RESEARCH ARTICLE

REVISED Investigating the effect of e-cigarette use on quitting smoking in adults aged 25 years or more using the PATH study [version 3; peer review: 3 approved, 1 not approved]

Peter N. Lee [1], John S. Fry [2]

[1]P.N.Lee Statistics and Computing, Sutton, Surrey, SM2 5DA, UK
[2]RoeLee Statistics Ltd, Sutton, Surrey, SM2 5DA, UK

v3 **First published:** 07 Sep 2020, **9**:1099
https://doi.org/10.12688/f1000research.26167.1
Second version: 12 Mar 2021, **9**:1099
https://doi.org/10.12688/f1000research.26167.2
Latest published: 20 Jun 2022, **9**:1099
https://doi.org/10.12688/f1000research.26167.3

Abstract

Background: The evidence on harms and benefits of e-cigarettes partly concerns whether their use encourages smokers to quit. We addressed this using data from the nationally representative PATH study, with detailed accounting for potential confounding variables.
Methods: We considered adults aged 25+. Our original analyses, reported in version 1 of this paper, used data for Waves 1 to 3, separate analyses considering Waves 1 to 2, 2 to 3 and 1 to 3. These related baseline ever e-cigarette use (or e-product use at Wave 2) to quitting at follow-up, adjusting for confounders derived from 55 candidates. Sensitivity analyses omitted ever other product users, linked quitting to current e-cigarette use, and used values of some predictors modified using follow-up data. Additional analyses used data for Waves 1 to 4, separately considering sustained, delayed and temporary quitting during Waves 1 to 3, 2 to 4 and 1 to 4. Sensitivity analyses considered 30-day quitting, restricted attention to smokers attempting to quit, and considered ever smokeless tobacco or snus use.
Results: In the original analyses, unadjusted odds ratios (ORs) of quitting smoking for ever e-cigarette use were 1.29 (95% CI 1.01-1.66), 1.52 (1.26-1.83) and 1.47 (1.19-1.82) for the Wave 1 to 2, 2 to 3, and 1 to 3 analyses. These reduced after adjustment, to 1.23 (0.94-1.61), 1.51 (1.24-1.85) and 1.39 (1.11-1.74). Quitting rates remained elevated in users in all sensitivity analyses. The additional analyses found associations of e-cigarette use with sustained, delayed and temporary quitting, associations little affected by considering 30-day quitting, and only slightly reduced restricting attention to quit attempters. Ever use of smokeless tobacco or snus also predicted increased quitting.
Conclusions: As does most evidence from clinical trials, other analyses of PATH, and other epidemiological studies, our results

Open Peer Review

Approval Status ✗ ✓ ✓ ✓

	1	2	3	4
version 3 (revision) 20 Jun 2022	✗ view	✓ view	✓ view	✓ view
version 2 (revision) 12 Mar 2021	✗ view	? view	? view	? view
version 1 07 Sep 2020	✗ view			

1. **John P. Pierce**, University of California, San Diego, San Diego, USA
Ruifeng Chen, University of California, San Diego, San Diego, USA
Tarik Benmarhnia, University of California San Diego, San Diego, USA
University of California San Diego, San Diego, USA
Karen Messer, University of California, San Diego, San Diego, USA

2. **Riccardo Polosa**, University of Catania, Catania, Italy

3. **Alan G. Kaplan**, University of Toronto,

suggest using e-cigarettes helps adult smokers to quit.

Keywords
Cigarettes, Confounding, Over-adjustment, E-cigarettes, Cessation, Modelling

Toronto, Canada

4. **Arielle S. Selya**, PinneyAssociates, Inc., Pittsburgh, USA

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

Corresponding author: Peter N. Lee (PeterLee@pnlee.co.uk)

Author roles: Lee PN: Conceptualization, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Fry JS**: Data Curation, Formal Analysis, Investigation, Methodology, Software, Validation, Writing – Review & Editing

Competing interests: Both authors are long term consultants to the tobacco industry and organizations, including the funder of this study.

Grant information: Financial support for the original analyses based on Waves 1, 2 and 3 was provided by Philip Morris Products SA. Financial support for the additional analysis based on Waves 1 to 4 was provided by P N Lee Statistics and Computing Ltd. While some technical comments were provided by Philip Morris Products SA on drafts of the statistical plan for the original analysis and for version 1 of this publication, the final versions remain the responsibility of the authors.
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Lee PN and Fry JS. **Investigating the effect of e-cigarette use on quitting smoking in adults aged 25 years or more using the PATH study [version 3; peer review: 3 approved, 1 not approved]** F1000Research 2022, **9**:1099 https://doi.org/10.12688/f1000research.26167.3

First published: 07 Sep 2020, **9**:1099 https://doi.org/10.12688/f1000research.26167.1

REVISED **Amendments from Version 2**

In response to the comments made by Drs. Selya, Kaplan and Polosa and a reread of the text the following changes have been made to the paper.

In the abstract, the word "forever" has been replaced by "for ever" in the results section, and "As does most..." has been replaced by "Consistent with most..." in the conclusions section.

In the first paragraph of the introduction the first sentence has been extended to refer to some evidence that risk of cardiovascular and respiratory disease from e-cigarette use is much less than that from smoking, and "smoking" and "smoker" have been defined by adding "cigarette" before the words.

A new second paragraph of the introduction clarifies what is meant by "quitting" and "smoking" in the remainder of the report.

In the introduction an additional reference has been included to the list of studies reporting higher quit rates in e-cigarette users.

In Table 2, Table 3, Table 4, Table 6 and Table 7 significant odds ratios are highlighted in bold, as mentioned when Table 2 is introduced.

In the discussion, the paragraph describing "The strengths of our work..." has been modified to note the possibility of selection bias in the PATH study.

Near the end of the discussion, in the paragraph starting "While, it is clear..." an extra sentence mentions the possibility of analyses relating quitting to the extent of e-cigarette use.

In the conclusion, "adults" has been replaced by "US adults" in the first line, and a statement is added at the end to state that our results "seem likely to apply to other countries and time periods."

None of the results of the analyses have been changed and replies to the reviewers cover all the points they made.

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

It was considered by experts that e-cigarettes cause far less harm to their users than do cigarettes (Nutt *et al.*, 2014), a view supported by limited epidemiological evidence for cardiovascular disease (e.g. Berlowitz *et al.*, 2022; Critcher & Siegel, 2021; Rodu & Plurphanswat, 2020) and respiratory disease (e.g. Antwi & Rhodes, 2022; Osei *et al.*, 2020). However, the introduction of e-cigarettes may theoretically have various other adverse and beneficial effects (Lee *et al.*, 2019). Adverse effects would occur if the use of e-cigarettes encouraged initiation of cigarette smoking, if cigarette smokers intending to quit take up e-cigarettes instead, or if cigarette smokers take up e-cigarettes without reducing their cigarette consumption. Beneficial effects would occur if individuals who would otherwise have continued cigarette smoking switch instead to e-cigarette use, if simultaneous use of e-cigarettes helps cigarette smokers to materially reduce their cigarette consumption, or if use of e-cigarettes helps established cigarette smokers to quit. Here we present results relating to the last of these possibilities, the effect of e-cigarette use on quitting.

Note that the term "quitters", as used here, relates to those who were smoking at baseline, but not at the end of follow-up, even though they may later relapse to smoking. Some prefer the term "discontinuation of cigarette smoking" (Kasza *et al.*, 2021). Here, we use "quitting" to relate to cigarette smoking, regardless of use of, or switching to, e-cigarettes or other nicotine products, and use "smoking", not further defined, to relate to cigarettes.

Information on e-cigarette use as an aid to quitting comes from various sources. Evidence from randomised controlled trials comparing smokers assigned a nicotine e-cigarette or a placebo (Baldassarri *et al.*, 2018; Bullen *et al.*, 2013; Caponnetto *et al.*, 2013; Caponnetto *et al.*, 2019; Eisenberg *et al.*, 2020; Masiero *et al.*, 2019), comparing e-cigarettes with NRT (Hajek *et al.*, 2019; Li *et al.*, 2020) or comparing e-cigarettes with nicotine patches (Walker *et al.*, 2020) generally indicates higher quit rates in the nicotine e-cigarette group, although not all the differences cited were statistically significant (at $p < 0.05$), and one study did not find such higher quit rates (Halpern *et al.*, 2018). A non-randomised study in which smokers were offered free e-cigarettes (Hajek *et al.*, 2015) also found that those who accepted them were more likely to quit. That the evidence from trials suggests higher quit rates in those using e-cigarettes is also consistent with the findings of recent reviews (Grabovac *et al.*, 2020; Hartmann-Boyce *et al.*, 2020; Zhang *et al.*, 2021). While such evidence avoids uncontrolled confounding it can be argued that such trials do not fully reflect what happens in the general population, where smokers choose to try or not try e-cigarettes without being allocated them.

Evidence that smoking rates have declined in the US and UK over a period where e-cigarette use has been increasing (Beard *et al.*, 2020; West *et al.*, 2016b; Zhu *et al.*, 2017) is suggestive of a beneficial effect of e-cigarette use on quitting, but is limited by the difficulty of taking account of other factors affecting smoking rates.

Epidemiological studies are an alternative approach, but while most of such studies show a positive relationship between e-cigarettes and smoking cessation, recent reviews have considered that the evidence is inconclusive due to the low quality of the research (Malas *et al.*, 2016; National Academies of Sciences Engineering and Medicine, 2018). Problems involve the use of cross-sectional studies, the use of unrepresentative populations, the use of non-comparable control groups, failure to limit attention to established e-cigarette users, and the failure fully to take into account the many factors associated with quitting smoking. An expert reaction (West *et al.*, 2016a) made clear that a meta-analysis perversely claiming that e-cigarette use was associated with a reduced risk of quitting (Kalkhoran & Glantz, 2016) suffered from such weaknesses. Restricting attention to cohort studies (other than the study we analyse here) which determine e-cigarette use at baseline and quitting at follow-up, it is clear that by now there are quite a number of studies which report somewhat higher quit rates in those using e-cigarettes, (e.g. (Gomajee *et al.*, 2019; Mantey *et al.*, 2017; Piper *et al.*, 2019; Snow *et al.*, 2018; Young-Wolff *et al.*, 2018; Zhuang *et al.*, 2016), and though there are also many that did

not find any clear association, (e.g. (Bowler *et al.*, 2017; Brose *et al.*, 2015; Chiang *et al.*, 2019; Comiford *et al.*, 2021; Flacco *et al.*, 2019; Grana *et al.*, 2014; Gravely *et al.*, 2020; Harrington *et al.*, 2015; Jackson *et al.*, 2020; Lozano *et al.*, 2019; Pasquereau *et al.*, 2017; Sweet *et al.*, 2019; Wang *et al.*, 2017; Wu *et al.*, 2018), it is rare to find studies (Al-Delaimy *et al.*, 2015; Weaver *et al.*, 2018) suggesting that e-cigarettes inhibits quitting.

Here we describe results from a prospective study aimed at avoiding such weaknesses. The main objective of our analyses is to quantify the relationship between e-cigarette use in smokers and subsequent cessation of smoking, with detailed adjustment for the multitude of factors that may differ between e-cigarette users and non-users. Our analyses are based on the Population Assessment of Tobacco and Health (PATH) study, a nationally representative cohort study of tobacco use and how it affects the health of people in the US. Wave 1 was conducted from 12 September 2013 to 15 December 2014, and our analyses are based on data for this Wave and from annual follow-ups. The data files made publicly available include extensive information on use of various types of tobacco products and on numerous variables linked to initiation of tobacco. In order to avoid complexities caused by consideration of younger adults who may only recently have initiated cigarette smoking, possibly only on a temporary basis, attention is limited to adults aged 25 years or more, an age when initiation of cigarettes is less common.

This paper updates an earlier version that described analyses based on follow-up to Wave 3. The current version takes into account comments on the earlier version made by reviewers Chen and Pierce and also includes additional analyses based on follow-up to Wave 4 aimed at providing further understanding (Chen & Pierce, 2020). There are differences of opinion, described later, in how analyses of smoking cessation should be conducted (Glasser *et al.*, 2020; Pierce *et al.*, 2020b) and we consider a variety of approaches.

Methods

Original analyses based on data from Waves 1, 2 and 3

Separate sets of analyses have been conducted for three periods, from Wave 1 to Wave 2 (period 1), from Wave 2 to Wave 3 (period 2) and from Wave 1 to Wave 3 (period 3). The analyses are based on individuals with relevant data available at Waves 1, 2 and 3 on smoking and e-cigarette use, and take account of the person-based weights of the baseline population. All analyses are limited to individuals aged 25 years or over at baseline.

Some studies of data from Waves 1 to 3 of the PATH study (Benmarhnia *et al.*, 2018; Pierce *et al.*, 2020a; Watkins *et al.*, 2020) have limited analyses to quit attempters, but others (Berry *et al.*, 2019; Kalkhoran *et al.*, 2020; Verplaetse *et al.*, 2019) have not. Although such a limitation more closely mimics randomised control trials (Pierce *et al.*, 2020c) we preferred not to do so in our original analyses, and to avoid bias by adjusting for aspects of quitting in analyses. Our approach uses a larger sample size and provides results that are more representative of the whole population of baseline smokers.

A current cigarette smoker is a "current established cigarette user" defined as "has ever smoked a cigarette, has smoked more than 100 cigarettes in life time, and currently smokes every day or some days", while a former cigarette smoker is a "former established cigarette user" defined as "has ever smoked a cigarette, has smoked more than 100 cigarettes in life time, and now does not smoke at all". Those who are neither current nor former cigarette smokers at baseline are not considered in the analyses.

A current e-cigarette user is a "current established e-cigarette user" defined as "has ever used an e-cigarette, has used fairly regularly and uses every day or some days", while a former e-cigarette user is a "former established e-cigarette user" defined as "has ever used an e-cigarette, has used fairly regularly, and currently does not use at all". An ever e-cigarette user is either a current or former e-cigarette user. At Wave 2 those who smoked other e-products (such as e-cigars, e-pipes or e-hookahs) are also included, so the definition relates to e-product rather than e-cigarette use.

For each period, the analyses relate ever e-cigarette use at baseline to the probability of being an established former smoker at follow-up (referred to subsequently as either "quitting" or "quitting during follow-up"), with adjustment for predictor variables measured at baseline. The predictor variables have been selected from a pre-defined list of candidates classified into eight groups: demographics (A); general aspects of smoking (B); aspects of smoking specifically related to quitting (C); smoking by family and friends (D); awareness of hazards of smoking (E); health status (F); alcohol and drugs (G); and others (H).

