional youths who were under 12 at the time of Wave 1 are added into the Youth data when they reach the age of 12 at a subsequent Wave.

In our main analyses we included youths who had never smoked cigarettes by Wave 1, and had data on smoking initiation by Wave 2. We constructed a propensity score for ever e-cigarette use using variables recorded at Wave 1 and found that adjustment reduced the unadjusted OR markedly, from 5.70 (95% CI 4.33-7.50) to 2.48 (1.85-3.31), 2.47 (1.79-3.42) or 1.85 (1.35-2.53), whether adjustment was made using quintiles of the propensity score, using propensity as a continuous variable, or using each variable making up the score. In sensitivity analyses we confirmed that adjustment explained most of the apparent gateway effect.

Although we found that confounding was a major factor, explaining most of the observed gateway effect, we were particularly concerned about the possibility of over-adjustment, if taking up e-cigarettes had affected the values of some of the Wave 1 predictor variables considered. At the time, we noted that the possibility of over-adjustment could be avoided using data from Waves 1, 2 and 3 of the PATH study, by relating initiation of cigarette smoking at Wave 3 to vaping at Wave 2, restricting attention to those who, at Wave 1, had never vaped, and using propensity indicators recorded at Wave 1 linked to uptake of e-cigarettes by Wave 2.

Here we describe the results of extensive analyses conducted based on Waves 1, 2 and 3. The main objective was to conduct the analyses avoiding the possibility of over-adjustment which was envisaged at the time of our earlier paper (Lee & Fry, 2019), but we also include a variety of sensitivity and alternative analyses for reasons described below.

Methods

Some aspects of the analyses described here are the same as those described earlier (Lee & Fry, 2019) and are not presented again here. The selection of demographic and other predictor variables is as before, except that in some analyses we use exact age (12, 13, 14, 15, 16 and 17), which could now for the first time be estimated from the age group (12 to 14, 15 to 17) at the three Waves and the Wave when youths became adults (18+). Use of the person-level weights provided in the PATH study database is as before, as is the process by which a sequence of logistic regression analyses is used to develop the shorter list of demographic variables to be used in forming the propensity scores.

Our main analysis M1 is the analysis envisaged in our earlier paper (Lee & Fry, 2019) aimed at avoiding the possibility of over-adjustment in the analyses based only on Waves 1 and 2. It is based on those with data at Waves 1, 2 and 3 who had never smoked cigarettes by Wave 2 and had never used e-cigarettes by Wave 1. This analysis predicts Wave 3 ever smoking from Wave 2 ever e-product use, with

adjustment based on Wave 1 predictors used to derive a propensity index for taking up e-products between Waves 1 and 2, and exact age being used in preference to grouped age. Note that, whereas in Wave 1 questions in PATH related only to e-cigarette use, in Waves 2 and 3 questions related to ever e-product use, which also included use of e-cigars, e-pipes and e-hookahs.

As in our earlier paper (Lee & Fry, 2019) we also conducted four sensitivity analyses (S1 to S4) of analysis M1 which are otherwise similar, except for the following differences:

S1. Those who had ever used other tobacco products at Wave 1 are excluded;

S2. Ever use of other tobacco products at Wave 1 is included as an additional predictor variable;

S3. The analysis is based on a propensity score for ever cigarette smoking rather than for ever vaping; or

S4. The analysis is based on a propensity score for ever use of any tobacco product rather than for ever vaping.

Note that in our original paper (Lee & Fry, 2019) we also presented results of a further sensitivity analysis, based on linking current vaping to current smoking. This was not repeated here as numbers of new current smokers in current vapers were verylow.

Main analysis M2 is similar to M1, except that analysis adjusts for the propensity index as originally derived (Lee & Fry, 2019), based on 12 variables recorded at Wave 1. This was conducted to gain insight into how critically the estimates of the gateway effect depended on the precise propensity index used. Alternative versions of M2 substitute exact age rather than grouped age in deriving the propensity index, and/or included Wave 1 vapers in the analysis.

Main analysis M3 adjusts for a propensity index derived by linking Wave 2 predictors to Wave 2 e-product use. This is a replicate of the analysis conducted originally (Lee & Fry, 2019), but using a different period of taking up cigarettes. Data for Wave 1 were ignored, except that where the data for a characteristic was "ever in last 12 months", Wave 1 data were used to define "ever". An alternative version of M3 replaces grouped age by exact age in deriving the propensity index.

Apart from analyses linking Wave 2 e-product use to additional cigarette smoking at Wave 3 in those who had never smoked at Wave 2, two additional analyses (A1 and A2) were also conducted.

Additional analysis A1 relates e-cigarette use at Wave 1 to cigarette smoking at Wave 2 as in our earlier publication (Lee & Fry, 2019), but is based on individuals who provided data at all three Waves. One version of this uses the same 12 variables as before to develop the propensity index, the other replaces grouped age by exact age. The OR from this analysis can be combined with that reported for main

analysis M2 to give a combined estimate of the gateway effect for Wave 1 to 2 initiation and Wave 2 to 3 initiation based on the same set of variables determined at Wave 1.

Additional analysis A2 ignores Wave 2 data and relates e-cigarette use at Wave 1 to cigarette smoking at Wave 3 using the same 12 variables as before, but replacing grouped age by exact age.

Consideration of residual confounding was also taken into account for three of the analyses described above (M1, M3, A1), all involving exact age. In each case, the list of predictor variables was unaltered from that used originally, but the values of the predictor variables and of the propensity index were revised based on data available at all three Waves. For age, individual year of age at Wave 1 was used, while gender and Hispanic origin did not change between Waves. For the other variables used to form the propensity index, we used all the available data, generally choosing the response most associated with increased e-cigarette use where response varied between Waves (see Additional File Table 1, *Extended data*, for further details (Lee, 2020)).

For analyses M1, M3 and A1, alternative versions were also run in which the number of variables adjusted for was increased by also including interactions of age with each of the other three predictors most strongly linked to the relevant gateway effect.

Software
Relevant data were transferred for analysis to a ROELEE database, and analysed using the ROELEE program (Release 59, Build 49). All these analyses could be run using the GLM Package and the Step Function from the R Program (https://www.r-project.org/).

Results
M1: Relating initiation of cigarette smoking between Waves 2 and 3 to ever e-product use at Wave 2, with adjustment for Wave 1 predictors linked to uptake of e-cigarettes between Waves 1 and 2
Initial analyses linked exact age, four other demographic variables (gender, Hispanic origin, race and census region) and 60 other selected predictor variables to ever e-product use at Wave 2 in those who had not smoked or used e-cigarettes at Wave 1. A propensity index based on 16 variables was derived using the three step process described earlier (Lee & Fry, 2019). Additional File Table 2 (see *Extended data* (Lee, 2020)) shows the steps at which different variables were eliminated from consideration, while Table 1 gives the fitted equation for the propensity index.

As shown in Table 2, adjustment for propensity removed about half the excess OR (i.e. OR−1), the unadjusted OR of 5.60 (95% CI 4.52-6.93) reducing to either 3.37 (2.65-4.28) or 3.11 (2.47-3.92), depending on whether adjustment was as a continuous variable or as quintiles. A similar reduction in the OR, to 3.27 (2.57-4.16), was achieved by adjusting for the 16 variables individually. It can also be seen that, for the first seven variables adjusted for, the adjusted OR decreased steadily, to 3.25. Further adjustment had little or no effect, with introducing additional variables sometimes slightly increasing the estimated OR and sometimes slightly decreasing it.

Four sensitivity analyses of M1 were carried out, fuller details being given in Table 3 to Table 6 of the Additional File (see *Extended data* (Lee, 2020)).

Compared to M1, S1 excluded those who had ever used products other than cigarettes or e-cigarettes at Wave 1, both in the construction of the propensity index and in estimating the gateway effect. Whereas M1 involved 8260 youths, of which 409 initiated smoking between Waves 2 and 3, S1 involved 7945, of which 359 took up smoking. The propensity index developed for S1 involved all the 16 variables shown in Table 2, except for "Number of times seen Movie 4" and "Think you will try a cigarette soon". Here, the pattern of results is similar to that for Table 2, with the unadjusted OR of 5.66 (95% CI 4.49-7.13) reducing to either 3.45 (2.67–4.46), 3.24 (2.53–4.15), or 3.23 (2.49–4.18), depending on whether adjustment was made for propensity as a continuous variable, propensity as quintiles, or all the 14 variablesindividually.

Compared to M1, the only difference for S2 was that ever smoked other tobacco products at Wave 1 was added to the 16 variables used in M1 to make up the propensity score, and was forced into the regression models. Starting with the same unadjusted OR as M1, the adjusted ORs were very similar; 3.37 (2.64–4.29), 3.07 (2.44-3.87) and 3.20 (2.50-4.08), after adjustment for propensity (continuous), propensity (quintiles), or all the individual variables.

Whereas M1 (and S1 and S2) adjusted for variables found to be predictive of initiating e-product use at Wave 2, S3 adjusted for variables predictive of cigarette smoking. Here, the final model included 27 variables. The unadjusted OR of 5.65 (95% CI 4.55-7.01) slightly differed from that in M1 as the individuals considered had to have non-missing data on 27 variables rather than 16. However, the overall effect of adjustment was again similar, with the OR reducing to 3.28 (2.56-4.22) after adjustment for all 27 variables. As for M1, adjustment for the first four variables had the most effect. Adjustment for the first seven variables reduced the OR to 3.26 (2.57-4.13), similar to the OR after adjustment for all 27. Propensity adjustment was not carried out in S3.

Compared to M1, S4 adjusted for variables predictive of take-up of any tobacco product between Waves 1 and 2. Here, the propensity index was based on 18 variables, with the unadjusted OR of 5.74 (4.55-7.23) reducing to 3.31 (95% CI 2.56-4.28), 3.19 (2.48-4.09), or 3.21 (2.47-4.18), after adjustment for propensity (continuous), propensity (quintiles), or all the individual variables. Adjustment for all 18 variables had a similar effect to adjustment for the most important 10 variables, where the OR was 3.20 (2.47-4.14).

M2: Relating initiation of cigarette smoking between Waves 2 and 3 to ever e-product use at Wave 2, with adjustment for the same Wave 1 predictors as previously reported (Lee & Fry, 2019)
Here, instead of deriving the Wave 1 predictors linked to uptake of e-cigarettes between Waves 1 and 2, analysis M2 uses the same set of Wave 1 predictors used in our earlier work (Lee & Fry, 2019), the results being shown in Table 3. Here, the unadjusted OR of 5.74 (95% CI 4.62-7.13) reduced to 3.54 (2.81-4.45)

Table 1. Predicting Wave 2 ever e-product use from 16 Wave 1 predictor variables (Main analysis M1).