The specific predictor variables are listed in the Results section, with fuller details of their definition given in the *Extended data.* While the variables were chosen as being suggested by the literature as being related to smoking, the *Extended data* also provides information, based on Wave 1, of their association with ever e-cigarette use. As shown there, ever use was highly significantly ($p < 0.001$) more frequent in the young and in females, and after adjustment for age and sex, was also highly significantly related to a range of the predictor variables considered, being less frequent in Hispanics and Blacks, and more frequent in those with more income or education, those who ever use other tobacco products, those who have a perceived greater need for tobacco, those who have tried to quit more often, those who plan to quit, those who find it hard to stop smoking and those who have used quitting aids. Users were also clearly more likely to have significant problems more recently with sleeping, anxiety and distress, to see a doctor more often, to use the internet often, and to use various different types of drugs (but not cocaine or crack). At most weak relationships were seen with smoking by family and friends, awareness of the hazards of smoking, use of alcohol, body mass index, or self-perception of physical health or quality of life. Little relationship was also seen between ever e-cigarette use and daily cigarette consumption, a finding which was reported earlier (Lee *et al.*, 2020) where it was suggested that it was explained by smokers taking up e-cigarettes having higher

consumption initially, reduced by partial replacement of cigarettes by e-cigarettes.

Where the baseline of the period studied is Wave 1, the values of the predictor variables used are as recorded at Wave 1. Where it is Wave 2, the values of some variables are amended to take into account data from Wave 1, as described in the *Extended data*.

For each period, the analysis was conducted in seven stages, preliminary counts and six further steps, each involving weighted logistic regression analyses.

Counts Restricted to individuals who were current cigarette smokers at baseline, a frequency table was prepared, separated by quitting during follow-up, of e-cigarette use at baseline by each of the adjustment variables. Missing values are shown, to indicate variables with high levels of missing values requiring special consideration in analysis.

Step 1 This is conducted in eight parts, each part corresponding to a group of predictor variables (A to H). For each part, the regressions first relate each predictor variable individually to quitting, with stepwise forward multiple regressions then carried out, with the most significant predictor variable introduced first, then the next most significant, and so on, until no more variable can be added that is significant at $p < 0.01$.

Step 2 This is in three sections, each involving stepwise forward multiple regressions. The first section considers all the variables found to be significant in Step 1 from groups A, B and C, the second considers those significant from groups D, E and F, and the third those significant from groups G and H.

Step 3 A final stepwise regression considers all the predictor variables remaining as significant in step 2. This generates a final list of predictors to be considered when relating ever e-cigarette use to quitting.

Each analysis in steps 1 to 3 is restricted to those with non-missing data for all the predictor variables considered in the particular analysis.

The final three steps are then based on all individuals with data on all the predictor variables in the final list.

Step 4 An unadjusted analysis relates ever e-cigarette use to quitting.

Step 5 Stepwise regression analyses are run, introducing the predictor variables in the final list first, and then adding ever e-cigarettes as a predictor.

Step 6 Stepwise regressions similar to those in step 5 are run, but introducing ever e-cigarette use first rather than last.

The principal results produced by the regression analyses are the odds ratios (ORs) and 95% confidence intervals (CIs) relating to each predictor of interest, and the significance of introducing that predictor into the model.

While the main analyses relate quitting cigarettes during follow-up to ever e-cigarette use at baseline and the predictor variables considered include use of nicotine products other than cigarettes or e-cigarettes, four sensitivity analyses (S1 to S4) were also conducted, which are intended to give additional information on how dependent the ORs derived in the main analysis are on exactly how they are conducted. S1 restricts attention to individuals who have never used other nicotine products; S2 links quitting to current (rather than ever) e-cigarette use at baseline; S3 adjusts, where necessary, for variables which take account of data recorded at the end of follow-up rather than just at baseline; and S4, which applies only to the analyses based on quitting between Waves 1 and 3, additionally adjusts for whether the individual had already quit by Wave 2.

In each of S1 to S4 the analyses run were as in steps 4 to 6 of the main analyses and used the final set of predictor variables derived for the period they related to.

For most of the 55 predictor variables considered, there were relatively few missing values, and the regressions could be run excluding the individuals with missing values for the predictors considered without material loss of power. However, for two predictors, where there were about 8% of missing values, individuals with missing data were assigned average values. Thus, for household income in the past 12 months, where data were recorded in five increasing levels, individuals recorded as unknown were assigned an income in the third level, $25,000 to $49,999, while for poverty status, where data were recorded in three levels, <100%, 100–199% and 200+% of the poverty guideline, individuals recorded as unknown were assigned a status in the second level. For living with a regular smoker who smoked inside your home during childhood, where about 16% of individuals were classified as "not ascertained" rather than "yes" or "no", this answer was included as a separate level, thus the predictor was treated in analysis as having three levels.

For some predictors with multiple levels, the regression analyses were based on a single trend variable. This was only appropriate where the predictor variable represented increasing (or decreasing) levels of a characteristic.

Generally, the analyses were based on the values of predictors as recorded at the baseline Wave. Where the baseline Wave was Wave 2, however, and data were not available at Wave 2, Wave 1 data were used if appropriate. Also, if the Wave 2 predictor related to ever having done something, particularly when the variable concerned action in the last 12 months, individuals were counted as ever having done so if this was reported at Wave 1 or 2.

Further details of the process, particularly for the calculation of numbers of cigarettes per day, are given in the *Extended data*.

Additional analyses based on data from Waves 1 to 4

While our original analyses only consider overall quitting, our additional analyses separately consider sustained quitting (quitting seen at all follow-up years), temporary quitting (quitting seen at some follow-up years, but not the final one) and delayed quitting (quitting seen at final follow-up, but not all other years since baseline). We also carry out sensitivity analyses with quitting defined as having quit for 30 days at the relevant Wave, and restricting attention to smokers attempting to quit. For comparative purposes, we also carry out analyses comparing rates of sustained, temporary and delayed quitting smoking in smokeless tobacco users and snus users. Much of the methodology is as described for the analyses based on data from Waves 1, 2 and 3.

Separate sets of analyses have been carried out for three periods: from Wave 1 (baseline) to Waves 2 and 3 (follow-up period); from Wave 2 to Waves 3 and 4; and from Wave 1 to Waves 2, 3 and 4. Each analysis is based on individuals with relevant data available on smoking and e-cigarette use at all the Waves considered in that analysis, is limited to individuals aged 25 years or over at baseline, and takes account of the person-based weights of the baseline population. Each analysis restricts attention to baseline established cigarette smokers as defined earlier and compares ever to never regular e-cigarette users at baseline in regard to the probabilities of persistent quitting, temporary quitting or delayed quitting. Adjustment for potential confounding variables is as described above, with logistic regression analyses being carried out to determine which of a list of candidate predictors should be included in the model relating e-cigarette use to the three different definitions of quitting.

For each follow-up period, four sensitivity analyses have been carried out:

Sensitivity analysis 5: The definition of quitting relates to being a 30-day quitter at the relevant Wave, the analysis otherwise being identical;

Sensitivity analysis 6: The analyses are restricted to those cigarette smokers who ever quit or attempted to quit in the year following baseline;

Sensitivity analysis 7: Instead of comparing never and ever users of e-cigarettes, never and ever users of smokeless tobacco are compared.

Sensitivity analysis 8: Here, never and ever users of snus are compared.

Results

Analyses based on data from Waves 1, 2 and 3

Table 1 shows the predictor variables used in the final regression analysis or excluded at various stages of the preliminary analyses.

For the analyses based on Waves 1 and 2, for example, 54 predictors were considered, 11 in group A, 8 in B, 8 in C, 4 in D, 4 in E, 8 in F, 9 in G, and 2 in H. Of the 55 predictors

Table 1. Predictor variables included in the final regression analysis (Y) or excluded at steps 1, 2 or 3 (X1, X2, X3).

	Levels of variable[a]	Wave 1 to 2 quitting	Wave 2 to 3 quitting	Wave 1 to 3 quitting
All smokers at baseline		8,924	7,825	8,924
Not followed at subsequent waves[b]		2,421 (27.1%)	978 (12.5%)	2,434 (27.3%)
Smokers at baseline		6,503	6,847	6,490
Quit by follow-up		655 (10.1%)	633 (9.2%)	901 (13.9%)
Demographics (A)				
Age range	5	Y	X3	X2
Gender	2	X1	X1	X1
Hispanic origin	2	X2	X2	X2
Race	3	X1	X1	X1
Census region	4	X1	X1	X1
Total household income	5T	Y	Y	Y
Poverty status	3T	X1	-	X1
Total number in the household	5T	X1	-	X1
Highest grade level of school completed	6T	X2	Y	X2
Currently enrolled in a degree program	2	X1	X1	X1

	Levels of variable[a]	Wave 1 to 2 quitting	Wave 2 to 3 quitting	Wave 1 to 3 quitting
Current employment status	8	X1	X1	X1
Aspects of smoking – general (B)				
Age range started smoking cigarettes fairly regularly	6	X1	X1	X1
Current someday cigarette smokers	2	Y	Y	Y
Cigarettes per day	C	Y	X3	Y
Ever used other tobacco products	2	X1	X1	X1
Frequently crave tobacco product(s)	5T	X1	X1	X1
Usually wants to smoke/use tobacco right after waking	5T	Y	Y	Y
After not smoking for a while, need to smoke to avoid discomfort	5T	X1	X1	X1
Can only go a couple of hours without smoking/tobacco	5T	X1	X1	X1
Aspects of smoking – specifically related to quitting (C)				
Have tried to quit completely	2	Y	Y	Y
Would find it hard to stop smoking/tobacco for a while	5T	X2	X2	X2
Times stopped smoking for one day or more in past year	4T	X1	X1	X1
Ever used a nicotine patch, gum, inhaler, nasal spray, lozenge or pill	2	X1	X1	X1
Ever used Chantix, varenicline or bupropion (Wellbutrin, Zyban)	2	X1	X1	Y
Plans to quit smoking/using tobacco product(s) for good	2	X1	X1	X1
Smoking/using tobacco product(s) really helps me feel better if feeling down	5	X1	X1	X1
Extent disapproval of smoking from friends and family led to thinking about quitting in past year	3T	X1	-	X1
Smoking by family and friends (D)				
Rules about smoking a combustible tobacco	3T	Y	X3	Y
Anyone who lives with you now smoke cigarettes	2	X3	X1	X2
Most people I spend time with are tobacco users	5T	X3	X3	X2
Lived with regular smoker who smoked inside your home during childhood	3	X1	Y	X2
Awareness of hazards of smoking (E)				
How often have you seen a list of chemicals in tobacco products in last 12 months	5T	X1	X1	X1
How often noticed health warnings on cigarette packages in past 30 days	5T	X1	X1	X1
Overall opinion of tobacco	5T	Y	X3	X2
Perception of harmfulness of cigarettes to health	5T	X1	X1	Y
Health status (F)				
Saw a medical doctor in past 12 months	2	X2	X1	X1
Body mass index	C	Y	X3	X1
Self-perception of physical health	5T	X1	X2	X1

	Levels of variable[a]	Wave 1 to 2 quitting	Wave 2 to 3 quitting	Wave 1 to 3 quitting
Self-perception of quality of life	5T	X3	X3	X3
Last time significant problems with:				
Feeling very trapped, lonely, sad, etc.	4T	X1	X1	X1
Sleep troubles	4T	X1	X1	X1
Feeling very anxious, nervous, tense, etc.	4T	X1	X1	X1
Becoming very distressed with something reminded of past	4T	X1	X1	X1
Alcohol and drugs (G)				
Ever used alcohol	2	X1	X1	X1
Last time used alcohol or other drugs weekly or more often	5T	X1	X1	X1
Days drank an alcoholic beverage in past 30 days	31T	X1	X1	X1
Ever used marijuana, hash, THC or grass	2	X1	X1	X1
Ever used unprescribed Ritalin or Adderall	2	X1	X1	X1
Ever used unprescribed painkillers, sedatives or tranquilizers	2	X1	X1	X1
Ever used cocaine or crack	2	X1	X1	X1
Ever used stimulants like methamphetamine or speed	2	X1	X1	X1
Ever used any other drugs like heroin, inhalants, solvents, hallucinogens	2	X1	X1	X1
Other (H)				
Hours spent watching TV on a typical day	5T	X1	X3	X3
How often uses the Internet	7T	X3	-	X3
Time a day on social media sites	5T	-	X1	-

[a]C = continuous variable, T = treated as a linear trend variable in regressions
[b]These numbers include a few missing values related to e-cigarette status at baseline and smoking status at subsequent waves

listed in Table 1, there was one variable in group H with no Wave 1 data. Of the 54 predictors considered in the Wave 1 and 2 analyses, 37 were excluded at step 1, marked X1 in Table 1. A further 4 were excluded at step 2 (X2). This left 13 variables considered in step 3, of which 4 were excluded (X3), with 9 included in the final model (Y).

For the analyses based on Waves 2 and 3 there were data available on 51 predictors, with 45 excluded (34 X1, 3 X2 and 8 X3) and 6 included in the final model. For those based on Waves 1 and 3 there were data on 54 predictors, with 46 excluded (35 X1, 8 X2 and 3 X3) and 8 included in the final model.

Table 2 summarises the results of the main analyses. Here, and in later tables, ORs significant at $p<0.05$ are shown in boldface. Each analysis was based on between 6,000 and 7,000 adults with the percentage quitting varying from 9.1% to 13.1%. The unadjusted gateway-out effect varied from 1.29 to 1.52 in the three analyses. Adjustment only slightly reduced the estimates, the fully adjusted ORs being 1.23 (95%CI 0.94-1.61) for Wave 1 to 2, 1.51 (1.24-1.85) for Wave 2 to 3, and 1.39 (1.11-1.74) for Wave 1 to 3.

Table 3 shows the full models used, showing the effect estimates for each of the predictor variables used to adjust the relationship of ever regular e-cigarette use to quitting. Where the same adjustment variable was included in each model, the effect estimates were generally quite similar and always in the same direction. As regards aspects of smoking, smokers were found to be less likely to quit if they were everyday smokers, were more likely to smoke right after waking up, had not previously tried to quit, smoked more cigarettes per day, lived in a home with more relaxed rules about smoking, lived with a smoker in childhood, had a better opinion of tobacco, or had a lesser perception of cigarettes as harmful. They were also less likely to quit if they had ever used the pharmaceutical aids to quitting Chantix, varenicline or buproprion (Wellbutrin, Zyban). Smokers were also less likely to quit if they were worse off and worse educated. Older age (particularly above age 74 years) and greater BMI were also associated with a greater likelihood to quit.