Variable[a]	Levels	N	OR (95% CI)
Exact age	12	1518	1.00 (base)
	13	1474	1.71 (1.23-2.38)
	14	1451	1.97 (1.43-2.71)
	15	1376	2.25 (1.65-3.08)
	16	1188	2.55 (1.86-3.51)
	17	1051	3.75 (2.72-5.15)
Ever been curious about smoking a cigarette			0.86 (0.76-0.97)[b]
Think you will smoke a cigarette in the next year			0.59 (0.48-0.71)[c]
Anyone who lives with you now use tobacco	Cigarettes, cigars, cigarillos, filtered cigars	2140	1.00 (base)
	Smokeless or other tobacco only	319	1.73 (1.26-2.37)
	No-one living in the home uses tobacco	5599	0.78 (0.65-0.94)
Ever used alcohol at all	Yes	2483	1.00 (base)
	No	5575	0.53 (0.45-0.62)
Agree/disagree: like new and exciting experiences, even if I have to break the rules	Strongly agree	285	1.00 (base)
	Agree	1252	0.71 (0.52-0.97)
	Neither agree nor disagree	2107	0.64 (0.47-0.87)
	Disagree	2404	0.38 (0.28-0.53)
	Strongly disagree	2010	0.46 (0.32-0.65)
Youth's grade performance in school in past 12 months	Mostly A's	2342	1.00 (base)
	A's or B's	2849	1.30 (1.07-1.58)
	Mostly B's	702	1.60 (1.22-2.10)
	B's or C's	1346	1.47 (1.17–1.85)
	Mostly C's	325	2.16 (1.52-3.09)
	C's or D's	334	2.74 (1.95-3.86)
	Mostly D's	45	2.09 (0.90-4.87)
	D's or F's	71	2.54 (1.34-4.81)
	Mostly F's	10	1.85 (0.26-12.91)
	School is ungraded	34	1.80 (0.54-6.06)
How often you visit your Facebook, Google Plus, MySpace, Twitter or other	Several times a day	2464	1.00 (base)
	About once a day	2284	0.67 (0.56-0.80)
	3–5 days a week	1006	0.73 (0.58-0.92)
	1–2 days a week	732	0.51 (0.37-0.69)
	Never	1572	0.40 (0.31-0.53)

Variable[a]	Levels	N	OR (95% CI)
Agree/disagree: I think I would enjoy using tobacco	Strongly agree	18	1.00 (base)
	Agree	95	0.42 (0.14-1.31)
	Disagree	1517	0.57 (0.20-1.58)
	Strongly disagree	6428	0.35 (0.12-1.01)
Hispanic origin	Hispanic	2332	1.00 (base)
	Not Hispanic	5726	0.67 (0.57-0.79)
Became very distressed when something reminded of past	Past month	1940	1.00 (base)
	2–12 months	1137	0.86 (0.70-1.07)
	Over a year	906	0.71 (0.55-0.92)
	Never	4075	0.74 (0.62-0.89)
Cigarettes or tobacco might be available to youth at parent or guardian's home	Yes	1057	1.00 (base)
	No	7001	0.65 (0.52-0.80)
Money received in total during an average week	None	2771	1.00 (base)
	Less than $1	331	1.34 (0.91-1.96)
	$1 to $5	1234	1.26 (0.99-1.61)
	$6 to $10	1019	1.40 (1.10-1.79)
	$11 to $20	1289	1.42 (1.14-1.77)
	$21 to $50	751	1.36 (1.06-1.75)
	$51 to $100	337	1.53 (1.11-2.10)
	$101 to $150	160	2.02 (1.33-3.06)
	$151 or more	166	1.96 (1.29-2.99)
Last time 2+ times: had a hard time paying attention at school, work or home	Past month	2700	1.00 (base)
	2–12 months	1402	0.75 (0.62-0.92)
	Over a year	819	0.84 (0.64-1.09)
	Never	3137	0.72 (0.59-0.87)
Number of times seen Movie 4	Never	6839	1.00 (base)
	Once	858	0.91 (0.73-1.11)
	Twice	190	1.24 (0.83-1.86)
	3 or more times	171	1.91 (1.29-2.82)
Think you will try a cigarette soon			1.99 (1.17-3.37)[d]

Note: The model is based on 8058 youths with data on all 16 predictors who neither smoked nor used e-cigarettes at Wave 1.

[a] The variables are shown in order of their inclusion into the model.

[b] The OR is per unit of the graded variable which represents decreasing curiosity.

[c] The OR is per unit of the graded variable which represents decreasing likelihood.

[d] The OR is per unit of the graded variable which represents decreasing likelihood, with those originally entered as missing because they thought that they would not smoke a cigarette in the next year scored as "definitely not" (Level 4).

after adjustment for propensity as quintiles and to 3.45 (2.72-4.37) after adjusting for the individual variables. While adjustment here removed about half the excess OR, the reduction was less, to 4.53 (3.62-5.68), after adjustment for propensity as a continuous variable. The reductions were similar if exact age rather than age group was included in the list of variables. Here, the unadjusted OR was reduced to 3.51 (2.79-4.41) after adjustment for propensity as quintiles,

Table 2. Relating Wave 3 ever smoking to Wave 2 ever e-product use (Main analysis M1).

Adjustment variables	OR (95% CI)
None	5.60 (4.52-6.93)
Propensity score as quintiles	3.11 (2.47-3.92)
Propensity score as a continuous variable	3.37 (2.65-4.28)
Exact age	4.87 (3.91-6.06)
+ Ever been curious about smoking a cigarette	4.27 (3.41-5.34)
+ Think you will smoke a cigarette in the next year	3.84 (3.06-4.82)
+ Anyone who lives with you now use tobacco	3.73 (2.97-4.69)
+ Ever used alcohol at all	3.48 (2.76-4.38)
+ Agree/disagree: Like new and exciting experiences even if I have to break the rules	3.39 (2.68-4.28)
+ Youth's grade performance in school in past 12 months	3.25 (2.57-4.12)
+ How often you visit your Facebook, Google Plus, MySpace, Twitter or other	3.17 (2.50-4.01)
+ I think I would enjoy using tobacco	3.17 (2.50-4.02)
+ Hispanic origin	3.22 (2.54-4.09)
+ Last time a significant problem with: becoming very distressed when something reminded of past	3.19 (2.51-4.05)
+ Cigarettes or tobacco might be available to youth at parent or guardian's home	3.17 (2.50-4.02)
+ Money received in total during an average week	3.25 (2.56-4.13)
+ Last time 2+ times: Had a hard time paying attention at school, work or home	3.22 (2.53-4.09)
+ Number of times seen Movie 4	3.28 (2.57-4.17)
+ Think you will try a cigarette soon	3.27 (2.57-4.16)

Notes: The table shows the effects of adjustment based on the Wave 1 predictors used to derive a propensity index for taking up e-products between Wave 1 and 2. The analyses are based on those with data at Waves 1, 2 and 3 who had never smoked cigarettes by Wave 2 and had never used e-cigarettes by Wave 1. Between Waves 2 and 3 261/7367 (3.54%) of never users of e-products at Wave 2 took up smoking, while 148/893 (16.57%) of ever users did so. For individuals who were 16 or 17 at Wave 1, adult data were used to determine e-product use and cigarette smoking at later Waves. The table includes the results of a stepwise regression based on successively including the most significant adjustment variables, given that ever e-product use at Wave 2 was included in the model.

4.59 (3.66-5.74) after adjustment for propensity as a continuous variable, and 3.39 (2.67-4.30) after adjustment for the individual variables.

Similar analyses were also run that did not exclude those who had used e-cigarettes by Wave 1. This increased the number of ever e-product users who took up smoking from 146 to 201, and slightly increased the unadjusted OR to 5.95 (4.89-7.23). However, the pattern of decline following adjustment was quite similar. For example, the OR adjusted for the individual variables reduced to 3.31 (2.65-4.12) using grouped age and to 3.26 (2.62-4.06) using exact age.

M3: Relating initiation of cigarette smoking between Waves 2 and 3 to ever e-product use at Wave 3, with adjustment for Wave 2 predictors

As noted in the Methods section, M3 is essentially a replicate of our earlier work (Lee & Fry, 2019), but using a different period of introduction of cigarettes. The propensity score developed was based on 18 variables, using age group or exact age as alternatives. The results, shown in Table 4, indicate that, as earlier (Lee & Fry, 2019), a large proportion of the unadjusted association can be explained by adjustment. The largest proportion was explained by adjusting for the 18 variables making up the propensity score, with the unadjusted OR of 6.70 (95% CI 5.40-8.32) reducing to 2.25 (1.74-2.91) or 2.75 (1.75-2.93) depending on whether the list of variables included age range or exact age. However, most of this reduction could be explained by adjustment for propensity.

Combining the Wave 2 to 3 results shown in Table 4 with the Wave 1 to 2 results reported earlier (Lee & Fry, 2019) by fixed-effect meta-analysis gives an unadjusted OR of 6.30 (5.31-7.46), which is reduced to 2.65 (2.24-3.18), 2.53 (2.07-3.10) or 2.08 (1.70-2.54) depending on whether adjustment is for propensity (quintiles), propensity (continuous) or all the variables making

Table 3. Relating Wave 3 ever smoking to Wave 2 ever e-product use (Main analysis M2).

Adjustment variables		OR (95% CI)
None		5.74 (4.62-7.13)
Propensity score as quintiles		3.54 (2.81-4.45)
Propensity score as continuous variable		4.53 (3.62-5.68)
Age range		5.20 (4.17-6.49)
+	Ever used alcohol at all	4.45 (3.54-5.58)
+	Ever been curious about smoking a cigarette	4.10 (3.26-5.16)
+	Think you will smoke a cigarette in the next year	3.70 (2.94-4.68)
+	Agree/disagree: Prefer friends who are exciting and unpredictable	3.65 (2.89-4.61)
+	Reaction if parent/guardian found you using tobacco	3.64 (2.88-4.60)
+	Gender	3.63 (2.87-4.58)
+	Agree/disagree: I think I would enjoy using tobacco	3.63 (2.87-4.59)
+	Agree/disagree: Some products are safer than others	3.63 (2.87-4.59)
+	Ever used prescription drug not prescribed to you: Ritalin or Adderall	3.67 (2.90-4.64)
+	Has a Facebook, Google Plus, MySpace, Twitter or other social networking	3.53 (2.79-4.47)
+	Anyone who lives with you now use tobacco	3.45 (2.72-4.37)

Notes: The table shows the effects of adjustment based on the same Wave 1 predictors as used in our original paper (Lee & Fry, 2019). The analyses are based on those with data at Waves 1, 2 and 3 who had never smoked cigarettes by Wave 2 and had never used e-products by Wave 1. Between Waves 2 and 3, 249/7133 (3.49%) of never users of e-products at Wave 2 took up smoking, while 146/880 (16.59%) of ever users did so. For individuals who were 16 or 17 at Wave 1, adult data were used to determine e-product use and cigarette smoking at later Waves. The table includes the results of a stepwise regression based on successively including the most significant adjustment variables, given that ever e-product use at Wave 2 was included in the model.

up the propensity score. This represents reductions in the excess OR of, respectively, 68.9%, 71.1% or 79.8%.