Table 4 summarises the results of the sensitivity analyses, showing the estimated ORs in each case from the fully adjusted

Table 2. Effect of adjustment on the OR (95% CI) for the relationship of ever regular e-cigarette use[a] to quitting.

	Wave 1 to 2 quitting	Wave 2 to 3 quitting	Wave 1 to 3 quitting
Unweighted numbers			
Total – in baseline	6,503	6,847	6,490
Excluded from final regression	262 (4.0%)	89 (1.3%)	175 (2.7%)
Included in final regression	6,241	6,758	6,315
Total ever e-cigarette users – in baseline	727	1,306	726
Excluded from final regression	24 (3.3%)	12 (0.9%)	16 (2.2%)
Included in final regression	703	1,294	710
Quit	78 (11.1%)	160 (12.4%)	118 (16.6%)
Total never e-cigarette users – in baseline	5,776	5,541	5,764
Excluded from final regression	238 (4.1%)	77 (1.4%)	159 (2.8%)
Included in final regression	5,538	5,464	5,605
Quit	503 (9.1%)	456 (8.3%)	711 (12.7%)
Weighted ORs and 96% CIs			
Unadjusted	**1.29** (1.01-1.66)	**1.52** (1.26-1.83)	**1.47** (1.19-1.82)
Adjusted for four most important variables	1.17 (0.90-1.52)	**1.54** (1.26-1.88)	**1.43** (1.14-.1.78)
Adjusted for all variables included in final list	1.23 (0.94-1.61) [9 variables]	**1.51** (1.24-1.85) [6 variables]	**1.39** (1.11-1.74) [8 variables]

[a]Where the baseline is Wave 1, the predictor is ever regular e-cigarette use, where it is Wave 2, it is ever regular e-product use

Table 3. ORs related to quitting cigarettes in the final models used in the main analysis.

	Wave 1 to 2 quitting	Wave 2 to 3 quitting	Wave 1 to 3 quitting
Ever regularly used e-cigarette = yes	1.23 (0.94-1.61)	**1.51** (1.24-1.85)	**1.39** (1.11-1.74)
Age range			
25–34	Reference	Not included	Not included
35–44	0.95 (0.74-1.21)		
45–54	0.85 (0.66-1.10)		
55–64	1.20 (0.92-1.57)		
65–74	1.42 (0.98-2.06)		
75+	**3.31** (1.84-5.97)		
Total household income (per level increasing)	**1.14** (1.05-1.23)	**1.16** (1.07-1.25)	**1.21** (1.13-1.29)
Current some day smoker = no	**0.43** (0.34-0.54)	**0.36** (0.30-0.44)	**0.52** (0.43-0.64)
Highest grade or level at school completed (per level increasing)	Not included	**1.10** (1.03-1.18)	Not included
Per cigarette per day	**0.97** (0.96-0.99)	Not included	**0.97** (0.96-0.98)

	Wave 1 to 2 quitting	Wave 2 to 3 quitting	Wave 1 to 3 quitting
Usually wants to smoke/use tobacco right after waking up (per level increasing)	**0.89** (0.83-0.95)	**0.79** (0.74-0.84)	**0.85** (0.81-0.90)
Have tried to quit completely = no	**0.62** (0.51-0.75)	**0.64** (0.53-0.77)	**0.69** (0.58-0.82)
Ever used Chantix, varenicline or buproprion (Wellbutrin, Zyban)	Not included	Not included	**0.78** (0.65-0.94)
Rules about smoking combustible tobacco at home (per level of decreasing stringency)	**0.77** (0.68-0.88)	Not included	**0.78** (0.70-0.87)
Lived with a regular smoker who smoked inside your home in childhood = no	Not included	**1.41** (1.18-1.68)	Not included
Overall opinion of tobacco (per level of increasing negativity)	**1.17** (1.07-1.29)	Not included	Not included
Perception of harmfulness of cigarettes to health (per level increasing)	Not included	Not included	**1.13** (1.03-1.24)
Per unit of body mass index	**1.02** (1.01-1.03)	Not included	Not included

Table 4. Comparing adjusted ORs for the effect of e-cigarette use on quitting in the main and sensitivity analyses.

	Wave 1 to 2 quitting		Wave 2 to 3 quitting		Wave 1 to 3 quitting	
	N(n)	OR (95% CI)	N(n)	OR (95% CI)	N(n)	OR (95% CI)
Main model	581 (78)	1.23 (0.94-1.61)	616 (160)	**1.51** (1.24-1.85)	829 (118)	**1.39** (1.11-1.74)
Sensitivity analysis 1 (Omitting ever users of other nicotine products)	148 (16)	**2.04** (1.15-3.62)	122 (20)	1.69 (0.96-2.99)	217 (25)	**2.22** (1.38-3.57)
Sensitivity analysis 2 (Linking quitting to current rather than ever e-cigarette use at baseline)	581 (64)	**1.41** (1.06-1.89)	615 (89)	**1.30** (1.01-1.67)	829 (95)	**1.56** (1.21-2.00)
Sensitivity analysis 3 (Adjusting for variables taking account of data recorded at both baseline and end of follow-up)	655 (82)	1.20 (0.92-1.57)	591 (160)	**1.66** (1.35-2.04)	901 (121)	**1.43** (1.14-1.79)
Sensitivity analysis 4 (Adjust also for quitting by Wave 2)		Not applicable		Not applicable	443 (64)	**1.43** (1.11-1.84)

N = total number quitting

n = number of quitters among e-cigarette users (current users in sensitivity analysis 2, ever users otherwise)

analysis. The first line of results ("Main model") repeats the estimates shown in Table 3.

Sensitivity analysis 1 excludes those who had ever used other nicotine products. The number of quitters is substantially reduced, as is the number using e-cigarettes (or e-products). However, the OR is increased, with ever regular users of e-cigarettes about twice as likely to quit cigarettes by the end of the follow-up period, though the CIs of the ORs are relatively wide.

In sensitivity analysis 2, quitting is linked to current rather than ever e-cigarette use. Here the ORs tend to be somewhat higher than in the main analysis (though not for the Wave 2 to 3 analysis).

The results for both sensitivity analysis 1 and 2 seem consistent with smokers being more likely to quit if, at baseline, e-cigarettes formed a more important part of the total tobacco use.

Sensitivity analysis 3 adjusts, where necessary, for variables which are modified to take account of data recorded at the end of follow-up, and not just at baseline, in an attempt to minimise "residual confounding". The ORs were quite similar to those in the main analysis for Wave 1 to 2, or Wave 1 to 3 quitting, but were somewhat increased for Wave 2 to 3 quitting.

Sensitivity analysis 4, only applicable to the Wave 1 to 3 quitting analyses, adjusted also for having quit by Wave 2. This slightly increased the estimate from the main analysis.

Analyses based on data from Waves 1 to 4

Table 5 shows which predictor variables were included in the regression analysis for the three main analyses and all the sensitivity analyses. Seven predictor variables were included in at least 10 of the 15 regression analyses, with a further three included in at least five, and 11 other predictors occurring in at least one. The direction of the associations was generally consistent, with quitting cigarettes more likely in those who, for example, smoked someday rather than every day, had previously tried to quit, who were less likely to smoke right after waking up, were aged 75 or more, had a higher income, and who smoked less cigarettes a day.

Table 6 shows the results of the main analyses. The nine unadjusted ORs for each combination of period and type of quitting were all greater than 1.00, ranging from 1.10 for temporary quitting for Wave 1 to 2/3, to 1.68, for temporary quitting for Wave 2 to 3/4. Adjustment for all the variables included in the final list generally slightly decreased the ORs, though there were some exceptions, with the adjusted OR significant

Table 5. Predictor variables included in the regression analyses in the order they were included.

Variable	Levels of Variable	Wave 1 to 2/3 quitting					Wave 2 to 3/4 quitting					Wave 2/3/4 quitting				
		M	S5	S6	S7	S8	M	S5	S6	S7	S8	M	S5	S6	S7	S8
Age range	6	8		6	8	6	7		6	7	7	8		8	8	8
Gender	2							9								
Total household income	5T	7	3	4	10	4	1	1	1	1	1	10	4	5	10	10
Currently enrolled in a degree program	2							6								
Current someday cigarette smokers	2	1	1	1	1	1	2	2	2	2	2	1	1	1	1	1
Cigarettes per day	C	2	2		2							2	2	6	2	2
Frequently crave tobacco product(s)	5T			2		2								2		
Usually wants to smoke/use tobacco right after waking	5T	5			7		3	4	3	3	3	7			7	7
Have tried to quit completely	2	3			4		5	5		5	4	3	8		4	3
Would find it hard to stop smoking/tobacco for a while	5T		6										6			
Plans to quit smoking/using tobacco product(s) for good	2			3		3								3		
Rules about smoking a combustible tobacco	3T	4	7	5	3	5						4	7	4	3	4
Most people I spend time with are tobacco users	5T				5							5			5	5
Lived with regular smoker who smoked inside your home during childhood	3						4	3	4	4	5					
How often have you seen a list of chemicals in tobacco products in last 12 months	5T								7							
How often noticed health warnings on cigarette packages in past 30 days	5T													9		
Overall opinion of tobacco	5T	6	5		6							6	5		6	6
Body mass index	C	9		7	9	7	6	8	5	6	6	9		7	9	9
Becoming very distressed with something reminded of past	4T							7								
Ever used marijuana, hash, THC or grass	2		4										3			
Hours spent watching TV on a typical day	5T						8				8					
Total adjustment variables		9	7	7	10	7	8	9	7	7	8	10	8	9	10	10

C = continuous variable, M = Main analysis, S = Sensitivity analysis, T = treated as a linear trend in regressions

Table 6. Effect of adjustment on the OR (95% CI) for the relationship of ever regular e-cigarette use[a] to quitting.

Type of quitting	Statistic	Wave 1 to 2/3 quitting	Wave 2 to 3/4 quitting	Wave 1 to 2/3/4 quitting
Delayed	Number in baseline in final regression	5,660	5,346	4,956
	Number quitting	448	392	606
	Unadjusted	**1.50** (1.13-1.97)	1.28 (1.00-1.64)	**1.52** (1.19-1.94)
	Adjusted for four most important variables	**1.36** (1.02-1.82)	1.29 (1.00-1.66)	**1.41** (1.10-1.82)
	Adjusted for all variables included in final list	**1.38** (1.03-1.85)	1.25 (0.97-1.62)	**1.43** (1.10-1.85)
Temporary	Number in baseline in final regression	5,413	5,149	4,699
	Number quitting	201	195	349
	Unadjusted	1.10 (0.71-1.70)	**1.68** (1.22-2.32)	1.34 (0.97-1.86)
	Adjusted for four most important variables	0.91 (0.58-1.42)	**1.74** (1.25-2.43)	1.20 (0.86-1.69)
	Adjusted for all variables included in final list	0.93 (0.59-1.46)	**1.60** (1.14-2.25)	1.26 (0.89-1.77)
Sustained	Number in baseline in final regression	5,602	5,298	4,622
	Number quitting	380	344	272
	Unadjusted	**1.48** (1.10-1.99)	**1.49** (1.16-1.91)	1.29 (0.89-1.86)
	Adjusted for four most important variables	**1.41** (1.03-1.93)	**1.59** (1.22-2.06)	1.33 (0.91-1.96)
	Adjusted for all variables included in final list	**1.51** (1.09-2.08)	**1.48** (1.13-1.94)	**1.52** (1.02-2.26)

[a]Where the baseline is Wave 1, the predictor is ever regular e-cigarette use, where the baseline is Wave 2, the predictor is ever regular e-product use

(at $p < 0.05$) in seven of the nine cases. Notably all the fully adjusted ORs for sustained quitting were positive and significant, with estimates close to 1.50 for each period studied.

Table 7 summarises the adjusted results for the main and sensitivity analyses, again for each combination of period and type of quitting. Of the 45 ORs, 42 are positive (> 1.0) with 20 of these statistically significant, and three are negative (< 1.0) with none of these significant. Associations are clearly evident for 30-day quitting, and when restricted by those attempting to quit in the year following baseline. Interestingly, associations are seen, in some cases larger than for e-cigarette use, both for smokeless tobacco and for snus use.

Discussion

Discussion of results based on Waves 1, 2 and 3

The first set of analyses described in this report summarise evidence from Waves 1, 2 and 3 of the US PATH study relating to the possibility that e-cigarette use may increase the likelihood of smokers quitting cigarettes. All of the adjusted ORs estimated, which as shown in Table 4 varied between 1.20 and 2.22, were consistent with this possibility, although not all the estimates were statistically significant at $p < 0.05$. Compared to the estimates from the main model, which related ever e-cigarette use at baseline to quitting by follow-up, ORs were increased (though based on far fewer quitters) when those who had ever used other products were omitted from the analysis. The ORs were also increased, in the analysis with Wave 1 as the baseline, when quitting was linked to current rather than ever e-cigarette use. In both the sensitivity analyses where the ORs were increased, e-cigarette use would have formed a greater proportion of current tobacco use at baseline.

Eight other related analyses based on the first three Waves 1 of the PATH study have previously been published. The first seven analyses summarised below (Benmarhnia *et al.*, 2018; Berry *et al.*, 2019; Glasser *et al.*, 2021; Kalkhoran *et al.*, 2020; Kurti *et al.*, 2020; Verplaetse *et al.*, 2019; Watkins *et al.*, 2020) are consistent with e-cigarette use increasing the probability of quitting cigarettes, despite variation in whether Wave 3 data has been used or not, whether analyses are restricted to those attempting quitting at baseline, the definition of abstinence used, the

Table 7. Comparing adjusted ORs for the effect of e-cigarette, smokeless tobacco or snus use on quitting in the main and sensitivity analyses.