A1: Relating initiation of cigarette smoking between Waves 1 and 2 to ever e-cigarette use at Wave 1, based on individuals who provided data at all three Waves

Table 5 summarizes the main results of these analyses and compares them with those reported earlier (Lee & Fry, 2019). While the original analyses were based on 9423 youths, 421 of whom initiated smoking, the new analyses were based on 8700 youths, 389 of whom initiated smoking. As can be seen, the results in the original analysis, based on grouped age, were similar to those from the new analyses, whether grouped or exact age was used.

The results from analysis A1 for grouped age may theoretically be combined with those from analysis M2 shown in Table 3, as they both use the Wave 1 predictors from our original paper (Lee & Fry, 2019), with exact age replacing grouped age, and are both based on individuals with data at all three Waves. However, as illustrated by the results adjusted for all 12 variables, where the ORs are 3.45 (95% CI 2.72-4.37) from Table 3 and 1.97 (1.42-2.73) from Table 5, these estimates are heterogeneous (p<0.001), providing a random-effects combined estimate of 2.64 (1.52-4.57).

A2: Relating Wave 3 ever smoking to Wave 1 e-cigarette use, ignoring Wave 2 data

This analysis is similar to that reported originally (Lee & Fry, 2019) but relates to a longer follow-up period, and uses exact rather than grouped age. The results of this analysis, shown in Table 6, are quite similar to those shown in Table 5. Again, an unadjusted OR is markedly reduced by adjusting for propensity, whether as quintiles or as a continuous variable, and is further reduced by adjusting for all the 12 individual variables considered.

Attempting to account for residual confounding

Table 7 summarizes the main results shown in Table 2 for main analysis M1, which make no allowance for residual confounding, and compares them with the results of an analysis using the same list of predictor variables, but with values modified in an attempt to adjust for residual confounding. As can be seen, markedly more of the unadjusted association was explained when allowance for residual confounding was made, with the adjusted ORs in the range 2.36 to 2.46 when allowance was made, compared with 3.11 to 3.37 when it was not. Note that the unadjusted ORs in the two sets of results vary slightly, as missing values in some individuals in the original analyses were replaced by estimates taken from other Waves.

Table 4. Relating Wave 3 ever smoking to Wave 2 ever e-product use (Main analysis M3).

Adjustment variables	Using age group OR (95% CI)	Using exact age OR (95% CI)
None	6.70 (5.40-8.32)	6.70 (5.40-8.32)
Propensity score as quintiles	2.77 (2.19-3.50)	2.74 (2.17-3.48)
Propensity score as a continuous variable	2.57 (1.98-3.33)	2.60 (2.00-3.36)
Age range	5.78 (4.62-7.22)	-
Exact age	-	5.45 (4.36-6.83)
+ Last time a significant problem with: feeling very trapped, lonely, sad, blue, depressed	5.22 (4.17-6.54)	4.95 (3.94-6.21)
+ Reaction if parent/guardian found you using tobacco	4.89 (3.89-6.14)	4.66 (3.70-5.87)
+ Money received in total during an average week	4.65 (3.69-5.86)	4.52 (3.59-5.71)
+ Number of times seen Movie 3	4.31 (3.41-5.44)	4.20 (3.32-5.31)
+ Number of times seen Movie 4	4.12 (3.25-5.21)	4.02 (3.18-5.10)
+ Ever been curious about smoking a cigarette	3.45 (2.71-4.38)	3.36 (2.64-4.28)
+ Think you will smoke a cigarette in the next year	2.89 (2.26-3.70)	2.86 (2.24-3.66)
+ Ever used alcohol at all	2.63 (2.05-3.37)	2.63 (2.05-3.38)
+ In past 12 months, youth's grade performance at school	2.51 (1.95-3.22)	2.51 (1.95-3.23)
+ Agree/disagree: using tobacco would help me calm down when I am angry	2.43 (1.89-3.12)	2.43 (1.89-3.13)
+ How often you visit your social media accounts	2.43 (1.88-3.12)	2.45 (1.90-3.15)
+ Would smoke if one of your friends offered you one	2.37 (1.84-3.06)	2.39 (1.86-3.09)
+ Anyone who lives with you now use tobacco	2.34 (1.81-3.02)	2.36 (1.83-3.04)
+ Think you will try a cigarette soon	2.33 (1.81-3.01)	2.35 (1.82-3.03)
+ Agree disagree: some tobacco products are safer than others	2.30 (1.78-2.97)	2.32 (1.79-2.99)
+ Youth has a curfew or set time to be home on school nights	2.29 (1.77-2.95)	2.30 (1.78-2.98)
+ Ever used prescription drug not prescribed to you: Ritalin or Adderall	2.25 (1.74-2.91)	2.27 (1.75-2.93)

Notes: The table shows the effects of adjustment based on Wave 2 predictors linked to use of e-products in Wave 2. The analyses are based on those with data at Waves 2 and 3 ignoring data from Wave 1. Between Waves 2 and 3, 228/8233 (2.77%) of never users of e-products at Wave 2 took up smoking, while 145/949 (15.28%) of ever users did so. For individuals who were 17 at Wave 2, adult data were used to determine cigarette smoking at Wave 3. The table includes the results of a stepwise regression based on successively including the most significant adjustment variables, given that ever e-product use at Wave 2 was included in the model. The first set of ORs is based on a model including age group, while the second is based on a model including exact age.

Table 5. Relating Wave 2 ever smoking to Wave 1 ever e-cigarette use - original (Lee & Fry, 2019) and A1 ORs.

Adjustment variables	Data on two Waves	Data on all three Waves	
	Originally reported OR (95% CI)	Grouped age OR (95% CI)	Exact age OR (95% CI)
None	5.70 (4.33-7.50)	5.99 (4.52-7.95)	5.99 (4.52-7.95)
Propensity score as quintiles	2.48 (1.85-3.31)	2.65 (1.96-3.58)	2.59 (1.92-3.50)
Propensity score as continuous variable	2.47 (1.79-3.42)	2.67 (1.92-3.72)	2.64 (1.89-3.68)
Grouped age	4.81 (3.64-6.35)	5.04 (3.78-6.72)	-
Exact age	-	-	4.81 (3.60-6.42)
+11 further variables	1.85 (1.35-2.53)	1.97 (1.42-2.73)	1.98 (1.43-2.75)

Notes: Each set of ORs is based on those who had never smoked cigarettes by Wave 1. The first analysis is as summarized in Table 1. The last two analyses only exclude those without data at Wave 3.

Table 6. Relating Wave 3 ever smoking to Wave 1 ever e-cigarette use using exact age.

Adjustment variables	OR (95% CI)
None	5.65 (4.50-7.10)
Propensity score as quintiles	2.48 (1.95-3.16)
Propensity score as continuous variable	2.61 (2.00-3.40)
Exact age	4.69 (3.71-5.93)
+ 11 further variables	1.97 (1.51-2.56)

Notes: The table shows the effects of adjustment based on the same Wave 1 predictors as used in our original paper (Lee & Fry, 2019) but replacing age range by exact age. The set of ORs is based on those with data at Waves 1, 2 and 3 who had never smoked cigarettes by Wave 1. Between Waves 1 and 3, 716/8334 (8.59%) of never users of e-cigarettes at Wave 1 took up smoking, while 123/366 (33.61%) of ever users did so. The table includes the results of a stepwise regression based on successively including the most significant adjustment variables, given that ever e-product use at Wave 1 was included in the model.

Table 7. Effect of allowance for residual confounding in main analysis M1.

Adjustment variables	M1 – no allowance OR (95% CI)	M1 – allowance OR (95% CI)
None	5.60 (4.52-6.93)	5.65 (4.58-6.98)
Propensity score as quintiles	3.11 (2.47-3.92)	2.40 (1.91-3.02)
Propensity score as a continuous variable	3.37 (2.65-4.28)	2.46 (1.93-3.14)
All 16 variables individually	3.27 (2.57-4.16)	2.36 (1.85-3.02)

Notes: The "no allowance" results correspond to those in Table 6.

The analyses are based on those with data at Waves 1, 2 and 3 who had never smoked cigarettes by Wave 2 and had never used e-cigarettes by Wave 1. Between Waves 2 and 3 261/7367 (3.54%) of never users of e-products at Wave 2 took up smoking, while 148/893 (16.57%) of ever users did so in the population considered in the "no allowance" analyses The corresponding figures in the "allowance" analyses were 267/7682 (3.48%) and 150/915 (16.39%). For individuals who were 16 or 17 at Wave 1, adult data were used to determine e-product use and cigarette smoking at later Waves. The table includes the results of a stepwise regression based on successively including the most significant adjustment variables, given that ever e-product use at Wave 2 was included in the model.

While allowance for residual confounding has quite a marked effect for analysis M1, the analysis which avoided the possibility of over-adjustment, it did not for analyses M3 and A2, which did not avoid this possibility. Detailed results are shown in Table 7 and Table 8 in the Additional File (see *Extended data* (Lee, 2020)).

Investigating whether introducing some interactions explains more of the gateway effect

Versions of analyses M1, M3 and A1 were also seen, in which the number of variables adjusted for was extended by also including interactions of age with each of the other three predictors most strongly linked to the gateway effect. For analysis M1, allowance for these interactions had virtually no effect, the original estimate of 3.27 (95% CI 2.57-4.16) shown in Table 2 without including interactions changing to 3.26 (2.55-4.15) when interactions were included in the model. For analysis M3, the estimate changed only from 2.27 (1.75-2.93) to 2.35 (1.81-3.05), while for analysis A1, it changed from 1.98 (1.43-2.75) to 2.06 (1.48-2.88).

Summary of results

Table 8 summarizes the results from 18 of the analyses described above, expressing the extent to which adjustment explained the unadjusted OR using the statistic $100 \times (OR_U - OR_A) / (OR_U - 1)$ where OR_U is the unadjusted OR, and OR_A is the adjusted OR. The most obvious impression from the table is that the results largely fall into two groups.

Results from the original analysis and for analyses M3, A1 and A2 (rows A, K to O, and Q to R of Table 8) all show that as much as about 80% of the unadjusted excess OR can be explained by adjustment for the full set of variables in the model, with somewhat less, typically about 70%, explained using propensity as quintiles or as a continuous variable.

In contrast, results from virtually all of analyses M1 and M2 (rows B to K) show that only about 50% of the unadjusted excess OR can be explained by adjustment for the full set of variables, with propensity as quintiles giving generally similar results.

The difference between these two groups is that the first set of results are subject to the problem of over-adjustment, with the values of the predictors used possibly having been affected by having used e-cigarettes. This is mainly so where the baseline Wave was Wave 1, but was also true for analysis M3 where Wave 1 data were essentially ignored. In contrast, the second set of results avoided over-adjustment by considering follow-up from Wave 2 to 3, with predictors based on Wave 1 data in youths who had never used e-cigarettes. However, in this second set of results the variables used were not as up-to-date as in the first analyses.

The variant analysis of M1, allowing for residual confounding (row P), gives an intermediate result, with about 70% of the excess risk being explained, whether by the full set of variables or by propensity. This analysis, however, does not avoid the problem of over-adjustment as it incorporates some information from Waves where individuals were already using e-cigarettes.

It is clear from Table 8 that many of the variables studied had little effect on the pattern of results. These included use of grouped or exact age, taking into account use of other products, and using predictors of cigarette smoking or any tobacco use rather than predictors of e-cigarette use.

Two other conclusions may be drawn from Table 8. One is that adjustment for propensity as quintiles or as a continuous variable generally gives very similar results, with the exception of

Table 8. Summary of results from analyses.

	Analysis	Baseline Wave	Follow-up Wave	Predictor	Age	Comment	Unadjusted OR	% Excess OR explained[a] P as Q[b]	P as C[c]	6 variables	All variables
A	Original	1	2	Ever e-cigs	Grouped	As published ((Lee & Fry, 2019))	5.70	68.5	68.7	78.1	81.9
B	M1	2	3	Ever e-cigs	Exact	Predictors revised based on those who were not Wave 1 e-users	5.60	54.1	48.5	48.0	50.7
C	M1/S1	2	3	Ever e-cigs	Exact	As M1 but excludes Wave 1 other product users	5.66	51.9	47.4	47.9	52.1
D	M1/S2	2	3	Ever e-cigs	Exact	As M1 but Wave 1 other product use included as predictor	5.60	55.0	48.3	50.2	52.2
E	M1/S3	2	3	Ever cigs	Exact	As M1 but adjusting for predictors of ever cigarette smoking	5.65	-	-	48.4	51.0
F	M1/S4	2	3	Ever any product	Exact	As M1 but adjusting for predictors of ever any tobacco use	5.74	53.8	51.3	45.1	53.4
G	M2	2	3	Ever e-cigs	Grouped	Original 12 predictors	5.74	46.4	25.5	44.3	48.3
H	M2 (variant)					Did not exclude Wave 1 e-users	5.95	50.3	28.7	49.3	53.3
I	M2 (variant)	2	3	Ever e-cigs	Exact	Original 12 predictors	5.74	47.0	24.3	46.0	49.6
J	M2 (variant)					Did not exclude Wave 1 e-users	5.95	50.7	28.3	50.5	54.3
K	M3	2	3	Ever e-cigs	Grouped	Predictors revised essentially ignoring Wave 1 data	6.70	68.9	72.5	45.3	78.1
L	M3 (variant)				Exact	As above but using exact age	6.70	69.5	71.9	47.0	77.8
M	A1	1	2	Ever e-cigs	Grouped	As original but based on those with data on all three Waves	5.99	66.9	66.5	76.8	80.6
N	A1 (variant)				Exact	As above but using exact age	5.99	68.1	67.1	77.0	80.4
O	A2	1	3	Ever e-cigs	Exact	Original predictors but ignoring Wave 2	5.65	68.2	65.4	74.4	79.1
P	M1 (variant)	2	3	Ever-e-cigs	Exact	As M1 but allows for residual confounding	5.65	69.9	68.6	60.0	70.8
Q	M3 (variant)	2	3	Ever e-cigs	Exact	As M3 but allows for residual confounding	6.67	75.3	74.3	51.5	80.2
R	A1 (variant)	1	2	Ever e-cigs	Exact	As A1 but allows for residual confounding	6.10	69.0	68.0	65.1	76.7

[a] % excess explained = $100*(OR_U - OR_A) / (OR_U - 1)$ where OR_U is the unadjusted OR, and OR_A is the adjusted OR.

[b] P as Q = propensity as quintiles.

[c] P as C = propensity as a continuous variable.

analysis M2 and its variants, where propensity as a continuous variable explained substantially less of the unadjusted excess OR. Inspection of the detailed modelling results showed that, whereas in other analyses, the logarithm of the OR increased fairly linearly with quintiles of propensity, in the case of analysis M2 and its variants it did not. Thus, in M1 for example, the log ORs by quintile were 0, 0.73, 1.11, 1.66 and 2.52, while in M2 they were 0, 0.21, 0.96, 1.51 and 2.19, with very little rise between quintiles 1 and 2.

The other is that adjustment for the first six variables in the model generally explained a very substantial part of the unadjusted excess OR explained by the full set. Though this was not true for analysis M2, it was still true that adjustment for the last eight or nine variables explained far less of the excess OR than did the first eight or nine.

Discussion

In our publication based on Waves 1 and 2 (Lee & Fry, 2019) our analyses showed that an unadjusted estimate of the gateway effect 5.70 (85% CI 4.33-7.50) could be considerably reduced by adjustment, to 1.59 (1.14-2.20) in the most striking case. Because of the marked reduction in the OR following adjustment, and the possibility of incomplete control for confounding we regarded it as "unclear whether prior vaping actually increases uptake of cigarette smoking". However, we did note the possibility of over-adjustment, with vaping at Wave 1 possibly having affected the recorded values of some of the variables used for adjustment.

At that time we noted that this possibility of over-adjustment could be addressed in analyses relating initiation of cigarette smoking at Wave 3 to vaping at Wave 2, restricting attention to those youths who, at Wave 1, had never vaped, and using adjustment variables recorded at Wave 1. This we have done in the analyses reported here, and our major finding is that adjustment reduced the excess risk far less, by only about 50% rather than about 80%, in our main analysis M1.

While these results more strongly support the existence of a true gateway effect of taking up vaping, there must still remain doubt about its magnitude. One reason is that predictors recorded a year before the baseline may not fully account for the characteristics of the youth at the start of follow-up. A second reason is that, although the PATH study records data on a whole range of possibly relevant characteristics, there may be some relevant predictors or interactions of predictors not considered. A third reason is that the answers to some of the questions may have been inaccurately measured. We have attempted to address this problem of residual confounding by amending values of predictors recorded at Wave 1 to take into account data recorded at later Waves. However, this problem re-introduces the problem of over-adjustment as Wave 2 and 3 values may have been affected by vaping. Theoretically, one could use data from Waves 1 to 4, using data for Waves 1 and 2 from youths who have never vaped to produce more accurate estimates of the predictors to use for a study of gateway effects between Waves 3 and 4. But this would add to the problem of using predictors recorded some time before follow-up.

Other issues are possible biases arising due to loss to follow-up and missing data. To address this in relation to our main analysis M1, we compared the distribution of the demographic variables age (at Wave 2), sex, Hispanic origin, race and census region between (A) the 8260 youths considered in Table 2, (B) the 716 for whom no data on cigarettes were available at Wave 3 (due mainly to lack of follow-up but partly to missing responses at Wave 3), and (C) the 537 for whom data on cigarettes at Wave 3 were available, but data were missing on one or more of the 16 predictors making up the propensity score. Compared to youths in group A, those in group B were somewhat more often White (weighted percentages 70.0 in A, 74.6 in B) and older (43.8% age 15–17 in A, 48,1% in B), but were otherwise very similar. Again compared to group A, those in group C were somewhat more likely to be Black (15.5% in A, 22.2% in C) and were clearly younger (56.2% age 12–14 in A, 70.7% in C). Again, little difference was seen in regard to sex, Hispanic origin or census origin. Given the overall loss of youths for whom results might have been available (1253/9513 = 13.1%) is not large, the generally quite small between-group differences seen, the lack of evidence of any interaction of age with other major predictors, and the fact that race did not feature in the derived propensity index, it seems unlikely to us that any material bias to our estimated ORs could arise due to loss to follow-up and missing data.

Since the time that we published our earlier analysis (Lee & Fry, 2019) and our paper on general considerations relating to vaping as a possible gateway into cigarette smoking (Lee et al., 2018) a number of other authors have presented evidence from other prospective studies (Bold et al., 2018; Chien et al., 2019; Kinnunen et al., 2019; Morgenstern et al., 2018; Pénzes et al., 2018; Primack et al., 2018; Treur et al., 2018). The studies vary in the extent to which potential confounding variables have been adjusted for, with large OR estimates tending to be reported in studies with more limited control. Thus, a study in the Netherlands (Treur et al., 2018), which adjusted only for sex, age education and a single indicator of propensity to smoke, reported an OR of 11.90 (95% CI 3.36-42.11) for the relationship between ever use of e-cigarettes with nicotine and initiation of cigarette smoking during follow-up. Also, a study in the US (Bold et al., 2018), which adjusted only for demographic variables and use of other tobacco products, reported ORs of 7.08 (2.34-21.42) and 3.87 (1.86-2.06) depending on the follow-up period studied, while another US study (Pénzes et al., 2018), with limited control for confounding variables, reported an OR of 3.57 (1.96-6.45). Apart from a US study (Primack et al., 2018) ,which reported an OR of 6.8 (1.7-28.3), following adjustment for ten covariates independently associated with initiation of smoking, most of the other studies that appear to have better control for confounding gave lower estimates. These included a study in Taiwan (Chien et al., 2019), which reported an OR of 2.14 (1.66-2.75), a study in Germany (Morgenstern et al., 2018), which reported an OR of 2.18 (1.65-2.87) and a study in Finland (Kinnunen et al., 2019), which reported that adjustment reduced the OR from 11.52 (4.91-26.56) to 2.92 (1.09-7.85). Notably, a study in Great Britain (East et al., 2018) reported an OR of 11.89 (3.56-39.72) estimated using the usual logistic

method, but a reduced value of 1.34 (1.05-1.72) using causal mediation analysis.

There have, by now, been a number of other papers that have studied the gateway effect in youths based on data from the PATH study. In our earlier paper (Lee & Fry, 2019), we commented on an early publication (Watkins *et al.*, 2018) based on data from Waves 1 and 2, noting that the list of variables adjusted for was quite restricted. Since then two other papers have been published based on Waves 1 and 2 (Cheng *et al.*, 2019; Stanton *et al.*, 2019) and one based on data from Waves 1 to 3 (Berry *et al.*, 2019). All of these studies took into account a more limited set of predictors than we had, and none used predictors assessed at a time before e-cigarette use was initiated. One study (Berry *et al.*, 2019) found that prior e-cigarette use among youths aged 12 to 15 years was associated with 4.09 times (95% CI 2.97-5.63) the odds of ever cigarette use and with 2.75 times (95% CI 1.60-4.73) the odds of current e-cigarettes use compared with no prior tobacco use, while another (Stanton *et al.*, 2019), based on the full youth sample, found that e-cigarette use was associated with 3.21 times (95% CI 1.95-5.45) the odds of ever cigarette smoking. Interestingly, the other study (Cheng *et al.*, 2019), again based on the full youth sample, using a somewhat different approach, found that while the latent construct "common liability to use tobacco products" was a robust predictor for the onset of cigarette smoking, ever e-cigarette use was not a significant predictor, after controlling for this construct.

Generally our results are consistent with the literature in confirming that a substantial proportion, but not all, of the observed association between e-cigarette use and subsequent initiation of cigarette smoking can be explained by adjustment for factors linked to susceptibility to tobacco. However, large cohort studies with high quality, accurate, data on a wide range of predictive factors recorded at regular intervals will be needed to gain better insight into the magnitude of any true causal effect of vaping. The PATH study with its multiple Waves and comprehensive questionnaire should prove more and more useful in the future. It will also provide information on the relationship between e-cigarette use and continued smoking, it being possible that some of those classified as taking up smoking at Wave 3 in our analyses would have only briefly taken up smoking.