		Wave 1 to 2/3 quitting		Wave 2 to 3/4 quitting		Wave 1 to 2/3/4 quitting	
Type of quitting	**Model**	**N (n)**	**OR (95% CI)**	**N (n)**	**OR (95% CI)**	**N (n)**	**OR (95% CI)**
Delayed	Main	448 (65)	**1.38** (1.03-1.85)	392 (91)	1.25 (0.97-1.62)	606 (89)	**1.43** (1.10-1.85)
	Sensitivity 5	377 (56)	**1.50** (1.11-2.04)	352 (84)	1.28 (0.99-1.67)	538 (83)	**1.53** (1.18-1.99)
	6	261 (40)	1.26 (0.86-1.86)	222 (61)	1.21 (0.87-1.66)	344 (50)	1.21 (0.85-1.72)
	7	449 (41)	1.16 (0.71-1.90)	396 (42)	1.07 (0.77-1.51)	603 (61)	**1.42** (1.05-1.91)
	8	476 (21)	1.79 (0.91-3.53)	394 (18)	1.16 (0.68-1.97)	608 (22)	1.32 (0.80-2.19)
Temporary	Main	201 (24)	0.93 (0.59-1.46)	195 (55)	**1.60** (1.14-2.25)	349 (48)	1.26 (0.89-1.77)
	Sensitivity 5	142 (20)	1.29 (0.79-2.09)	134 (39)	**1.69** (1.14-2.53)	258 (37)	1.31 (0.90-1.91)
	6	210 (24)	0.93 (0.58-1.47)	195 (55)	1.24 (0.87-1.75)	282 (44)	**1.48** (1.01-2.16)
	7	199 (18)	1.16 (0.69-1.96)	192 (30)	**1.79** (1.19-2.68)	345 (32)	1.14 (0.75-1.73)
	8	208 (9)	1.96 (0.97-3.96)	193 (19)	**3.29** (1.98-5.46)	347 (16)	**1.93** (1.08-3.43)
Sustained	Main	380 (54)	**1.51** (1.09-2.08)	344 (86)	**1.48** (1.13-1.94)	272 (33)	**1.52** (1.02-2.26)
	Sensitivity 5	289 (35)	1.36 (0.94-1.97)	243 (62)	**1.50** (1.11-2.02)	206 (22)	1.46 (0.93-2.31)
	6	425 (57)	**1.45** (1.03-2.05)	350 (87)	1.17 (0.88-1.56)	281 (33)	1.45 (0.95-2.22)
	7	385 (38)	**1.57** (1.04-2.35)	343 (37)	1.04 (0.71-1.50)	269 (28)	**1.76** (1.14-2.72)
	8	423 (19)	**2.30** (1.28-4.14)	345 (12)	0.80 (0.43-1.52)	272 (11)	1.99 (0.99-3.98)

N = total number quitting for the given type

n = number of quitters among users

Main Comparison of ever and never regular e-cigarette users

Sensitivity 5 As main, but relates to 30-day quitting at the relevant wave

Sensitivity 6 As main, but excluding those not attempting to quit in first year of follow-up

Sensitivity 7 As main, but comparison of ever and never smokeless tobacco users

Sensitivity 8 As main, but comparison of ever and never snus users

confounding variables adjusted for, the age range of the population studied, and other analytical details. However, a final analysis by Pierce *et al.* (2020a) only reported a small and non-significant increase in quitting related to e-cigarette use.

An analysis of 3,093 quit attempters based on adult data from Waves 1 and 2 (Benmarhnia *et al.*, 2018) considered two endpoints – abstinence from smoking for at least 30 days and reduced cigarette consumption – and reported a significant increase in both endpoints related to using e-cigarettes to quit during the previous year, but no significant increase in either endpoint related to the use of approved pharmaceutical aids.

Another analysis based on Waves 1 and 2 (Berry *et al.*, 2019), here limiting attention to adults aged 25 years or more, studied factors related to 30-day cigarette cessation and to at least a 50% reduction in cigarette consumption in multivariable logistic regression analyses, which included a number of the variables included as predictors in our analyses. While the model included e-cigarette use, this was defined not at baseline, but as new e-cigarette use at Wave 2. In this analysis large ORs were reported for everyday e-cigarette use both for cessation (7.88, 95% CI 4.45-13.95) and for a 50% reduction in cigarette consumption (5.70, 3.47-9.35).

A further analysis based on Waves 1 and 2 (Verplaetse *et al.*, 2019) considered adults aged 18+ years and reported that, compared to those who had never used e-cigarettes at Wave 1, quitting was increased in Wave 1 daily users (OR 1.56. 95%CI 1.12-2.18) but not in Wave 1 nondaily users (0.83, 0.68-1.02). Age, race and education were the only adjustment variables considered.

Based mainly on data from Waves 1 and 2, an analysis limited to women aged 18-49 years (Kurti *et al.*, 2020) and adjusted for demographic and psychosocial characteristics and pregnancy status concluded that use of e-cigarettes by smokers at Wave 1 was associated with an increased odds of quitting at Wave 2.

Analyses based on data from Waves 1, 2 and 3 (Watkins *et al.*, 2020), conducted separately for adults aged 18-24 years and 25+ years, studied the relation of a variety of cessation strategies to short-term cessation (quit at Wave 2) and long-term cessation (quit at both Waves 2 and 3). Adjustments were made for a range of covariates. The authors reported that "substitution with e-cigarettes" did not predict long-term cessation but predicted short-term cessation for older daily smokers of 5 or more cigarettes a day.

An analysis based on data for adults from Waves 1, 2 and 3 (Kalkhoran *et al.*, 2020), related current e-cigarette use at Wave 1 (defined as daily, non-daily or none) in cigarette smokers at Wave 1 to three cigarette abstinence endpoints: at Wave 2, at Wave 3 or at Waves 2 and 3 (prolonged abstinence). Adjustments were made for a fixed set of variables: age, sex, race/ethnicity, education, income, cigarettes per day, and having a first cigarette within 30 minutes of waking. Non-daily e-cigarette use was only associated with a small, non-significant increase in each of the abstinence endpoints, but daily e-cigarette use was associated with a clear increase in all three endpoints, with adjusted ORs of 1.53 (95%CI 1.04-2.23) for Wave 2 abstinence, 1.57 (1.12-2.21) for Wave 3 abstinence, and 1.77 (1.08-2.89) for abstinence at both Waves 2 and 3. These results particularly seem quite similar to ours.

Another analysis of data from Waves 1, 2 and 3 (Glasser *et al.*, 2021) found that smokers using e-cigarettes daily or increasing to daily use over the 3 waves were 2–4 times more likely to have quit smoking, both in the short and the long-term ($p < 0.001$). However, smokers using e-cigarettes less often or not at all were less likely to quit.

A fourth analysis based on data from Waves 1, 2 and 3 (Pierce *et al.*, 2020a) restricted attention to adult (ages 18+) smokers identified at Wave 1 who reported a quit attempt before Wave 2 and completed Wave 3. 12-month abstinence at Wave 3 among e-cigarette users was slightly but non-significantly reduced as compared both to users of pharmacotherapy to quit or no product.

The strengths of our work include the use of a prospective study design based on a study population which is reasonably representative of the US (though subject to some selection bias), and analyses which take account of a very large number of other predictors of quitting, and restrict attention to established e-cigarette use.

Limitations relate to the relatively small number of quitters, leading to the decision not to study heterogeneity of the results by basic variables, such as sex, race or age group. Our decision to limit attention to those aged at least 25 years was based on the desire not to include young smokers whose smoking habits were not well established.

Discussion of additional results based on Waves 1 to 4

A publication based on the PATH study that reported a positive association of e-cigarette use with quitting by Glasser *et al.* (2021) was criticised by Pierce *et al.* (2020b), who themselves had found no significant association (Pierce *et al.*, 2020a), on the grounds that they included smokers not wanting to quit or making a quit attempt, and used a design that did not assess e-cigarette exposure before the smoking cessation outcome was assessed. In their reply, Glasser *et al.* (2020), pointed out that asking different questions requires different methods, and that while the study by Pierce *et al.* (2020a) was "framed as an intervention study", their study "attempted to answer a broader question; the impact of e-cigarettes on cigarette smoking cessation among the full sample of smokers in the PATH study." Our first set of analyses did assess e-cigarette exposure before the smoking cessation outcome, so no revised analysis was necessary here. However, though our analyses were also an attempt to answer the broader question of Glasser *et al.*, we did include a sensitivity analysis (6) in our analyses based on Waves 1 to 4 to show the effect of limiting attention to those considering quitting smoking. Conducting such a sensitivity analysis had also been noted in version 1 of this paper as an option for consideration in further analysis, using the additional data from Wave 4. Version 1 had also noted the possibility of studying sustained quitting, considered in the additional results along with delayed and temporary quitting, and of analysing 30 day quitting, considered in sensitivity analysis 5.

The additional results based on Waves 1 to 4, illustrate that there is an association of e-cigarette use at baseline with subsequent quitting, whether this be delayed, temporary or sustained, that the association is little affected by considering 30-day quitting rather than not being still an established smoker at the time of interview, and that though the ORs are perhaps reduced slightly by restricting attention to those attempting to quit, they generally remain positive and in some analyses statistically significant.

The additional results show that cigarette smokers who also use smokeless tobacco or also use snus are also more likely to quit smoking, with some of the ORs for snus use larger than those for e-cigarettes. These results seem consistent with the general proposition that, even after detailed adjustment for potential confounding variables, those who both smoke and use a reduced risk tobacco product are more likely to quit smoking than those who do not also use the reduced risk product.

While it is clear that even more analyses could be run using the PATH study, the conclusions will inevitably be limited by sample size considerations, and a larger and well-designed study could provide a clearer picture. Further analyses could, for example, relate the probability of quitting to the extent of e-cigarette use, not considered in our analyses.

Two other analyses of e-cigarettes and quitting have been conducted based on Waves 1 to 4 of the PATH study.

In an analysis considering a variety of transitions in tobacco use between Waves, Brouwer *et al.* (2020) reported that cigarette smokers using e-cigarettes were more likely to quit cigarettes than were exclusive cigarette smokers (hazard ratio 1.9, 95%CI 1.6 to 2.3).

In contrast, Chen *et al.* (2020) concluded that "e-cigarettes may not be an effective cessation aid for adult smokers and instead may contribute to nicotine dependence". They found that among smokers using e-cigarettes to help quit, rates of long-term abstinence were only 2% higher (95%CI –3% to 7%) than in matched smokers not using e-cigarettes, and also that fewer e-cigarette users were long-term abstinent from all nicotine products (Difference –4%, 95%CI –7% to –1%), though this second finding is not specifically related to quitting cigarette smoking.

Conclusion

Our results clearly suggest that among US adults aged 25 years or more, most of whom would not have initiated smoking recently, e-cigarettes may assist in helping smokers to quit, particularly if, at baseline, e-cigarettes form an important part of total tobacco use – i.e. for individuals who at baseline did not use products other than cigarettes or e-cigarettes, and who were current rather than ever e-cigarette users. These conclusions apply whether delayed, temporary or sustained quitting is considered. They are independent of the definition of quitting used, whether all cigarette smokers are considered or only those considering quitting. The results seem consistent with most of the evidence from clinical trials, other analyses of the PATH study, and other epidemiological studies, and seem likely to apply to other countries and time periods.

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.v8 (United States Department of Health and Human Services (USDHHS), 2018).

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: Investigating the effect of e-cigarette use on quitting smoking in adults aged 25 or more using the PATH study https://doi.org/10.17605/OSF.IO/5XWQP (Lee *et al.*, 2020).

This project contains the following extended data file:

- Additional file_fuller details regarding the predictor variables used_v2.docx

Acknowledgements

We thank Esther Afolalu for assistance in acquiring the data from the PATH study, and Zheng Sponsiello-Wang and Christelle Chrea for providing technical comments at various stages. We also thank Jan Hamling for assistance in running the analyses, and Yvonne Cooper and Diana Morris for typing various drafts of the paper.

References

Al-Delaimy WK, Myers MG, Leas EC, *et al.*: **E-cigarette use in the past and quitting behavior in the future: a population-based study.** *Am J Public Health.* 2015; **105**(6): 1213–1219. Erratum appears in Am J Public Health. 2015; **105**(9): e7.
PubMed Abstract | Publisher Full Text | Free Full Text

Antwi GO, Rhodes DL: **Association between e-cigarette use and chronic obstructive pulmonary disease in non-asthmatic adults in the USA.** *J Public Health (Oxf).* 2022; **44**(1): 158–64.
PubMed Abstract | Publisher Full Text

Baldassarri SR, Bernstein SL, Chupp GL, *et al.*: **Electronic cigarettes for adults with tobacco dependence enrolled in a tobacco treatment program: A pilot study.** *Addict Behav.* 2018; **80**: 1–5.
PubMed Abstract | Publisher Full Text | Free Full Text

Beard E, West R, Michie S, *et al.*: **Association of prevalence of electronic cigarette use with smoking cessation and cigarette consumption in England: a time-series analysis between 2006 and 2017.** *Addiction.* 2020; **115**(5): 961–974.
PubMed Abstract | Publisher Full Text | Free Full Text

Benmarhnia T, Pierce JP, Leas E, *et al.*: **Can e-cigarettes and pharmaceutical aids increase smoking cessation and reduce cigarette consumption? Findings from a nationally representative cohort of American smokers.** *Am J Epidemiol.* 2018; **187**(11): 2397–2404.
PubMed Abstract | Publisher Full Text | Free Full Text

Berlowitz JB, Xie W, Harlow AF, *et al.*: **E-Cigarette Use and Risk of Cardiovascular Disease: A Longitudinal Analysis of the PATH Study (2013-2019).** *Circulation.* 2022; **145**(20): 1557–9.
PubMed Abstract | Publisher Full Text

Berry KM, Reynolds LM, Collins JM, *et al.*: **E-cigarette initiation and associated changes in smoking cessation and reduction: the Population Assessment of Tobacco and Health Study, 2013-2015.** *Tob Control.* 2019; **28**(1): 42–49.
PubMed Abstract | Publisher Full Text | Free Full Text

Bowler RP, Hansel NN, Jacobson S, *et al.*: **Electronic cigarette use in US adults at risk for or with COPD: Analysis from two observational cohorts.** *J Gen Intern Med.* 2017; **32**(12): 1315–1322.
PubMed Abstract | Publisher Full Text | Free Full Text

Brose LS, Hitchman SC, Brown J, *et al.*: **Is the use of electronic cigarettes while smoking associated with smoking cessation attempts, cessation and reduced cigarette consumption? A survey with a 1-year follow-up.** *Addiction.* 2015; **110**(7): 1160–8.
PubMed Abstract | Publisher Full Text | Free Full Text

Brouwer AF, Jeon J, Hirschtick JL, *et al.*: **Transitions between cigarette, ENDS and dual use in adults in the PATH study (waves 1-4): multistate transition modelling accounting for complex survey design.** *Tob Control.* 2020; tobaccocontrol-2020-055967.
PubMed Abstract | Publisher Full Text

Bullen C, Howe C, Laugesen M, *et al.*: **Electronic cigarettes for smoking cessation: a randomised controlled trial.** *Lancet.* 2013; **382**(9905): 1629–37.
PubMed Abstract | Publisher Full Text

Caponnetto P, Campagna D, Cibella F, *et al.*: **EffiCiency and safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study.** *PLoS One.* 2013; **8**(6): e66317. Erratum appears in PLoS One. 2014; **9**(1): PLoS One. 2014; **9**(1). doi: **10.1371/annotation/e12c22d3-a42b-455d-9100-6c7ee45d58d0**.
PubMed Abstract | Publisher Full Text | Free Full Text

Caponnetto P, DiPiazza J, Cappello GC, *et al.*: **Multimodal smoking cessation in a real-life setting: Combining motivational interviewing with official therapy and reduced risk products.** *Tob Use Insights.* 2019; **12**: 1179173x19878435.
PubMed Abstract | Publisher Full Text | Free Full Text

Chen R, Pierce J: **Peer Review Report For: Investigating the effect of e-cigarette use on quitting smoking in adults aged 25 years or more using the PATH study [version 1; peer review: 1 not approved].** *F1000Res.* 2020; **9**: 1099.
Publisher Full Text

Chen R, Pierce JP, Leas EC, *et al.*: **Use of electronic cigarettes to aid long-term smoking cessation in the United States: Prospective evidence from the PATH Cohort Study.** *Am J Epidemiol.* 2020; **189**(12): 1529–1537. Erratum appears in Am J Epidemiol. 2020; **189**(12): 1640.
PubMed Abstract | Publisher Full Text | Free Full Text

Chiang SC, Abroms LC, Cleary SD, *et al.*: **E-cigarettes and smoking cessation: a prospective study of a national sample of pregnant smokers.** *BMC Public Health.* 2019; **19**(1): 964.
PubMed Abstract | Publisher Full Text | Free Full Text

Comiford AL, Rhoades DA, Spicer P, *et al.*: **Impact of e-cigarette use among a cohort of American Indian cigarette smokers: associations with cigarette smoking cessation and cigarette consumption.** *Tob Control.* 2021; **30**(1): 103–107.
PubMed Abstract | Publisher Full Text

Critcher CR, Siegel M: **Re-examining the association between e-cigarette use and myocardial infarction: A cautionary tale.** *Am J Prev Med.* 2021; **61**(4): 474–82.
PubMed Abstract | Publisher Full Text

Eisenberg MJ, Hébert-Losier A, Windle SB, *et al.*: **Effect of e-cigarettes plus counseling vs counseling alone on smoking cessation: A randomized clinical trial.** *JAMA.* 2020; **324**(18): 1844–1854.
PubMed Abstract | Publisher Full Text | Free Full Text

Flacco ME, Ferrante M, Fiore M, *et al.*: **Cohort study of electronic cigarette use: safety and effectiveness after 4 years of follow-up.** *Eur Rev Med Pharmacol Sci.* 2019; **23**(1): 402–412.
PubMed Abstract | Publisher Full Text

Glasser A, Giovenco DP, Levy DT, *et al.*: **E-cigarettes and cessation: Asking different questions requires different methods.** *Nicotine Tob Res.* 2020; ntaa249.
PubMed Abstract | Publisher Full Text

Glasser AM, Johnson AL, Niaura RS, *et al.*: **Youth vaping and tobacco use in context in the United States: Results from the 2018 National Youth Tobacco Survey.** *Nicotine Tob Res.* 2021; **23**(3): 447–453.
PubMed Abstract | Publisher Full Text

Gomajee R, El-Khoury F, Goldberg M, *et al.*: **Association between electronic cigarette use and smoking reduction in France.** *JAMA Intern Med.* 2019; **179**(9): 1193–200.
PubMed Abstract | Publisher Full Text | Free Full Text

Grabovac I, Oberndorfer M, Fischer J, *et al.*: **Effectiveness of electronic cigarettes in smoking cessation: a systematic review and meta-analysis.** *Nicotine Tob Res.* 2020; ntaa181.
PubMed Abstract | Publisher Full Text

Grana RA, Popova L, Ling PM: **A longitudinal analysis of electronic cigarette use and smoking cessation.** *JAMA Intern Med.* 2014; **174**(5): 812–3.
PubMed Abstract | Publisher Full Text | Free Full Text

Gravely S, Meng G, Cummings KM, *et al.*: **Changes in smoking and vaping over 18 months among smokers and recent ex-smokers: Longitudinal findings from the 2016 and 2018 ITC Four Country Smoking and Vaping Surveys.** *Int J Environ Res Public Health.* 2020; **17**(19): 7084.
PubMed Abstract | Publisher Full Text | Free Full Text

Hajek P, Corbin L, Ladmore D, *et al.*: **Adding e-cigarettes to specialist stop-smoking treatment: City of London Pilot Project.** *J Addict Res Ther.* 2015; **6**: 244.
Publisher Full Text

Hajek P, Phillips-Waller A, Przulj D, *et al.*: **A randomized trial of E-cigarettes versus nicotine-replacement therapy.** *N Engl J Med.* 2019; **380**(7): 629–637.
PubMed Abstract | Publisher Full Text

Halpern SD, Harhay MO, Saulsgiver K, *et al.*: **A pragmatic trial of E-cigarettes, incentives, and drugs for smoking cessation.** *N Engl J Med.* 2018; **378**(24): 2302–2310.
PubMed Abstract | Publisher Full Text

Harrington KF, Cheong J, Hendricks S, *et al.*: **E-cigarette and traditional cigarette use among smokers during hospitalization and 6 months later.** *Cancer Epidemiol Biomarkers Prev.* 2015; **24**(4): 762.
Publisher Full Text

Hartmann-Boyce J, McRobbie H, Lindson N, *et al.*: **Electronic cigarettes for smoking cessation.** *Cochrane Database Syst Rev.* 2020; **10**: Cd010216.
PubMed Abstract | Publisher Full Text

Jackson SE, Shahab L, West R, *et al.*: **Associations between dual use of e-cigarettes and smoking cessation: A prospective study of smokers in England.** *Addict Behav.* 2020; **103**: 106230.
PubMed Abstract | Publisher Full Text | Free Full Text

Kalkhoran S, Chang Y, Rigotti NA: **Electronic Cigarette Use and Cigarette Abstinence Over 2 Years Among U.S. Smokers in the Population Assessment of Tobacco and Health Study.** *Nicotine Tob Res.* 2020; **22**(5): 728–733.
PubMed Abstract | Publisher Full Text | Free Full Text

Kalkhoran S, Glantz SA: **E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis.** *Lancet Respir Med.* 2016; **4**(2): 116–28.
PubMed Abstract | Publisher Full Text | Free Full Text

Kasza KA, Edwards KC, Gravely S, *et al.*: **Adults' e-cigarette flavor use and cigarette quit attempts: Population assessment of tobacco and health study findings.** *Am J Prev Med.* 2021; **60**(2): 300–2.
PubMed Abstract | Publisher Full Text | Free Full Text

Kurti AN, Bunn JY, Tang K, *et al.*: **Impact of electronic nicotine delivery systems and other respondent characteristics on tobacco use transitions among a U.S. national sample of women of reproductive age.** *Drug Alcohol Depend.* 2020; **207**: 107801.
PubMed Abstract | Publisher Full Text | Free Full Text

Lee PN, Coombs KJ, Afolalu EF: **Considerations related to vaping as a possible gateway into cigarette smoking: an analytical review [version 3; peer review: 2 approved].** *F1000Res.* 2019; **7**: 1915.
PubMed Abstract | Publisher Full Text | Free Full Text

Lee PN, Fry JS, Forey BA, *et al.*: **Cigarette consumption in adult dual users of cigarettes and e-cigarettes: a review of the evidence, including new results from the PATH study [version 1; peer review: awaiting peer review].** *F1000Res.* 2020; **9**: 630.
Publisher Full Text

Li J, Hajek P, Pesola F, *et al.*: **Cost-effectiveness of e-cigarettes compared with nicotine replacement therapy in stop smoking services in England (TEC study): a randomized controlled trial.** *Addiction.* 2020; **115**(3): 507–517.
PubMed Abstract | Publisher Full Text | Free Full Text

Lozano P, Arillo-Santillán E, Barrientos-Gutiérrez I, *et al.*: **E-cigarette use and its association with smoking reduction and cessation intentions among Mexican smokers.** (Uso de cigarros electrónicos y su asociación con la reducción en el consumo de cigarros convencionales y la intencion de dejar de fumar entre fumadores mexicanos). *Salud Publica Mex.* 2019; **61**(3): 276–285.
PubMed Abstract | Publisher Full Text | Free Full Text

Malas M, van der Tempel J, Schwartz R, *et al.*: **Electronic cigarettes for smoking cessation: A systematic review.** *Nicotine Tob Res.* 2016; **18**(10): 1926–1936.
PubMed Abstract | Publisher Full Text

Mantey DS, Cooper MR, Loukas A, *et al.*: **E-cigarette use and cigarette smoking cessation among Texas college students.** *Am J Health Behav.* 2017; **41**(6): 750–759.
PubMed Abstract | Publisher Full Text | Free Full Text

Masiero M, Lucchiari C, Mazzocco K, *et al.*: **E-cigarettes may support smokers with high smoking-related risk awareness to stop smoking in the short run: Preliminary results by randomized controlled trial.** *Nicotine Tob Res.* 2019; **21**(1): 119–126. Corrigendum appears in Nicotine Tob Res. 2020 Apr 17;22(4): 594–595.
PubMed Abstract | Publisher Full Text

National Academies of Sciences Engineering and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice: **Public health consequences of e-cigarettes.** The National Academies Press, Washington DC. 2018.
PubMed Abstract | Publisher Full Text

Nutt DJ, Phillips LD, Balfour D, *et al.*: **Estimating the harms of nicotine-containing products using the MCDA approach**. *Eur Addict Res.*2014; **20**(5): 218–225.
PubMed Abstract | Publisher Full Text

Osei AD, Mirbolouk M, Orimoloye OA, *et al.*: **Association between e-cigarette use and chronic obstructive pulmonary disease by smoking status: behavioral risk factor surveillance system 2016 and 2017.** *Am J Prev Med.* 2020; **58**(3): 336–42.
PubMed Abstract | Publisher Full Text

Pasquereau A, Guignard R, Andler R, *et al.*: **Electronic cigarettes, quit attempts and smoking cessation: a 6-month follow-up.** *Addiction.* 2017; **112**(9): 1620–1628.
PubMed Abstract | Publisher Full Text

Pierce JP, Benmarhnia T, Chen R, *et al.*: **Role of e-cigarettes and pharmacotherapy during attempts to quit cigarette smoking: The PATH Study 2013-16.** *PLoS One.* 2020a; **15**(9): e0237938.
PubMed Abstract | Publisher Full Text | Free Full Text

Pierce JP, Leas EC, Benmarhnia T, *et al.*: **E-cigarettes and cessation: the introduction of substantial bias in analyses of PATH Study.** *Nicotine Tob Res.* 2020b; ntaa234.
PubMed Abstract | Publisher Full Text

Pierce JP, Messer K, Leas EC, *et al.*: **A source of bias in studies of e-cigarettes and smoking cessation.** *Nicotine Tob Res.* 2020c; **22**(5): 861–862.
PubMed Abstract | Publisher Full Text | Free Full Text

Piper ME, Baker TB, Benowitz NL, *et al.*: **Changes in use patterns over 1 year among smokers and dual users of combustible and electronic cigarettes.** *Nicotine Tob Res.* 2019; **22**(5): 672–680. Corrigendum appears in Nicotine & Tobacco Research, ntz164, https://doi.org/10.1093/ntr/ntz164.
PubMed Abstract | Publisher Full Text

Rodu B, Plurphanswat N: **A re-analysis of e-cigarette use and heart attacks**

in PATH wave 1 data. *Addiction.* 2020; **115**(11): 2176–9.
PubMed Abstract | Publisher Full Text

Snow E, Johnson T, Ossip DJ, *et al.*: **Does e-cigarette use at baseline influence smoking cessation rates among 2-year college students?** *J Smok Cessat.* 2018; **13**(2): 110–120.
PubMed Abstract | Publisher Full Text | Free Full Text

Sweet L, Brasky TM, Cooper S, *et al.*: **Quitting behaviors among dual cigarette and e-cigarette users and cigarette smokers enrolled in the tobacco user adult cohort.** *Nicotine Tob Res.* 2019; **21**(3): 278–284.
PubMed Abstract | Publisher Full Text | Free Full Text

United States Department of Health and Human Services (USDHHS): **Population assessment of tobacco and health (PATH) Study [United States] Public-Use Files (ICPSR 36498-V8)**. Accessed: 2018.
Reference Source

Verplaetse TL, Moore KE, Pittman BP, *et al.*: **Intersection of e-cigarette use and gender on transitions in cigarette smoking status: Findings across Waves 1 and 2 of the Population Assessment of Tobacco and Health Study.** *Nicotine Tob Res.* 2019; **21**(10): 1423–1428.
PubMed Abstract | Publisher Full Text | Free Full Text

Walker N, Parag V, Verbiest M, *et al.*: **Nicotine patches used in combination with e-cigarettes (with and without nicotine) for smoking cessation: a pragmatic, randomised trial.** *Lancet Respir Med.* 2020; **8**(1): 54–64.
PubMed Abstract | Publisher Full Text

Wang MP, Li WH, Wu Y, *et al.*: **Electronic cigarette use is not associated with quitting of conventional cigarettes in youth smokers.** *Pediatr Res.* 2017; **82**(1): 14–18.
PubMed Abstract | Publisher Full Text

Watkins SL, Thrul J, Max W, *et al.*: **Real-world effectiveness of smoking cessation strategies for young and older adults: Findings from a nationally representative cohort.** *Nicotine Tob Res.* 2020; **22**(9): 1560–1568.
PubMed Abstract | Publisher Full Text | Free Full Text

Weaver SR, Huang J, Pechacek TF, *et al.*: **Are electronic nicotine delivery systems helping cigarette smokers quit? Evidence from a prospective cohort study of U.S. adult smokers, 2015–2016.** *PLoS One.* 2018; **13**(7): e0198047.
PubMed Abstract | Publisher Full Text | Free Full Text

West R, Bauld L, O'Connor R, *et al.*: **Expert reaction to meta-analysis looking at e-cigarette use and smoking cessation**. Accessed: 2016a March.
Reference Source

West R, Shahab L, Brown J: **Estimating the population impact of e-cigarettes on smoking cessation in England.** *Addiction.* 2016b; **111**(6): 1118–9.
PubMed Abstract | Publisher Full Text

Wu SY, Wang MP, Li WH, *et al.*: **Does electronic cigarette use predict abstinence from conventional cigarettes among smokers in Hong Kong?** *Int J Environ Res Public Health.* 2018; **15**(3): 400.
PubMed Abstract | Publisher Full Text | Free Full Text