There are, in theory, various effects of e-cigarettes (Lee *et al.*, 2018). Beneficial effects occur when individuals who would have continued to smoke take up vaping instead, and when vaping helps smokers to quit or reduce cigarette consumption. Adverse effects, apart from when vaping encourages individuals to start smoking, would occur if smokers who intended to quit switch instead to vaping, or if smokers add vaping to their usual consumption of cigarettes. When trying to estimate the health impact of e-cigarettes, one must consider all these effects.

A question of interest is the extent to which an estimated gateway effect could affect the total number of youths taking up cigarette smoking. As shown in the footnote to Table 1,

analysis M1 was based on 409 youths who had taken up smoking between Waves 2 and 3, including 148 who had ever used e-products at Wave 2. The weighted unadjusted data are consistent with 36.5% of these being ever e-product users and with an OR for the gateway effect of 5.60. Assuming the adjusted OR based on adjustment for the variables making up the propensity score, this percentage would reduce to 23.0%. For the estimated ORs of 3.37 or 3.11, based on adjustment for the propensity score as a continuous variable or quintiles, this percentage would only change slightly, to 23.6% or 22.0%. This percentage would clearly vary according to the relative frequency of e-product use and cigarette smoking among youths, and the number of extra smokers would need to be set against the beneficial effects described in the previous paragraph.

By using data from three Waves of the PATH study, the analyses of the gateway effect reported here improve on those reported earlier (Lee & Fry, 2019) based on the first two Waves by allowing potential confounding variables to be determined at a time before vaping started. Whereas the earlier analyses suggested that the adjustment for confounding explained about 80% of the unadjusted relationship between vaping and subsequent initiation of smoking, our current analyses suggest that adjustment explains only about 50%. This provides stronger evidence of a true effect of vaping, although doubt still remains about its true magnitude for reasons discussed.

Data availability
Underlying data
National Addiction & HIV Data Archive Program: Population Assessment of Tobacco and Health (PATH) Study [United States] Public-Use Files (ICPSR 36498). https://doi.org/10.3886/ICPSR36498.v9 (United States Department of Health and Human Services (USDHHS), 2019).

The data are available under the Terms of Use as set out by ICPSR, which can be accessed when users start the process of downloading the data.

Extended data
Open Science Framework: Further investigation of gateway effects using the PATH study https://doi.org/10.17605/OSF.IO/7ECQH (Lee, 2020).

This project contains the following extended data files:
- Gateway paper for F1000 Research_Additional file.docx

Data are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

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Open Peer Review

Current Peer Review Status: ✔ ❓ ✗ ❓

Version 2

Reviewer Report 19 April 2022

❓

Arielle S. Selya (iD)

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[2] Sanford School of Medicine, University of South Dakota, Vermillion, SD, USA

This manuscript follows on previous work by the authors using the PATH study to address the question of whether e-cigarettes act as a "gateway" to cigarette smoking among youth. Previous work showed that adjusting for propensity for e-cigarette use accounted for about 80% of the association between e-cigarette use and subsequent cigarette smoking. However, that previous study suffered from possible overadjustment (i.e., if e-cigarette use affected the covariates at Wave 1), and the current study addresses this by examining another wave of PATH (i.e., covariates at W1, e-cigarette use at W2, and smoking outcome at W3). Analyses find that adjusting for shared risk (while avoiding overadjustment) explains about half of the association between e-cigarette use and smoking. This provides stronger evidence for a possible causal gateway mechanism than previously reported, though unaccounted-for confounding is still a limitation.

Major comments:
- I agree with previous reviewer Shu Xu that covariate balance should be reported as part of good practice in using propensity score methods. E.g., standardized mean difference of < 0.2 or ratio of variances across groups between 0.2 and 2 (Kainz *et al.*, 2017[1]). Presenting covariate balance, even (or especially) if it does not achieve exact balance, is important to evaluate the degree to which any unadjusted-for bias still remains in the adjusted associations.

- What is the rationale for using PATH Waves 1-3 when Waves 4 and 5 (and for youth, 4.5) are available? Waves 1-3 are quite old now and the results may not generalize to the newer e-cigarette market.

- The authors have a paragraph discussing why there may be doubts about the magnitude of the suspected gateway association. Other reasons worth adding are (1) the issue of how well covariate balance was achieved (see the above point) and (2) that the presence of measurement error in certain variables (especially for latent constructs such as risk-seeking)

can itself lead to spurious association (Westfall *et al.*, 2016[3]).

Minor comments:
- Consider giving an example to explain the concept of overadjustment in the Introduction -- this is central to the value of this study, but is not a well-known statistical issue in this field.

- Consider citing other studies supporting common liability, e.g. Sun *et al.* (2022[4]), Sokol *et al.* (2021[5]).

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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: I am an employee of Pinney Associates, Inc., which provides consulting services on tobacco harm reduction to JUUL Labs, Inc. JUUL had no role in this review, and my expertise is based on my prior academic position. I confirm that my potential conflict of interest

did not affect my ability to write an objective and unbiased review of the article.

Reviewer Expertise: Tobacco use behavior, methodology, youth

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 18 August 2021

https://doi.org/10.5256/f1000research.30516.r87806

✖ **Jean Long** [ID]
Health Research Board, Dublin, Ireland

Overall comments:
Overall, the authors need to complete an objective examination of the research based on findings rather than commentary or opinion. For example, the literature search, extraction, and referencing for the introduction requires reworking. I have not checked the referencing in the discussion but suggest the authors do so to ensure avoidance of error. The research question should use a PICO approach and then explain the rationale for doing the research (including explanation of confounding, residual confounding, and sensitivity analysis). The five-point statement has ethical and duty of care implications and should be removed. I have extensive comments on the introduction below. The methods as currently presented are not repeatable by other researchers and I have made extensive recommendations for rewriting (see below). The tables of results were for the most part clear, but the endnotes require work and I have made some recommendations for these and a small number of recommendations for the tables themselves. I have made little comment on the results text as I believe it requires a redrafting using a professional writer or editor. When the editor is finished with your work, please check the table numbers and numbers quoted in the text to ensure that they align, and they report the findings accurately. I also suggest the table headings are rewritten by the professional writer as they are difficult to understand on first reading. The discussion is confusing, contradictory, and incomplete when dealing with the excess risk contributed by e-cigarette use on initiation of smoking tobacco use or gateway effect, and requires complete rewriting supported by evidence-based research findings under the headings: main findings, comparison of findings with other research (beginning with your own, other primary studies (already there for the most part) and then systematic reviews), strengths and limitations of the research (including how you addressed your limitations), and finally implications for policy and practice (using best practice). I have provided detailed guidance below on the discussion. These steps would help a reader read and understand the paper. I could not recommend this paper for publication without a major rewrite and an improvement in objectivity, clarity, transparency, and an evidence-based analysis of the policy and research implications. I make more specific comments below.

Is the work clearly and accurately presented and does it cite the current literature? No.
The systematic review literature is incomplete as there are more appropriate papers, with a particular emphasis on teenagers, that should be summarised. I recommend a thorough examination of the findings of the following papers and the inclusion of papers that are appropriate to the study population. I recommend that you quote the research findings and not commentary or opinion. I provide an example using the Khouja *et al.* paper on citation section.

The current text reads as if the above named are the two papers, but I think this is not correct. As later we see text "the second paper". Please amend.

Is "it" in the sentence "It made a number of relevant points" Soneji *et al.* or Lee *et al.*? Please reference for the reader. I suggest that you quote the three points from Lee *et al.* (I suspect it is this paper) as it would be more accurate, and they should be expressed as theories as this is how they are phrased in Lee *et al.*

Your five-point statement requires reconsideration, specifically "Any true gateway effect would only alter smoking prevalence modestly" implies that it is okay to allow some teenagers (mainly children) to start vaping and then move to smoke. My understanding of e-cigarettes and vaping is that the industry does not allow teenagers under 18 years to vape, as this point is repeated on a regular basis in the Irish media by those representing the industry.

I suspect many people would disagree with you on the topic that it is okay to allow teenagers to start vaping and for over 20% to continue to smoke to help adults to stop smoking; there are some ethical and child protection issues here. In addition, there is no evidence to demonstrate taking-up vaping while giving-up smoking has reduced mortality, which is implied in your five-point statement. The longest study I can find on vaping is 24 months and it does not deal with mortality. I would also point out that vaping is not a necessary step to smoking cessation and that there are other equally or more effective interventions. In addition, there are some papers that show that vaping plus smoking is as harmful to the users health as smoking, and therefore, there is no benefit to dual use.

With respect to the point "In youths in the US and UK in 2014–2016 smoking prevalence declined more rapidly than the preceding trend would predict, contrary to what might be expected if any large gateway effect existed." I put the opposite forward for consideration - it is possible that the decrease in smoking would have been even larger if e-cigarettes did not exist. This is an equally valid point and I think to date there is no evidence either way. In addition, I would add that one teenage child starting to vape and/or smoke is one too many.

Please reference the six additional studies "six additional studies" as this is an important part of reproducibility.

The authors should present the findings of Khouja *et al.* rather than using incomplete statements of commentary taken from the discussion. The point of your current paper is to determine if confounding has been adequately controlled for, not to justify the use of e-cigarettes. I suggest you present objective findings as they will speak for themselves.

Here is what you should consider quoting from Khouja *et al.*, obviously you will need to summarise it:

"The results of individual studies included in the main meta-analysis are: unadjusted [OR: 4.59, 95% CI: 3.60 to 5.85] and (adjusted OR: [2.92, 95% CI: 2.30 to 3.71]). Effect sizes (ORs) ranged from 2.46 to 12.31 (unadjusted) and [2.30 to 3.71] adjusted. All estimates were considered to show strong evidence of a positive association between e-cigarette use among non-smokers and later smoking in unadjusted analyses. Covariates included in the adjusted analyses varied on a study-by-study basis. After adjustment, effects in all but three studies remained strong."

With respect to "relying on self-reported measures", I note, based on experience, that none of the existing cohort studies did biochemical verification of outcomes as they relied on the tried and tested questions about ever use, recent or last year use, and current or last 30 days use and these measures are accepted the world over for surveying the use of tobacco products, licit drugs, and illicit drugs. The most common measure of both e-cigarette and cigarette use was 'ever use' of either product, an indicator which has been critiqued by researchers in one paper [56], as it did not observe whether the teenagers used the product once in their young life, or if they used it regularly. 'Past-30-day use' has gotten the same censure. However, the use of these indicators has been justified, with a recent study by Birge *et al.* finding that over two-thirds of smokers who ever consumed a single puff of a tobacco cigarette during adolescence became, for a time, regular smokers [57].
Taken from: O'Brien D, see citations.

I would point out that you are relying on self-reported measures in all three studies, and if use of this data is inaccurate and misleading, a better use of time and resources might be to fund PATH to do independent biochemical verification of very current use and then run the analysis. However, I worked on the topics of alcohol, tobacco, and drugs for the past 20 years and in my experience, the findings will be that self-reported measures underestimate use indicating that the situation is more serious than demonstrated in surveys or cohort studies.