Young-Wolff KC, Klebaner D, Folck B, *et al.*: **Documentation of e-cigarette use and associations with smoking from 2012 to 2015 in an integrated healthcare delivery system.** *Prev Med.* 2018; **109**: 113–118.
PubMed Abstract | Publisher Full Text | Free Full Text

Zhang YY, Bu FL, Dong F, *et al.*: **The effect of e-cigarettes on smoking cessation and cigarette smoking initiation: An evidence-based rapid review and meta-analysis.** *Tob Induc Dis.* 2021; **19**: 04.
PubMed Abstract | Publisher Full Text | Free Full Text

Zhu SH, Zhuang YL, Wong S, *et al.*: **E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys.** *BMJ.* 2017; **358**: j3262.
PubMed Abstract | Publisher Full Text | Free Full Text

Zhuang YL, Cummins SE, Sun JY, *et al.*: **Long-term e-cigarette use and smoking cessation: a longitudinal study with US population.** *Tob Control.* 2016; **25**(Suppl 1): i90–i95.
PubMed Abstract | Publisher Full Text | Free Full Text

Open Peer Review

Current Peer Review Status: ✗ ✓ ✓ ✓

Version 3

Reviewer Report 06 July 2022

https://doi.org/10.5256/f1000research.135096.r141345

✗ **John P. Pierce**
Moores Cancer Center, Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, San Diego, CA, USA
Tarik Benmarhnia
[1] Division of Epidemiology. Herbert Wertheim School of Public Health and Human Longevity Science, University of California San Diego, San Diego, CA, USA
[2] Scripps Institution of Oceanography, University of California San Diego, San Diego, CA, USA
Karen Messer
Herbert Wertheim School of Public Health and Moores Cancer Center, University of California, San Diego, San Diego, CA, USA

The authors disagree with all of our points without refutation and have announced their intention not to revise in response to our concerns. This includes our concerns on two critical scientific methods issues: 1) by not restricting the study population to those who had made a quit attempt, the study is tainted by reverse causation and 2) that the variable selection strategy employed opens the study to major collider bias. Our prior evaluation stands. This paper cannot be approved.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: 1. John Pierce, behavioral epidemiology with an emphasis on tobacco use 2. Tarik Benmarhnia, epidemiological methods 3. Karen Messer, statistical methods

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

Reviewer Report 30 June 2022

https://doi.org/10.5256/f1000research.135096.r141344

Riccardo Polosa
Center of Excellence for the Acceleration of HArm Reduction (CoEHAR), Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

I have reviewed this new version. Revisions are appropriate and I have no additional comments.

Competing Interests: RP is full tenured professor of Internal Medicine at the University of Catania (Italy) and Medical Director of the Institute for Internal Medicine and Clinical Immunology at the same University. In relation to his recent work in the area of respiratory diseases, clinical immunology, and tobacco control, RP has received lecture fees and research funding from Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, MSD, Boehringer Ingelheim, Novartis, Duska Therapeutics, and Forest Laboratories. Lecture fees from a number of European EC industry and trade associations (including FIVAPE in France and FIESEL in Italy) were directly donated to vaper advocacy noprofit organizations. RP has also received grants from European Commission initiatives (U-BIOPRED and AIRPROM) and from the Integral Rheumatology & Immunology Specialists Net- work (IRIS) initiative. He has also served as a consultant for Pfizer, Global Health Alliance for treatment of tobacco dependence, CV Therapeutics, Boehringer Ingelheim, Novartis, Duska Therapeutics, ECITA (Electronic Cigarette Industry Trade Association, in the UK), Arbi Group Srl., Health Diplomats, and Sermo Inc. RP has served on the Medical and Scientific Advisory Board of Cordex Pharma, Inc., CV Therapeutics, Duska Therapeutics Inc, Pfizer, and PharmaCielo. RP is also founder of the Center for Tobacco prevention and treatment (CPCT) at the University of Catania and of the Center of Excellence for the acceleration of HArm Reduction (CoEHAR) at the same Uni- versity, which has received support from Foundation for a Smoke Free World to conduct 8 independent investigator-initiated research projects on harm reduction. RP currently involved in a patent application concerning an app tracker for smoking behaviour developed for ECLAT Srl. RP is also currently involved in the following pro bono activities: scientific advisor for LIAF, Lega Italiana Anti Fumo (Italian ac-ronym for Italian Anti-Smoking League), the Consumer Advocates for Smoke-free Alternatives (CASAA) and the International Network of Nicotine Consumers Organizations (INNCO); Chair of the European Technical Committee for standardization on “Requirements and test methods for emissions of electronic cigarettes” (CEN/TC 437; WG4). I confirm that these potential conflicts of interest did not affect my ability to write an objective and unbiased review of the article.

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.

Reviewer Report 22 June 2022

https://doi.org/10.5256/f1000research.135096.r141346

Arielle S. Selya
PinneyAssociates, Inc., Pittsburgh, PA, USA

No further comments.

Competing Interests: I am an employee of PinneyAssociates, Inc., which provides consulting services on tobacco harm reduction on an exclusive basis to JUUL Labs, Inc. JUUL had no role in this review. I confirm that this potential conflict of interest did not affect my ability to write an objective and unbiased review of the article.

Reviewer Expertise: Tobacco use behavior

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.

Reviewer Report 21 June 2022

https://doi.org/10.5256/f1000research.135096.r141343

Alan G. Kaplan
Family Physician Airways Group of Canada, University of Toronto, Toronto, ON, Canada

The authors did respond to my responses, other than making it more clinical which they recognized was not in their domain.

Competing Interests: No competing interests were disclosed.

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.

Version 2

Reviewer Report 20 May 2022

https://doi.org/10.5256/f1000research.54961.r134820

?

Arielle S. Selya
PinneyAssociates, Inc., Pittsburgh, PA, USA

This manuscript examines the association between e-cigarette use and subsequently discontinuing smoking, using PATH data from adults 25+. E-cigarette use is associated with discontinuing smoking after adjusting for a wide range of covariates, and this association is robust across an impressive range of sensitivity analyses (e.g. omitting users of other tobacco products; using several different outcome measures, including sustained, delayed, and temporary discontinuing smoking; restricting analyses to those who made a quit attempt). While (as the authors note) there have been several similar studies on this question using PATH, a particular advantage of this one in my judgment is including those smokers who did not make a quit attempt (thus capturing some of the accidental switching phenomenon that seems to make e-cigarettes so effective). Another advantage is including former smokers in the analysis, as that captures more people who already successfully switched between waves, as opposed to other studies which subset to who's still smoking at the time of data collection.

Major comments:

- Consider changing "quitting" to "discontinuation of smoking" throughout. The word "quitting" has connotations of formal smoking cessation, which involves explicitly setting quit goals, taking certain actions for the purpose of quitting, etc. However, as the authors point out, this does not apply to the entire sample: most smokers at any given time are not immediately planning to quit, if ever. For this reason, the PATH team has used the term "discontinuation of smoking" to make this distinction (see Kasza *et al.*, 2021[1]). Using this terminology rather than "quitting" may also help to clarify some of the criticisms to the V1 of this manuscript and the Glasser study (i.e. whether those who made no attempt to quit should be included).

- Is it the case that successful switchers between waves were included in the analysis? I believe this is the case based on including both former and current smokers. If so, that is a great strength of this paper compared to most others (which usually focus only on those who remain current smokers, and thus exclude those who successfully switched to e-cigarettes between waves), and is worth explicitly pointing out.

Minor comments:

- Missing word (?) in Abstract, 1st sentence of Results ("ORs of quitting smoking forever e-cigarette use were…").

- The tables which present ORs could present significant ones (not crossing 1) as boldface for easier presentation of the many results.

References

1. Kasza K, Edwards K, Kimmel H, Anesetti-Rothermel A, et al.: Association of e-Cigarette Use With Discontinuation of Cigarette Smoking Among Adult Smokers Who Were Initially Never Planning to

Quit. *JAMA Network Open*. 2021; **4** (12). 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?
Yes

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: I am an employee of PinneyAssociates, Inc., which provides consulting services on tobacco harm reduction on an exclusive basis to JUUL Labs, Inc. JUUL had no role in this review. I confirm that this potential conflict of interest did not affect my ability to write an objective and unbiased review of the article.

Reviewer Expertise: Tobacco use behavior

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 10 Jun 2022

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

We thank Dr Selya for her comments.

As regards the first major comment of Dr. Selya, we have not changed “quitting” to “discontinuation of smoking” throughout, as we have already published a very large number of papers using quitting in the sense that we do, and one that is widely understood by epidemiologists. However we have added an extra paragraph (2) in the discussion which explains our terminology. Thus the paragraph starts:
Note that the term “quitters”, as used here, relates to those who were smoking at baseline, but not at the end of follow-up, even though they may later relapse to smoking. Some prefer the term “discontinuation of cigarette smoking”,
the paragraph then going on to cite the reference to Kasza et al., 2021 that Dr. Selya mentioned.

The same paragraph answers the second major comment of Dr. Selya regarding the inclusion of switchers in the analysis. Thus, the paragraph goes on to state:
Here, we use "quitting" to relate to cigarette smoking, regardless of use of, or switching to, e-cigarettes or other nicotine products,
the paragraph then going on to point out that we
use "smoking", not further defined, to relate to cigarettes.

Finally the minor comments have been dealt with by:
1) Correcting the typo of **forever** to **for ever** and;
2) Making significant ORs in boldface in Tables 2, 3, 4, 6 and 7 with a note in the text about this when introducing Table 2.

We hope that our paper can now be approved.

Competing Interests: We are long term consultants to the tobacco ibdustry

Reviewer Report 14 January 2022

https://doi.org/10.5256/f1000research.54961.r119744

?

Alan G. Kaplan
Family Physician Airways Group of Canada, University of Toronto, Toronto, ON, Canada

This study was to review from another larger trial regarding factors to affect smoking cessation that looked at e-cigarette efficacy in such.

I found this to be a very difficult study to read, very statistical, which is fine, but not very clinical. You discuss multiple waves, but I am not sure how relevant these are with regards to e-cigarettes and cessation.

The findings are very important to reinforce the potential value of e-cigarettes for smoking cessation, but there is no balance regarding the potential adverse effects of e-cigarettes which are a concern for many physicians.

While multiple paramaters are reviewed as possible confounders, other pharmacotherapeutic smoking cessation options are not included.

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?
Partly

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: Respiratory illness and chronic pain

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 10 Jun 2022

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

We thank Dr. Kaplan for his comments.

As regards the comment "I found it to be a very difficult study to read, very statistical, which is fine, but not very clinical" all we can say is that neither of the authors are medically qualified, and both are statisticians, and as there were a large number of analyses to describe, the paper was inevitably rather statistical.

Dr. Kaplan also says "You discuss multiple waves, but I am not sure how relevant these are with regards to e-cigarettes and cessation." Clearly, when studying cessation one needs data at two time points (waves), to have individuals changing from being smokers to non-smokers, i.e. quitting. Our original analyses carried out data for Waves 1 to 3, Waves 1 to 2, and Waves 2 to 3, partly to see how consistent our findings were over the different periods considered. Our later analyses used Wave 4 as well to allow us to study in detail sustained, delayed and temporary quitting, and to test consistency of our results for different periods (Waves 1 to 3, 2 to 4, and 1 to 4). Note that you need data from at least three time points to study these forms of quitting. Thus sustained quitting is YNN, delayed quitting is YYN- and temporary quitting is YNY, where Y (yes) indicates smoking and N (no) indicates not smoking.

Dr. Kaplan says that there is no balance regarding the potential adverse effects of e-

cigarettes which are a concern for many physicians. In response to this we would point out that the introduction to the paper did already mention in general terms the various possible upsides and downsides of e-cigarettes. However, we have slightly extended the initial sentence to mention some of the evidence supporting the view that any effects of e-cigarettes on health are substantially less than those of smoking. As the paper is specifically about the relationship of e-cigarette use to quitting cigarettes, we would rather not, in a paper that is already rather long, to attempt to summarize all the evidence relating to health effects, let alone the other areas that we refer to in the first paragraph, such as on initiation and cigarette consumption.

The final point of Dr. Kaplan was that we did not consider pharmacotherapeutic smoking cessation options other than e-cigarettes as possible confounders. However, we did consider them – please see the inclusion of "Ever used Chantix, varenicline or buproprion (Wellbutrin, Zyban)" in Tables 1 and 3.

We hope that our paper can now be approved.

Competing Interests: We are long term consultants to the tobacco industry

Reviewer Report 24 November 2021

https://doi.org/10.5256/f1000research.54961.r97677

?

Riccardo Polosa
Center of Excellence for the Acceleration of HArm Reduction (CoEHAR), Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

This paper investigates whether switching to e-cigarette use causes people to stop smoking, using data from the nationally representative PATH study. Significant elevated quit rates were reported. While there are identifiable imperfections in this study there are no apparent fatal flaws. If the entire literature on the topic looked like this, we would be fairly well informed. I have the following suggestions for improvement:

There are several causal pathways at work here and the authors appear to have covered most angles accounting for several potential confounding variables. However, the authors should reassure the readers that their multivariate models included variables that would be sufficient to calculate propensity to start or quit smoking.

The authors should make clear if the population of current smokers at baseline excludes those who have previously tried and failed e-cigarettes prior to enrollment as this "hard core" population may have an impact on subsequent quit rates. Anyone who already tried e-cigarettes and is still

smoking is less likely to quit over a given period than people who still smoke but have never tried e-cigarettes. This is what happens when you remove most success stories from the study population. Moreover, it can be speculated that many of those who were inclined to switch to vaping would have already done so prior to enrollment, creating a stock-flow bias. These possibilities should be discussed in the text.

At the individual level, the counterfactual of primary interest is whether someone successfully quits smoking because vaping exists, when either they would have failed to quit as they did without the aid of vaping *or* never would have even made the attempt but for trying vaping. I am not sure this has been addressed in the paper – e.g. by comparing at-risk people (people who smoke, and thus are at-risk for quitting) who have the exposure (which might be defined as trying vaping or some greater level of usage) to those who do not, trying to control for confounding.

Details of vaping behavior (e.g. daily use at follow-up) may be important predictors of elevated quit rates. Those who vaped daily may considerably more likely to be smoking abstinent than average, while those who used them less-than-daily were a bit less likely. It would be interesting to stratify the analysis separating daily vs occasional (i.e. less-than-daily) e-cigarette use at follow up to see if there is a "dose/exposure-related" effect on the observed quit rates.

The most compelling evidence that vaping causes *some* smoking cessation, though it does not allow for quantification, is the countless individual testimonials of quitting with vaping, including many accidental quitter stories and stories of having abandoned hope of quitting until vaping became an option. This evidence should be addressed, even as background.

Some important papers are not cited here, e.g. Gomajee *et al.*, 2019, in which the authors looked at a large (the data included over 5000 people who smoke and 2000 who did formerly) nationally representative cohort in France, with recruitment starting in 2012 and following participants for an average of two years at the time their results were reported. Data was collected on not just recent e-cigarette use but also on when someone started vaping regularly, a simple useful question that is woefully missing from most studies.

The possibility of self-selection bias for the PATH study must be acknowledged in the text.

To the authors' credit, they do not delve into offhand speculation about policy implications or statements of personal opinions, and are refreshingly epistemically modest. However, they should discuss how their time- and country-specific behavioral data might or might not generalize outside US, and suggest potential implications of their findings.

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: RP is full tenured professor of Internal Medicine at the University of Catania (Italy) and Medical Director of the Institute for Internal Medicine and Clinical Immunology at the same University. In relation to his recent work in the area of respiratory diseases, clinical immunology, and tobacco control, RP has received lecture fees and research funding from Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, MSD, Boehringer Ingelheim, Novartis, Duska Therapeutics, and Forest Laboratories. Lecture fees from a number of European EC industry and trade associations (including FIVAPE in France and FIESEL in Italy) were directly donated to vaper advocacy noprofit organizations. RP has also received grants from European Commission initiatives (U-BIOPRED and AIRPROM) and from the Integral Rheumatology & Immunology Specialists Net- work (IRIS) initiative. He has also served as a consultant for Pfizer, Global Health Alliance for treatment of tobacco dependence, CV Therapeutics, Boehringer Ingelheim, Novartis, Duska Therapeutics, ECITA (Electronic Cigarette Industry Trade Association, in the UK), Arbi Group Srl., Health Diplomats, and Sermo Inc. RP has served on the Medical and Scientific Advisory Board of Cordex Pharma, Inc., CV Therapeutics, Duska Therapeutics Inc, Pfizer, and PharmaCielo. RP is also founder of the Center for Tobacco prevention and treatment (CPCT) at the University of Catania and of the Center of Excellence for the acceleration of HArm Reduction (CoEHAR) at the same Uni- versity, which has received support from Foundation for a Smoke Free World to conduct 8 independent investigator-initiated research projects on harm reduction. RP currently involved in a patent application concerning an app tracker for smoking behaviour developed for ECLAT Srl. RP is also currently involved in the following pro bono activities: scientific advisor for LIAF, Lega Italiana Anti Fumo (Italian ac-ronym for Italian Anti-Smoking League), the Consumer Advocates for Smoke-free Alternatives (CASAA) and the International Network of Nicotine Consumers Organizations (INNCO); Chair of the European Technical Committee for standardization on “Requirements and test methods for emissions of electronic cigarettes” (CEN/TC 437; WG4). I confirm that these potential conflicts of interest did not affect my ability to write an objective and unbiased review of the article.

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 10 Jun 2022

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

We thank Dr. Polosa for his comments.

Dr. Polosa notes that we should reassure readers that our multivariate models include variables sufficient to calculate propensity to start or quit smoking.
We note that our original discussion section already included a paragraph starting "The strengths of our work..." which included, as one of the strengths "analyses which take account of a very large numbers of other predictors of quitting". We did not consider propensity to start smoking, as the paper was about quitting. Though, of course, there might be some lurking relevant variable ignored, the list of predictors of quitting considered in our Table1 included as many as 55 variables.

In his next paragraph, Dr. Polosa asks that we make clear if the population of current smokers at baseline excludes those previously trying and failing e-cigarettes prior to enrolment.
In response to this we note that the fourth paragraph of the methods section defines what is meant by a current, former, or ever e-cigarette user, and that while our main model (results shown in Tables 2 and 3) relate to the relationship of quitting to ever e-cigarette use at baseline, sensitivity analysis 2 (results shown in Table 4) relate quitting to current e-cigarette use at baseline. Although there may be reasons, as Dr. Polosa states, why restricting attention to current e-cigarette users at baseline might show a stronger relationship, in practice there was no significant difference between the odds ratios for the main model and sensitivity analysis 2, both showing a positive relationship between e-cigarette use and quitting, as mentioned near the end of the first paragraph of the discussion.

In the following paragraph (starting "At the individual level...") Dr. Polosa states that we might compare quitting rates in people who smoke who have the exposure (e-cigarettes) and who do not have it, trying to control for confounding. But that is exactly what we have done – for example in Table 3, the odds ratio for "ever regularly used e-cigarette = yes" are based on a comparison with "ever regularly used e-cigarette = no" and are adjusted for the confounders described.

In the next paragraph (starting "Details of vaping behavior...") Dr. Polosa suggests that dose-response analyses relating quit rates to "dose" of e-cigarette use would be of interest. We agree, but given the extent of the analyses already presented, and the fact that new waves of PHIM are by now available, we would prefer to carry out such analyses for a possible later publication. The possibility of this is now mentioned in the discussion in the paragraph starting "While it is clear that even more analyses could be run...", where we have added the extra sentence "Further analyses could, for example, relate the probability of quitting to the extent of e-cigarette use, not considered in our analyses."
The following paragraph (starting "The most compelling evidence...") refers to "countless individual testimonials of quitting with vaping...". Without any reliable reference to this, we would not be able to say anything scientifically useful. We wonder whether those who try vaping to quit and find it didn't help report this as often as those who find it did work. Given the PATH study has no data here, we prefer not to go down this path.

Next, Dr. Polosa refers to some important papers not cited here, mentioning the paper by Gomajee et al., 2019. We have now included that paper in the reference list supporting the

statement that "it is clear that by now there are quite a number of studies which report somewhat higher quit rates in those using e-cigarettes" in the fourth paragraph of the introduction. However, please note that that list and the one following it are only a selection of papers finding or not finding a clear association, as noted by the "e.g." at the beginning of each list.
As regards raising the possibility of self-selection bias for the PATH study, we have modified the start of the paragraph in the discussion to read "The strengths of our work include the use of a prospective study design based on a study population which is reasonably representative of the US (though subject to some selection bias)...".

Finally, Dr. Polosa suggests that we discuss how our results might generalize outside the US. Here, without going into a detailed discussion covering all the major e-cigarette-using countries other than the US, we have just extended the conclusions section so that the final sentence now reads "The results seem consistent with most of the evidence from clinical trials, other analyses of the PATH study, and other epidemiological studies, and seem likely to apply to other countries and time periods."

We hope that our paper can now be approved.

Competing Interests: We are long term consultants to the tobacco industry

Reviewer Report 29 March 2021

https://doi.org/10.5256/f1000research.54961.r81318

Ruifeng Chen
Division of Biostatistics, University of California, San Diego, San Diego, CA, USA
Tarik Benmarhnia
[1] Division of Epidemiology. Herbert Wertheim School of Public Health and Human Longevity Science, University of California San Diego, San Diego, CA, USA
[2] Scripps Institution of Oceanography, University of California San Diego, San Diego, CA, USA
John P. Pierce
Moores Cancer Center, Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, San Diego, CA, USA

This paper has been rewritten to address concerns that were expressed with the initial version.

- **Previous comment: The introduction presents a somewhat limited review of the literature.**

Authors' Response: dismissed this comment, asserting that their presentation was a relatively succinct summary of the findings in the literature.

Reviewer 2nd response:
The National Academies of Science Engineering and Medicine[1] highlighted that the research addressed at least two different research questions. The first was that e-cigarettes with nicotine were more effective than e-cigarettes without nicotine in medium term abstinence after a quit attempt. The second is the effectiveness of e-cigarettes as cessation aids compared to any other method. It is this question that is the focus of this paper and the NASEM report noted that, as of 2018, RCT's had not really addressed this question
The authors now reference 10 randomized trials (RCTs) most of which do not address the research question that they are addressing in this paper.
Further, there are a number of different "systematic" reviews of this literature and they differ widely in their conclusions. Rather than present both sides, the authors "cherry-pick" from these reviews to support their hypothesis.

- **Previous comment on the importance of limiting consideration to people who had made a quit attempt.** This previous comment noted that the likelihood of a quit attempt was much higher in e-cigarette users in the PATH study (many who started using e-cigarettes did so because they were trying to quit) than it was in the control population. Thus, the higher probability of making a quit attempt could explain the difference in smoking cessation and so the difference should not be attributed to the use of e-cigarettes.

Authors' response - they have adjusted for quitting in some analyses but "*We did not say that the population needed to have made a recent quit attempt, as this was not a requirement in our study. Our analyses compared quit rates between e-cigarette users and non-users to try to answer the simpler, and highly relevant, question 'are e-cigarette users more likely to quit?'*
Reviewer 2nd response: Furthering our previous comment, there now are multiple publications demonstrating that e-cigarettes are the most popular choice for smokers looking for help during a quit attempt. In other words, those who make quit attempt are more likely to use e-cigarettes than those who don't make quit attempt, thus, to answer the authors "simpler" question - of course e-cigarette users are more likely to quit, because the reason they are using an e-cigarette is to help them quit. More generally speaking, this is an example of Simpson's paradox. The effects of e-cigarette use are totally different among those who make quit attempt and those who don't. The importance of not making this error in analyzing cohort studies was not originally brought up by our team. Rather, it was a warning included in the National Academies of Science, Engineering and Medicine 2018 report on e-cigarettes.

We noticed that the authors have made a minimum attempt to adjust for this confounder variable by using "Have tried to quit completely". This is not sufficient to address the problem. Firstly, the interaction between e-cigarette use and the quit attempts has been shown to be important in previous studies (those focused on recent quit attempters). Second, the variable "Have tried to quit completely" is not qualified by time in any way. Thus, the attempt to quit completely may have happened in the past year but the use of e-cigarettes may have happened before then. Thus, the exposure might have happened before the assessment of the confounder, a classical error for anyone studying an etiological problem. By refusing to separate their consideration to smokers who had made a quit attempt and who hadn't, the authors have introduced a substantial bias into their analysis that invalidates their findings

- **Is it appropriate to use an analytic strategy based on stepwise regressions to select model covariates that are then use to infer causal relationships between e-cigarettes and quitting outcomes.**

The authors main research question of interest is etiological (as opposed to one that seeks simply to describe the data or to address a predictive research questions (see Hernán 2018, Hernán, Hsu

et al. 2019)[2,3]. For an etiological question, the identification and conditioning on potential confounders is crucial. For such questions, selecting potential confounders in an outcome model (like a multivariable model) based on statistical criteria has been repeatedly shown to be erroneous (Greenland 1989, Smith 2018)[4,5] especially when covariates induced by the exposure and the outcome are included which may lead to collider-stratification bias. Therefore, the entire analytical plan has to be revisited as all effect estimates presented are based on an erroneous analytical approach and none of the ORs can be used to infer any relationship between e-cigarette use and cigarettes quitting.

References

1. Committee on the Review of the Health Effects of Electronic Nicotine Delivery Systems, Board on Population Health and Public Health Practice, Health and Medicine Division, National Academies of Sciences, Engineering, and Medicine: Public Health Consequences of E-Cigarettes. 2018. Publisher Full Text
2. Hernán MA: The C-Word: Scientific Euphemisms Do Not Improve Causal Inference From Observational Data.*Am J Public Health*. **108** (5): 616-619 PubMed Abstract | Publisher Full Text
3. Hernán M, Hsu J, Healy B: A Second Chance to Get Causal Inference Right: A Classification of Data Science Tasks. *CHANCE*. 2019; **32** (1): 42-49 Publisher Full Text
4. Greenland S: Modeling and variable selection in epidemiologic analysis.*Am J Public Health*. 1989; **79** (3): 340-9 PubMed Abstract | Publisher Full Text
5. Smith G: Step away from stepwise. *Journal of Big Data*. 2018; **5** (1). 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?
Yes

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: Behavioral Epidemiology, with a major focus on tobacco use behavior.

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

Author Response 08 Apr 2021

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

We thank Drs Chen and Pierce for their second set of comments. Our replies, disagreeing with virtually all the points they make, are given below italics. We do not intend to revise our paper further based on this second set of comments.

Not Approved
This paper has been rewritten to address concerns that were expressed with the initial version.

- **Previous comment: The introduction presents a somewhat limited review of the literature.**

Authors' Response: dismissed this comment, asserting that their presentation was a relatively succinct summary of the findings in the literature.
Reviewer 2nd response:
The National Academies of Science Engineering and Medicine[1] highlighted that the research addressed at least two different research questions. The first was that e-cigarettes with nicotine were more effective than e-cigarettes without nicotine in medium term abstinence after a quit attempt.

This first question is not particularly relevant to our paper, which is concerned with comparing quit rates in e-cigarette users as a whole versus non-users of e-cigarettes.

The second is the effectiveness of e-cigarettes as cessation aids compared to any other method. It is this question that is the focus of this paper

We don't understand why Drs Chen and Pierce think we were attempting to answer this second question? We weren't.

and the NASEM report noted that, as of 2018, RCT's had not really addressed this question
The authors now reference 10 randomized trials (RCTs) most of which do not address the research question that they are addressing in this paper.
Further, there are a number of different "systematic" reviews of this literature and they differ widely in their conclusions. Rather than present both sides, the authors "cherry-pick" from these reviews to support their hypothesis.

Drs Chen and Pierce are commenting on the paragraph in the introduction of our paper concerning randomized controlled trials. This was intended to give some context to our paper, though of course our main analyses concern evidence from a non-randomized epidemiological study. we had cited three references as suggesting that the evidence from randomized controlled trials was consistent with higher quit rates in those using e-cigarettes, one of these being a recent prestigious cochran report. While we had selected these three major reviews based on a look at the recent literature, there was certainly no intention to "cherry-pick", as we are accused of. Looking back at the reviews currently available, we could cite other reviews that consider that the evidence suggests (as it does) higher quit rates in e-cigarette users, but none that it suggest lower quit rates. We consider our paragraph to be a fair reflection of the evidence from rcts.