The research question needs to be phrased specifying the population (in the PATH study), the intervention of interest, the comparator, and the outcomes measured. The population are teenagers living in the USA and this needs to be included in the analysis and discussion. The intervention of interest is the move from e-cigarettes to tobacco cigarette smoking. The outcome of interest is initiated tobacco cigarette smoking. Your current objective requires rewriting base on the above guidance and then you should go on to explain the rationale for your analysis explaining the limitations of the 2018 analysis.

Is the study design appropriate and is the work technically sound? Partly.
I think the methods need to be rewritten as I had to read them three times to try and ascertain what the researchers did. Most readers will not do this, so a plain English and logical approach is required. The current paper requires the authors to read the 2018 paper before reading this paper and I do not think that this is good enough and it is very frustrating for a reader. Most people won't do this.

I recommend:
When presenting a cohort study, the following facts need to be presented: title of the cohort study, objective of the cohort study, a description of the study population, total sample in WAVE 1 and the phase 1 study response rate, loss to follow-up for WAVE 2 as compared to WAVE 1, for WAVE 3 as compared to WAVE 1, for WAVE 3 as compared to WAVE 2, A list of covariates for each wave and any changes between waves should be presented. In addition, I would explicitly state

the independent variable, dependent variable and covariates used in this analysis. Finally, the percentage of missing data for key variables needs to be reported. Response rates, loss to follow-up and missing data have implications for a valid and representative analysis, so I recommend that they are presented here and a judgement by the authors (Lee *et al.*) as to whether the quality of the PATH study is adequate for this analysis.

I would then describe any selections and exclusions of data from the original cohort explaining why you did this and what are the implications for validity and representativeness.

Then present the differences in how the PATH study variables were used in this study compared to the 2018 iteration. I would present them in a small table showing 2018 use and 2021 use as this would help the reader.

I recommend you state the variables included in the propensity index. In your tables there are no participants aged 18 or over while in your text 18+ is mentioned but not clearly explained. Please explain the situation to the reader and in the results provide exact numbers and proportions located in the adult data.

I recommend that you provide the reader with a description of a sensitivity analysis, explaining the rationale for doing the **four** sensitivity analyses, and the method you are using. You have a four bullet points, one for each sensitivity analysis, and I suggest you used these in a table with four columns (and five rows). The column titles are: Short title for sensitivity analysis; Sensitivity analysis descriptor; Rationale for each sensitivity analysis; Covariates for the sensitivity analysis. This would help with transparency and the reader.

I recommend that you delete the term 'main' and 'additional' from the **five** analyses as they are confusing and main implies that there is only one principal analysis when there are three main analyses and two additional analyses. I recommend that you title them: Analysis 1, Analysis 2, Analysis 3, Analysis 4 and Analysis 5; please make the same changes in your table and text in the results section. The five analyses could be summarised in a table with four columns and six rows. The column titles could be: Analysis number; description of the analysis; difference with respect to the 2018 paper, and rationale for this difference. This would save on text but increase clarity for the reader. Then, please tell the reader how the four sensitivity analyses relate to the five analyses.

I think the reader would want explanations of the ROELEE program, and the terms 'step function' and GLM package (considering what they are, why they are used, and how they are used).

Are sufficient details of methods and analysis provided to allow replication by others? No.
The authors need to provide a much clearer description of what they did and why they did what they did to allow replication. In addition, the selectors (syntax) used to identify the data downloaded from PATH is required. They also need to provide the two syntax for cleaning and analysing the data. Apart from the publicly available data from PATH, I can't access any of the supplementary information or additional files. This needs to be corrected by the journal.

If applicable, is the statistical analysis and its interpretation appropriate? I think it may well be.
I found the results text difficult to read and understand and suggest that a professional editor is employed to rewrite the text and ensure that the text matches the tables. When the editor is

finished with your work, please check the table numbers and numbers quoted in the text to ensure that they align. The tables are the best part of this report though I suggest some improvements for transparency and clarity. The endnotes require work and I have made some recommendations for these below and a small number of recommendations for the tables themselves. I also suggest the table headings are rewritten by the professional writer as they are difficult to understand on first reading.

Table 1 requires the following corrections: percentage of total beside each N in column 3, exact age [add in years]; the base and numbers (%) for Ever been curious about smoking a cigarette, Think you will smoke a cigarette in the next year, Think you will try a cigarette soon and whether the base is yes or no and what the current confidence intervals represent; and any other categories in the three variables to make the 8058. I know you have small letters at the end that may entitle you to present incomplete data, but the explainer does not explain the data to me. It would be more correct and transparent to provide the full data for this variable and you can put your summary OR at the end and explain why and how you are using it in the end note and how this affects your regression analysis.

In addition, Tables 2, 3, 4, 6, 7 require clearer end notes.

Please revise end note text as follows. Example for table 2 "Between Waves 2 and 3 261/7367 (3.54%) of never users of e-products at Wave 2 started smoking, while 148/893 (16.57%) of ever users of e-cigarettes started smoking" as the existing text is unclear. Please ensure correct numbers for the end note to tables 3, 4, 6, 7.

Please revise text as follows "For individuals who were 16 (n=) or 17(n=) at Wave 1, adult data (n=) were used to determine e-product use and cigarette smoking at later Waves; the percentage that were followed-up was %"; this increases transparency. Please ensure correct wave, age and numbers in tables 3, 4, 6, 7.

Are the conclusions drawn adequately supported by the results? No.
The discussion is confusing, contradictory, and incomplete when dealing with the excess risk contributed by e-cigarette use on initiation of smoking tobacco use or gateway effect, and requires complete rewriting supported by evidence-based research findings under the headings: main findings, comparison of findings with other research (beginning with your own, other primary studies (already there) and then systematic reviews), strengths and limitations of the research (including how you addressed your limitations), and finally implications for policy and practice (using best practice).
The first section of the discussion is not written in the usual format and is therefore confusing. I recommend that the authors should begin with a summary of their new analysis, then compare it to their previous analysis and explain why they have different results. The authors should then state clearly that there is a gateway effect and the minimum and maximise size of the gateway effect based on their best controlled analyses.

I don't think the authors should speculate on what is an acceptable magnitude of effect as any 95% confidence intervals that do not include '1' as this indicates a risk that e-cigarettes may introduce teenage children to take up smoking tobacco cigarettes. The authors need to consider their ethical responsibility and duty of care to children with respect to both e-cigarettes and tobacco cigarettes. Is between 22% and 24% of cigarette smoking in teenage children attributed

to initiation of smoking tobacco cigarettes? Please explain the implication of this statistic, if e-cigarettes were removed from this cohort, I estimate that 34 teenagers in this study would not have smoked tobacco cigarettes. If we multiply this figure up to the USA's teenage population, how many teenagers would not smoke?

The current tone of the discussion reads as if the authors are trying to absolve the e-cigarette industry of taking responsibility for the consequences of their product and create doubt about any excess risk or risk that may be attributable to e-cigarettes by blaming the quality of the survey data that the authors themselves decided to use; this contradicts the authors' earlier statement that there is a gateway effect and raises questions as to why the authors did an analysis on inadequate data. I would suggest that if the survey data is inadequate then they should refrain from publishing the analysis. I recommend that the authors should list specific covariates missing form PATH (if covariates are actually missing) that may explain the unaccounted for or residual confounding and avoid generalities. In addition, the authors or industry could provide funding (that is untied) to PATH to do biochemical verification of very current use to test reliability. This would improve the quality of the PATH cohort study.

There are no implications for research and policy presented here despite the admittance to a gateway effect and odds of initiating smoking that are above one. I recommend that the authors describe what actions should be taken by industry and national governments to stop children using e-cigarettes and smoking tobacco cigarettes. These actions should be evidence-based addressing regulation, price, limiting availability, and banning promotion as these are the types of actions that change behaviour. I would refrain from investing in education as the evidence indicates that this does not change behaviour.

The abstract needs to be rewritten once the paper is rewritten.

References
1. Glasser A, Abudayyeh H, Cantrell J, Niaura R: Patterns of E-Cigarette Use Among Youth and Young Adults: Review of the Impact of E-Cigarettes on Cigarette Smoking. *Nicotine & Tobacco Research*. 2019; **21** (10): 1320-1330 Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?
No

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
No

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology, public health and substance use

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 26 January 2021

https://doi.org/10.5256/f1000research.30516.r74455

✅ **James Sargent**
C. Everett Koop Institute, Norris Cotton Cancer Center, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA

I am satisfied with the authors' responses to my concerns. I find it of particular interest that, all else being equal (after propensity score adjustment), upwards of 20% of the youths taking up cigarette smoking can have their new onset smoking attributed to earlier use of e-cigarettes. I think this is a very important addition to the existing literature and speaks to the population-level importance of youth e-cigarette use.

Is the work clearly and accurately presented and does it cite the current literature?
No

Is the study design appropriate and is the work technically sound?
No

Are sufficient details of methods and analysis provided to allow replication by others?
No

If applicable, is the statistical analysis and its interpretation appropriate?
No

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Adolescent substance use.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 26 Jan 2021

Peter Lee, P.N.Lee Statistics and Computing Ltd., Sutton, UK

I thank the reviewer for approving the revised version of the manuscript.

Competing Interests: No competing interests were disclosed.

Reviewer Report 07 December 2020

https://doi.org/10.5256/f1000research.30516.r74456

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Shu Xu 🔗
[1] Department of Biostatistics, NYU School of Global Public Health, New York City, NY, USA
[2] New York University, New York, NY, USA

In the revised manuscript, authors have updated the manuscript with recent publications and also expand discussion based on the results of attrition analyses and current literature.

In my previous review, I have pointed out that the manuscript is hard to follow because readers need to refer to two previously published articles to figure out research details. It is understandable that authors should avoid reporting overlapping materials from published articles, however, I recommend authors (1) focus on the current study and provide a complete and independent introduction of the CURRENT study (by summarizing instead of repeating the details), and (2) relocate the similarities and differences between earlier study and current study to the Discussion section. The introduction should emphasize why and what are new in the current study. For example, testing the potential heterogeneity among participants at various ages would be a contribution to the literature. Currently, the analyses were introduced in the Methods and Results session, however, it is unclear why these analyses were needed.

Meanwhile, I would like to point out a few technical issues.
  1. Discussion: A 13% attrition rate in a longitudinal study may not be trivial. In missing data literature,[1] Schafer considered a missing rate of 5% or less is ignorable. Bennett maintained that statistical analysis is likely to be biased when more than 10% of data are missing. Authors need to clearly state the assumption and implication of removing participants with

missing data in a listwise fashion.

2. Reporting adjusted OR based on various adjustment approaches is not equivalent to achieving covariate balancing. Tables 2 – 4 may serve as sensitivity tests on how ORs would be impacted based on various adjustment of confounding. Given the manuscript focuses on the extent to which the exposure effect of e-cigarette can be explained by covariates, then it would be important to discuss (1) whether covariate balance has achieved in the data under study, and (2) what would be the possible consequence if any important covariate being ignored or not being measured in the current study.

References
1. Dong Y, Peng C: Principled missing data methods for researchers. *SpringerPlus*. 2013; **2** (1).
Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?
No

Is the study design appropriate and is the work technically sound?
No

Are sufficient details of methods and analysis provided to allow replication by others?
No

If applicable, is the statistical analysis and its interpretation appropriate?
No

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Longitudinal data analysis, propensity score methods, missing data method, tobacco research.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 29 Jan 2021
Peter Lee, P.N.Lee Statistics and Computing Ltd., Sutton, UK

Reply to further comments made by Shu Xu

We thank the reviewer for their further comments, but were rather disappointed by their content, especially given that the other reviewer James Sargent considered that he could now approve version 2 of our paper based on the revisions we had made.

In our paper Investigating gateway effects using the PATH study", published in F1000 Research in 2019 and based on Waves 1 and 2 of that study, we concluded that confounding is a major factor explaining most of the observed gateway effect, but were concerned about the possibility of over-adjustment if taking up e-cigarettes had affected the values of some of the Wave 1 predictor variables considered. We suggested in that paper that the possibility of over-adjustment could be avoided by relating initiation of cigarette smoking at Wave 3 to vaping at Wave 2, restricting attention to those who, at Wave 1, had never vaped, and using propensity indicators recorded at Wave 1 linked to uptake of e-cigarettes by Wave 2. This is noted in the penultimate paragraph of the introduction of our current paper, and as we stated in the following paragraph the main objective was to conduct such analyses, though we also pointed out that we also included a variety of sensitivity and alternative analyses for reasons we described further on in the paper.

Shu Xu recommends that we provide a "complete and independent" introduction of the current study and relocate the similarities and differences between the 2019 study and the current study to the discussion section. We totally disagree with this idea – the current study arose out of suggestions made in the 2019 study, and is effectively an improved extension of it. Accordingly it makes the paper much more understandable if, in the introduction, we start by summarizing what the 2019 study did and showed and make it absolutely clear that the current paper arose out of ideas proposed in the 2019 paper. It would, in our view, be totally wrong to discuss similarities and differences between the 2019 paper and the current study in the discussion, as it would then not make clear to the reader at the outset the main objective of our paper. Also, as so many of the methodological details were already described in the 2019 paper, there is really no need to give a greater description of what we did than is already in the methods. We would expect the interested reader to look back at our 2019 paper if necessary.

The first technical issue Shu Xu refers to relates to the 13% attrition rate which they argue may not be "trivial". We certainly did not regard it as trivial (describing it only as "not large"), since we conducted the various analyses summarized in the fourth paragraph of the discussion. While we accept that there is always some possibility of bias due to attrition we feel that the arguments expressed in the last sentence of this paragraph leading to our conclusion that "it seems unlikely to us that any material bias to our estimated ORs could arise due to loss to follow-up and missing data" still hold.

The other technical issue Shu Xu refers to concerns their belief that the reporting of adjusted ORs based on various adjustment approaches "is not equivalent to achieving covariate balancing." One is trying to answer the question "does a never smoking individual who vapes have a different probability of taking up smoking, as compared to a never smoking individual who does not vape and who also has the same set of smoking predictors as the one who vapes." As is generally the situation in epidemiological research, one cannot possibly ensure that one has achieved exact covariate balance and so we have used standard epidemiological techniques to deal with covariates. However, though we

have considered an extremely large number of variables (see Table 1 of the 2019 paper), certainly more than considered in most previous research on the gateway effect, we do already note (in the discussion in paragraph 3) that "there may be some relevant predictors or interactions of predictors not considered," and our analyses already give results with or without adjustment for a range of predictors. One cannot of course assess in practice the consequence of an important covariate not being measured in the current study, without knowing what the covariate is. One can do hypothetical analysis for a mystery confounder with certain properties, but that is clearly beyond the scope of this paper.   There are already many theoretical statistical papers in the literature which investigate the bias that failure to consider relevant covariates might have, but we see no reason to refer to that here – we already consider this in our other 2019 paper "Considerations related to vaping as a possible gateway into cigarette smoking: an analytical review."

We prefer to leave our paper in the form it currently is. If the arguments that we express here convince Shu Xu to change their verdict to "Approved" we would of course be pleased. If not, we will have to wait for the verdict of another peer reviewer before our paper can be sent to MedLine and other such databases.

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 13 October 2020

https://doi.org/10.5256/f1000research.26798.r71761

? Shu Xu

[1] Department of Biostatistics, NYU School of Global Public Health, New York City, NY, USA
[2] New York University, New York, NY, USA

The authors examined the association between youth prior e-cigarette use and increased risk of subsequent cigarette smoking using the Waves 1 – 3 data from the PATH study. This work is an extension of their previous studies which were published in Lee *et al.* (2018) and Lee and Fry (2019), the latter was based on the Waves 1 and 2 data from the PATH study. This study is interesting because the authors conducted three main analyses studying the association between e-cigarette use and subsequent cigarette smoking along with sensitivity analyses. This review emphasized the statistical methodology and results reporting. A few major concerns are below.

1. I feel the readability of this paper would be improved if authors could (1) focus on what is the limitation of the previous articles, (2) clearly state what are the new analyses about based on what has been done previously, and (3) state why versions of M1, M2, M3 were conducted and the logic behind them. The authors need to provide a full picture of the

study design and analytical plan of the current study. In case some details are overlapped with previous articles when referred to the previous article, authors need to at least summarize the details instead of releasing no specific information.

2. The main concern of the previous study is about the possibility of "over-adjustment," and the extent to which the association between prior e-cigarette use and subsequent cigarette initiation has been "over-adjusted." It would be critical to evaluate whether covariate balance was sufficient when propensity scores had been considered in the current analyses. Without covariate balance, the results of the current study may be considered unreliable. Thus, detailed results such as (a) propensity score distribution by e-cigarette exposure groups and (b) comparison of the extent of covariate imbalance are desired.

3. In the Methods section, authors need to clearly state how the missing values were treated in analyses of the current study. This also involved how authors treated the missing values when selecting covariates of versions of M1, M2, and M3. The results of the current study could be misleading if only participants with complete data were considered.

4. It was unclear to me why to study the continuous age and grouped age and compare the difference. It seems like continuous age provided an exact measure however grouped age did not. Putting participants into categories is rarely defensible unless authors provide further justification. It is also unclear to me why only interactions with age (no other covariates, for example, race) were considered.

Minor concerns are below.

1. In tables, in addition to individuals who were 16-17 at Wave 1, adult data were used. Please clarify, for those who were 15-16 at Wave 1 (those who were 18+ at Wave 3), whether adult data were also used in this study?

2. The abstract was very confusing. It failed to provide an overview of the study. For example, a clear introduction of the methods and results of M1 and have been presented. This information regarding M2 and M3 were not clearly reported.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Longitudinal data analysis, propensity score methods, missing data method, tobacco research.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 28 Oct 2020

Peter Lee, P.N.Lee Statistics and Computing Ltd., Sutton, UK

Reply to comments made by Shu Xu

We thank the reviewer for the time he has spent and the useful comments made. Our replies to the points made are given in bold face type, making it clear where we have amended the original version of the paper. Note that the changes made to the paper are also intended to answer the points made by James Sargent, the other reviewer. We hope that our answers and the changes to the paper will allow the revision to be approved.

Approved With Reservations
The authors examined the association between youth prior e-cigarette use and increased risk of subsequent cigarette smoking using the Waves 1 – 3 data from the PATH study. This work is an extension of their previous studies which were published in Lee *et al.* (2018) and Lee and Fry (2019), the latter was based on the Waves 1 and 2 data from the PATH study. This study is interesting because the authors conducted three main analyses studying the association between e-cigarette use and subsequent cigarette smoking along with sensitivity analyses. This review emphasized the statistical methodology and results reporting. A few major concerns are below.

- I feel the readability of this paper would be improved if authors could (1) focus on what is the limitation of the previous articles, (2) clearly state what are the new analyses about based on what has been done previously, and (3) state why versions of M1, M2, M3 were conducted and the logic behind them. The authors need to provide a full picture of the study design and analytical plan of the current study. In case some details are overlapped with previous articles when referred to the previous article, authors need to at least summarize the details instead of releasing no specific information.

The three paragraphs of the discussion starting "Our second paper.." describe in some detail the analyses we had previously conducted using data from Waves 1 and 2 only, what the main results of these analyses were, and the fact that the estimates were open to the possibility of over-adjustment if taking up e-cigarettes had affected the values of some of the Wave 1 predictor variables considered. It also makes it clear that our earlier paper described how this possibility could be avoided by using data from Waves 1, 2 and 3. We have now amended the final paragraph of the discussion to

make it clear that analysis M1 in the current paper was that envisaged in our earlier paper, and that this was the main objective of our work. In the methods section, there was already some comment on why we had conducted the other main analyses, the sensitivity analyses and the alternative analyses, but this has now been extended in various places to make it clearer. Where details of our analyses are the same as those in our earlier analyses, it seems needlessly duplicative to repeat these details in the current paper, and is not the usual thing to do in such a situation.

- The main concern of the previous study is about the possibility of "over-adjustment," and the extent to which the association between prior e-cigarette use and subsequent cigarette initiation has been "over-adjusted." It would be critical to evaluate whether covariate balance was sufficient when propensity scores had been considered in the current analyses. Without covariate balance, the results of the current study may be considered unreliable. Thus, detailed results such as (a) propensity score distribution by e-cigarette exposure groups and (b) comparison of the extent of covariate imbalance are desired.

Our latest paper has removed the possibility of over-adjustment in our previous work by the use of propensity indicators based on data recorded at Wave 1 in those who, at that time, had never vaped. The reviewer questions whether covariate balance is sufficient after the propensity scores are taken into account. This has been investigated in Tables 2, 3 and 4 for the three main analyses in turn by considering whether adjustment for the individual variables making up the propensity index materially affected the estimated gateway effect. The effect was generally quite small, suggesting that reasonable balance had been achieved. We think that including the additional material suggested by the reviewer would add little other than extra complexity. We also note that our previous paper did not include such material and was approved by the reviewers who considered it.

- In the Methods section, authors need to clearly state how the missing values were treated in analyses of the current study. This also involved how authors treated the missing values when selecting covariates of versions of M1, M2, and M3. The results of the current study could be misleading if only participants with complete data were considered.

As we note in the first sentence of the methods section "Some aspects of the analyses described here are the same as those described earlier (Lee & Fry, 2019) are not presented again here." In that paper we made it clear that all the logistic regression analyses used "required individuals with complete data on all variables", and that the various stages in developing propensity scores used "groups of conceptually-related variables, with missing values likely to be on the same individuals". We prefer not to repeat the description of this part of the methodology in the current paper. However, in the new paragraph we have added into the discussion (starting "Other issues are…"), we have addressed your point that basing the analysis only on complete data might be misleading. This point is similar to one raised by another reviewer. We hope you find this satisfactory.

- It was unclear to me why to study the continuous age and grouped age and compare the difference. It seems like continuous age provided an exact measure however grouped age did not. Putting participants into categories is rarely defensible unless authors provide further justification.

As regards age, the 2019 paper we had published based only on Wave 1 and 2

subdivided individuals into ages 12-14 and 15-17 as the data were only available in that form. Assuming that the Waves were conducted a year apart (which they approximately were) we could infer that those who were 12-14 at Wave 1 and 15-17 at Wave 2 were 14 at Wave 1 (and 15 at Wave 2), and that those who were 15-17 at Wave 1 and adults at Wave 2 were 17 at Wave 1 (and 18 at Wave 2). However we could not estimate the exact age of those who were 12, 13, 15 or 16 at Wave 1. The position changed in the analyses using Wave 3 as well, as we could define those who were 12-14 throughout as 12 at Wave 1, those who were 12-14 at Waves 1 and 2 and 15-17 at Wave 2 as 13 at Wave 1 and so on. While it would be preferable to use exact age throughout in some ways, here we were carrying out further analyses using the propensity index developed in the 2019 paper which included a term based on grouped age. As the paper presents the main analyses using both grouped age and exact age, and the results were much the same, there is no real problem.

- It is also unclear to me why only interactions with age (no other covariates, for example, race) were considered.

On the basis that age had a major effect on the rate of e-cigarette use and on uptake of smoking, we included interactions of age with the three predictors most strongly linked to the relevant gateway effect. As this had essentially no effect on the estimates of the gateway effect, we felt that looking at further interactions would not be worthwhile. Race was not a predictor that was included in the propensity index, so it seemed highly unlikely that including interactions with it would have had any major effect. It would of course have been theoretically possible to consider many more predictors, including interactions of each predictor with each other predictor, higher order interactions, or quadratic or cubic terms in some predictors, but one has to stop somewhere. However in the third paragraph of the discussion we have changed "there may be some relevant predictors not considered" to "there may be some relevant predictors or interactions of predictors not considered."

Minor concerns are below.

- In tables, in addition to individuals who were 16-17 at Wave 1, adult data were used. Please clarify, for those who were 15-16 at Wave 1 (those who were 18+ at Wave 3), whether adult data were also used in this study?

Those who were 17 at Wave 1 would have been 18 at Wave 2 so adult data would have been used. Similarly, those who were 16 at Wave 1 would have been 18 at Wave 3 so adult data would again have been used. However, those who were 15 at Wave 1 would not have been adults at Wave 3, so adult data were irrelevant. To avoid confusion we have changed age ranges like "16-17" to "16 or 17" in the various places they occurred in the paper.

- The abstract was very confusing. It failed to provide an overview of the study. For example, a clear introduction of the methods and results of M1 and have been presented. This information regarding M2 and M3 were not clearly reported.

We are constrained by the 300 word limit for the abstract, but have modified the abstract (particularly the methods section) to try to make things clearer.

- Is the work clearly and accurately presented and does it cite the current literature?

Yes

- Is the study design appropriate and is the work technically sound?

Partly

○ Are sufficient details of methods and analysis provided to allow replication by others?

Partly

○ If applicable, is the statistical analysis and its interpretation appropriate?

Partly

○ Are all the source data underlying the results available to ensure full reproducibility?

Yes

○ Are the conclusions drawn adequately supported by the results?

Yes

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
We hope that we have answered the reviewer's reservations adequately.

Competing Interests: The authors are both long term consultants to the tobacco industry

Reviewer Report 22 July 2020

https://doi.org/10.5256/f1000research.26798.r66520

? **James Sargent**
C. Everett Koop Institute, Norris Cotton Cancer Center, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA

This is a thoughtful analysis of PATH data to determine an unbiased estimate of the relation between initial e-cigarette use among never cigarette smokers and subsequent cigarette smoking. I particularly like the idea of using W1 predictors of W2 e-cigarette onset to parcel out the over adjustment that could occur if these variables are assessed at the same time. I also liked the multitude of sensitivity analyses that showed it doesn't really matter, for example, how propensity scores are modeled. I see no major weaknesses. However I have a few suggestions.

1. It might not be unreasonable to have a statistician review the analysis.

2. This is a complete case analysis. Given that there are missing data for each individual variable and that there is loss to follow up, the authors need to convince us with some sort of sensitivity analysis that the results are not largely affected by attrition bias.

3. The literature review makes it seem like these are the only authors who have published on gateway effects using PATH data. They need to cite other PATH papers, point out weaknesses in them, and help us understand why this publication is worthy of attention.

One worthy of particular attention used a propensity score analysis similar to these authors' W1-W2 analysis[1]

4. One limitation not mentioned is that cigarette smoking onset does not make addicted cigarette smoker. This needs to be mentioned as a limitation.

5. The authors miss some of the many studies that examined the relation between initial use of e-cigarettes and subsequent cigarette smoking. They could fill in that gap by mentioning and citing a meta-analysis conducted by Khouja in Tobacco Control that identified 17 prospective studies[2]. It is worth comparing their best estimate with the combined estimates presented in that meta analysis.

6. Finally, given that there have been so many prospective studies, and all have pointed to a gateway effect, it seems reasonable to conclude that there is one, that is, that use of these devices independently increases risk for subsequent use of cigarettes. I realize that we could continue to quibble about the effect size, but this study does a good job of convincing us that the relative risk is real and that it is substantial, around 3. It seems like it might be an opportunity to also help us understand the population significance of the finding. The authors could do that with this population-based sample (which includes weights) by determining what proportion of the observed cigarette initiation is attributable to the gateway effect using attributable risk methods (risk difference as opposed to risk ratio). They could use the weights to determine the number of new cigarette initiators there were in the US that year attributable to e-cigarette exposure. This would be a real and novel contribution that would help investigators compare the public health consequences to youth with the public health consequences resulting from increased smoking cessation.

References
1. Stanton C, Bansal-Travers M, Johnson A, Sharma E, et al.: Longitudinal e-Cigarette and Cigarette Use Among US Youth in the PATH Study (2013–2015). *JNCI: Journal of the National Cancer Institute*. 2019; **111** (10): 1088-1096 Publisher Full Text
2. Khouja JN, Suddell SF, Peters SE, Taylor AE, et al.: Is e-cigarette use in non-smoking young adults associated with later smoking? A systematic review and meta-analysis.*Tob Control*. 2020. PubMed Abstract | Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Adolescent substance use.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 28 Oct 2020
Peter Lee, P.N.Lee Statistics and Computing Ltd., Sutton, UK

Reply to comments made by James Sargent

We thank the reviewer for the time he has spent and the useful comments made. Our replies to the points made are given in bold face type, making it clear where we have amended the original version of the paper. Note that the changes made to the paper are also intended to answer the points made by Shu Xu, the other reviewer. We hope that our answers and the changes to the paper will allow the revision to be approved.

Approved With Reservations
This is a thoughtful analysis of PATH data to determine an unbiased estimate of the relation between initial e-cigarette use among never cigarette smokers and subsequent cigarette smoking. I particularly like the idea of using W1 predictors of W2 e-cigarette onset to parcel out the over adjustment that could occur if these variables are assessed at the same time. I also liked the multitude of sensitivity analyses that showed it doesn't really matter, for example, how propensity scores are modeled. I see no major weaknesses. However I have a few suggestions.
  ○ It might not be unreasonable to have a statistician review the analysis.

Both the authors of this paper are experienced statisticians, as is Shu Xu, the other reviewer.
  ○ This is a complete case analysis. Given that there are missing data for each individual variable and that there is loss to follow up, the authors need to convince us with some sort of sensitivity analysis that the results are not largely affected by attrition bias.

We have added a new paragraph into the discussion, starting "Other issues are..." and hope this meets the reviewer's point.
  ○ The literature review makes it seem like these are the only authors who have published on gateway effects using PATH data. They need to cite other PATH papers, point out weaknesses in them, and help us understand why this publication is worthy of attention. One worthy of particular attention used a propensity score analysis similar to these authors' W1-W2 analysis[1].

We have added a new paragraph in the discussion, after the one referring to other

studies on the gateway issue, to consider other studies using PATH data, including the Watkins study on which we had commented previously in our 2019 paper.

- One limitation not mentioned is that cigarette smoking onset does not make addicted cigarette smoker. This needs to be mentioned as a limitation.

At the end of the paragraph in the discussion starting "Generally our consistent" we have made the point that some of those recorded as taking up smoking at Wave 3 may only have taken it up for a short while, a limitation that can be answered better in analyses based also on data from later Waves.

- The authors miss some of the many studies that examined the relation between initial use of e-cigarettes and subsequent cigarette smoking. They could fill in that gap by mentioning and citing a meta-analysis conducted by Khouja in Tobacco Control that identified 17 prospective studies[2]. It is worth comparing their best estimate with the combined estimates presented in that meta analysis.

We are not sure why the reviewer thought we were not citing other studies. The first paragraph of the introduction refers to the meta-analysis of Soneji et al. which considered nine studies, while the second paragraph of the introduction refers to our 2018 paper which includes a detailed commentary on 15 studies. Also the fourth paragraph of the discussion refers to quite a number of recent studies. However, we have now made it clear in the paragraph summarizing conclusions from our 2018 paper that it considered 15 cohort studies that have reported unadjusted and adjusted estimates of the gateway effect, nine considered in the 2017 meta-analysis by Soneji et al. and six additional studies. We have also added a paragraph in the introduction mentioning the recent review by Khouja et al. that the reviewer referred to.

- Finally, given that there have been so many prospective studies, and all have pointed to a gateway effect, it seems reasonable to conclude that there is one, that is, that use of these devices independently increases risk for subsequent use of cigarettes. I realize that we could continue to quibble about the effect size, but this study does a good job of convincing us that the relative risk is real and that it is substantial, around 3. It seems like it might be an opportunity to also help us understand the population significance of the finding. The authors could do that with this population-based sample (which includes weights) by determining what proportion of the observed cigarette initiation is attributable to the gateway effect using attributable risk methods (risk difference as opposed to risk ratio). They could use the weights to determine the number of new cigarette initiators there were in the US that year attributable to e-cigarette exposure. This would be a real and novel contribution that would help investigators compare the public health consequences to youth with the public health consequences resulting from increased smoking cessation.

In order to illustrate the population effect we have added a new paragraph in the discussion (starting "A question of interest is..") which estimates the percentage of new smokers associated with exposure to e-cigarettes as about 23%.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

- Is the study design appropriate and is the work technically sound?

Yes

○ Are sufficient details of methods and analysis provided to allow replication by others?

Yes

○ If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

See comment above.

○ Are all the source data underlying the results available to ensure full reproducibility?

Yes

○ Are the conclusions drawn adequately supported by the results?

Yes

References

1. Stanton C, Bansal-Travers M, Johnson A, Sharma E, et al.: Longitudinal e-Cigarette and Cigarette Use Among US Youth in the PATH Study (2013–2015). *JNCI: Journal of the National Cancer Institute*. 2019; **111** (10): 1088-1096 Publisher Full Text

2. Khouja JN, Suddell SF, Peters SE, Taylor AE, et al.: Is e-cigarette use in non-smoking young adults associated with later smoking? A systematic review and meta-analysis.*Tob Control*. 2020. PubMed Abstract | Publisher Full Text

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
We hope that we have answered the reviewer's reservations adequately.

Competing Interests: The authors are both long term consultants to the tobacco industry

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