Previous comment on the importance of limiting consideration to people who had made a quit attempt. This previous comment noted that the likelihood of a quit attempt was much higher in e-cigarette users in the PATH study (many who started using e-cigarettes did so because they were trying to quit) than it was in the control population. Thus, the higher probability of making a quit attempt could explain the difference in smoking cessation and so the difference should not be attributed to the use of e-cigarettes.
Authors' response - they have adjusted for quitting in some analyses but "*We did not say that the population needed to have made a recent quit attempt, as this was not a requirement in our study. Our analyses compared quit rates between e-cigarette users and non-users to try to answer the simpler, and highly relevant, question 'are e-cigarette users more likely to quit?'*
Reviewer 2nd response: Furthering our previous comment, there now are multiple publications demonstrating that e-cigarettes are the most popular choice for smokers looking for help during a quit attempt. In other words, those who make quit attempt are more likely to use e-cigarettes than those who don't make quit attempt, thus, to answer the authors "simpler" question - of course e-cigarette users are more likely to quit, because the reason they are using an e-cigarette is to help them quit. More generally speaking, this is an example of Simpson's paradox. The effects of e-cigarette use are totally different among those who make quit attempt and those who don't. The importance of not making this error in analyzing cohort studies was not originally brought up by our team. Rather, it was a warning included in the National Academies of Science, Engineering and Medicine 2018 report on e-cigarettes.

We noticed that the authors have made a minimum attempt to adjust for this confounder variable by using "Have tried to quit completely". This is not sufficient to address the problem. Firstly, the interaction between e-cigarette use and the quit attempts has been shown to be important in previous studies (those focused on recent quit attempters). Second, the variable "Have tried to quit completely" is not qualified by time in any way. Thus, the attempt to quit completely may have happened in the past year but the use of e-cigarettes may have happened before then. Thus, the exposure might have happened before the assessment of the confounder, a classical error for anyone studying an etiological problem. By refusing to separate their consideration to smokers who had made a quit attempt and who hadn't, the authors have introduced a substantial bias into their analysis that invalidates their findings.

In using the word "refusing" in their final sentence, Chen and Pierce seem to have missed completely the highly relevant fact that in our analyses based on waves 1 to 4 we included a sensitivity analysis 6 excluding those not attempting to quit, and that for sustained quitting (perhaps the most relevant measure) the associations were weaker if anything than those seen in the main analysis, indicating that increased quitting rates were seen also in those not attempting to quit.

Is it appropriate to use an analytic strategy based on stepwise regressions to select model covariates that are then use to infer causal relationships between e-cigarettes and quitting outcomes.
The authors main research question of interest is etiological (as opposed to one that seeks simply to describe the data or to address a predictive research questions (see Hernán 2018, Hernán, Hsu *et al*. 2019)[2,3]. For an etiological question, the identification and conditioning

on potential confounders is crucial. For such questions, selecting potential confounders in an outcome model (like a multivariable model) based on statistical criteria has been repeatedly shown to be erroneous (Greenland 1989, Smith 2018)[4,5] especially when covariates induced by the exposure and the outcome are included which may lead to collider-stratification bias. Therefore, the entire analytical plan has to be revisited as all effect estimates presented are based on an erroneous analytical approach and none of the ORs can be used to infer any relationship between e-cigarette use and cigarettes quitting.

While we agree that in principle one shouldn't adjust for variables induced by the exposure and the outcome, I do not believe that we had done so here. The variables we adjusted for were generally characteristics that were present before take up of e-cig use and before quitting, and therefore would not cause problems with over-correction.

References

1. Committee on the Review of the Health Effects of Electronic Nicotine Delivery Systems, Board on Population Health and Public Health Practice, Health and Medicine Division, National Academies of Sciences, Engineering, and Medicine: Public Health Consequences of E-Cigarettes. 2018. Publisher Full Text
2. Hernán MA: The C-Word: Scientific Euphemisms Do Not Improve Causal Inference From Observational Data.*Am J Public Health*. **108** (5): 616-619 PubMed Abstract | Publisher Full Text
3. Hernán M, Hsu J, Healy B: A Second Chance to Get Causal Inference Right: A Classification of Data Science Tasks. *CHANCE*. 2019; **32** (1): 42-49 Publisher Full Text
4. Greenland S: Modeling and variable selection in epidemiologic analysis.*Am J Public Health*. 1989; **79** (3): 340-9 PubMed Abstract | Publisher Full Text
5. Smith G: Step away from stepwise. *Journal of Big Data*. 2018; **5** (1). Publisher Full Text

Competing Interests: As noted in the paper , we are long term consultants to the tobacco industry.

Version 1

Reviewer Report 14 September 2020

https://doi.org/10.5256/f1000research.28877.r70981

Ruifeng Chen

Division of Biostatistics, University of California, San Diego, San Diego, CA, USA

John P. Pierce
Moores Cancer Center, Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, San Diego, CA, USA

In the background of the abstract, the authors state that their goal is to address the research question whether e-cigarettes encourage smokers to quit using a quality nationally representative cohort study from the United States.

The introduction presents a somewhat limited review of the literature. In the discussion of the randomized trials the authors infer that these trials reached statistically significant findings where e-cigarettes were favored. This is a misrepresentation of the literature.

The authors note the following problems that have been identified with observational studies addressing the target research question: studies in which the exposure measure does not precede the outcome measure (as happens in cross-sectional studies), the use of non-representative populations, and failure to fully account for the many potential confounding factors. While these are appropriate criticisms of some of the literature, they are far from complete. For example, in 2018, the US National Academies of Science, Engineering and Medicine put out a major report on e-cigarettes where they expressed concern about the quality of some of the papers addressing whether these products were cessation aids: In addition to these three concerns, this report noted the importance of the study focusing on quit attempts with a comparable control group – this issue has been highlighted in the 2019 paper by Pierce *et al.* in Nicotine and Tobacco Research[1]. This analysis showed that the likelihood of a quit attempt was much higher in e-cigarette users in the PATH study (many who started using e-cigarettes did so because they were trying to quit) than in was in the control population. Thus, the higher probability of making a quit attempt could explain the difference in smoking cessation and so the difference should not be attributed to the use of e-cigarettes.

However, the authors go further and argue "*Problems involve the …failure to limit attention to established e-cigarette users,"* (Para 4 introduction). It is not clear what the authors mean by this? Do they mean that the study population need to have developed a consistent pattern of dual use of cigarettes and e-cigarettes? What is their justification for such a limitation when addressing the stated research question? It is apparent that they do not place such a limitation on their own analyses.

Indeed, the authors have not laid out specific research questions or hypotheses that guide the analyses that they undertake in this paper. This is an important omission.

In the methods, the authors state that analyses are based on individuals with relevant data available at Waves 1, 2 and 3 on smoking and e-cigarette use. They do not mention that the population needed to have made a recent quit attempt. As noted above, unless they demonstrate that the populations that they choose are comparable on this variable, then their study is confounded.

The methods are not at all clear about the outcome measure used in this analysis. In their section outlining their main analyses, the authors use the term "quitting during follow-up". What does this

mean? A logical interpretation is that a quit attempt was made in the year prior to the follow-up survey. However, the authors have not addressed the quit attempt data in the methods. Do they use a point prevalence of former smoking at the follow-up survey? If so, how can this be described as successful smoking cessation? This is one of the most critical points in the paper. Most other papers discussing successful quitting require abstinence for either 6 of 12 months at follow-up (see, Gilpin *et al*. 1997[2]). This is particularly important in an observational study when a person quit at follow-up could have quit only for the day before the survey, for example.

The potential confounders in this analysis include those variables that are associated with use of e-cigarettes as well as variables that are associated with successful cessation. The authors omit any discussion of variables associated with the probability of a smoker using an e-cigarette, thus seriously confounding their analyses. At least in a supplement, there should be a summary table of these predictors outlining how they are associated with e-cigarette use.

Analytic Plan: The analysis plan lays out a stepwise forward selection logistic regression, adjusted for selected covariates. What is unclear is how the authors use step 5 & 6 of their analytic plan in drawing their inferences.

There is a problem with the use of study weights. For their Wave 2 to Wave 3 analysis, it would seem that the appropriate weights would be the Wave 2 weights,

A figure laying out the different analyses with samples sizes (including loss to follow-up) would be very helpful to the reader.

Results: The unadjusted quitting rates by ever use of e-cigarettes should be presented a in table in the results section.

Also, the authors should report the percentage of subjects excluded in the multiple regressions.

Any reworking of this manuscript should discuss the four recent analyses that address e-cigarettes and smoking using the PATH data. All these papers use appropriate analytic procedures and arrive at opposite conclusions to those of the authors[3 - 6].

References

1. Pierce J, Messer K, Leas E, Kealey S, et al.: A Source of Bias in Studies of E-Cigarettes and Smoking Cessation. *Nicotine & Tobacco Research*. 2020; **22** (5): 861-862 Publisher Full Text
2. Gilpin EA, Pierce JP, Farkas AJ: Duration of smoking abstinence and success in quitting.*J Natl Cancer Inst*. 1997; **89** (8): 572-6 PubMed Abstract | Publisher Full Text
3. Pierce JP, Benmarhnia T, Chen R, White M, et al.: Role of e-cigarettes and pharmacotherapy during attempts to quit cigarette smoking: The PATH Study 2013-16.*PLoS One*. 2020; **15** (9): e0237938 PubMed Abstract | Publisher Full Text
4. Chen R, Pierce JP, Leas EC, White MM, et al.: E-Cigarette Use to Aid Long-Term Smoking Cessation in the US: Prospective Evidence from the PATH Cohort Study.*Am J Epidemiol*. 2020. PubMed Abstract | Publisher Full Text
5. Dai H, Leventhal A: Association of electronic cigarette vaping and subsequent smoking relapse among former smokers. *Drug and Alcohol Dependence*. 2019; **199**: 10-17 Publisher Full Text
6. Everard CD, Silveira ML, Kimmel HL, Marshall D, et al.: Association of Electronic Nicotine Delivery System Use With Cigarette Smoking Relapse Among Former Smokers in the United States.*JAMA*

Netw Open. 2020; **3** (6): e204813 PubMed Abstract | Publisher Full Text

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?
No

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

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?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Behavioral Epidemiology, with a major focus on tobacco use behavior.

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

Author Response 02 Oct 2020

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

We thank the reviewers for their comments which we attempt to answer in detail below. Please note that, as advised by the journal, our proposed changes to the paper have not, at this stage, been made, pending comments from other reviewers on our paper. Please also note that, as explained in more detail below, some of the points raised by the reviewers will be dealt with more fully in a further paper we are currently preparing based on data from Waves 1 to 4, as mentioned in the penultimate paragraph of the conclusions section. As will be evident, the reviewers original comments are in normal type and our replies and suggested changes to the paper are in bold. We hope that our reply and the changes will affect the reviewers' opinion of our work.

In the background of the abstract, the authors state that their goal is to address the research question whether e-cigarettes encourage smokers to quit using a quality nationally representative cohort study from the United States.

The introduction presents a somewhat limited review of the literature.

The introduction was never intended to be a fully detailed and comprehensive review of the extensive literature relating e-cigarettes to quitting, the main purpose of the paper being to describe the results of our own analyses. Nevertheless the introduction includes as many as 39 references, and we feel gives a relatively succinct summary of the findings from the literature available at the time of writing.

In the discussion of the randomized trials the authors infer that these trials reached statistically significant findings where e-cigarettes were favored. This is a misrepresentation of the literature.

We made no reference to statistical significance and had not intended to imply this. We were merely summarizing the direction of the differences reported in the papers cited, virtually all of which indicated a higher quit rate in the nicotine e-cigarette group. However to avoid confusion, the second sentence of the second paragraph of the discussion will be amended so that it ends

'...generally indicates higher quit rates in the nicotine e-cigarette group, although not all the differences cited were statistically significant (at $p<0.05$), and one study did not find such higher quit rates (Halpern et al., 2018).'

The authors note the following problems that have been identified with observational studies addressing the target research question: studies in which the exposure measure does not precede the outcome measure (as happens in cross-sectional studies), the use of non-representative populations, and failure to fully account for the many potential confounding factors. While these are appropriate criticisms of some of the literature, they are far from complete. For example, in 2018, the US National Academies of Science, Engineering and Medicine put out a major report on e-cigarettes where they expressed concern about the quality of some of the papers addressing whether these products were cessation aids:

We had already stated in the first sentence of paragraph 4 of the discussion that'...a recent review considered the evidence is inconclusive due to the low quality of the research' citing Malas et al. (2016). We will amend this to start '...recent reviews have considered the evidence...' and additionally cite the reference to the major report in 2018 that the reviewers mention.

In addition to these three concerns, this report noted the importance of the study focusing on quit attempts with a comparable control group – this issue has been highlighted in the 2019 paper by Pierce *et al.* in Nicotine and Tobacco Research[1].

In the second sentence of paragraph 4 of the discussion we will add 'the use of non-comparable control groups' after 'the use of unrepresentative populations'.

This analysis showed that the likelihood of a quit attempt was much higher in e-cigarette users in the PATH study (many who started using e-cigarettes did so because they were

trying to quit) than it was in the control population. Thus, the higher probability of making a quit attempt could explain the difference in smoking cessation and so the difference should not be attributed to the use of e-cigarettes.

We already do adjust for aspects of smoking related to quitting in our analyses, as shown in Tables 1 and 3.

However, the authors go further and argue "*Problems involve the …failure to limit attention to established e-cigarette users,"* (Para 4 introduction). It is not clear what the authors mean by this? Do they mean that the study population need to have developed a consistent pattern of dual use of cigarettes and e-cigarettes? What is their justification for such a limitation when addressing the stated research question? It is apparent that they do not place such a limitation on their own analyses.

It does not seem sensible to include among e-cigarette users those who have in the past tried them once or twice and abandoned them as they did not like them. The reviewers state that we did not limit attention to established users. This is untrue; that we do limit attention to established users is very clearly stated in the third paragraph of the methods section.

Indeed, the authors have not laid out specific research questions or hypotheses that guide the analyses that they undertake in this paper. This is an important omission.

In the introduction, the first sentence of the final paragraph is 'Here we describe results from a prospective study aimed at avoiding such weaknesses.' which might be regarded as a statement of our objectives. However we will insert a sentence after this to read:

'The main objective of our analyses is to quantify the relationship between e-cigarette use in smokers and subsequent cessation of smoking, with detailed adjustment for the multitude of factors that may differ between e-cigarette users and non-users.' We will also amend the next sentence to start 'Our analyses are based on' rather than 'It is based on…'.

In the methods, the authors state that analyses are based on individuals with relevant data available at Waves 1, 2 and 3 on smoking and e-cigarette use. They do not mention that the population needed to have made a recent quit attempt. As noted above, unless they demonstrate that the populations that they choose are comparable on this variable, then their study is confounded.

We did not say that the population needed to have made a recent quit attempt, as this was not a requirement in our study, and indeed was not a requirement of a number of the other studies we had cited in our discussion (Berry et al., 2019; Kalkhoran et al., 2019; Verplaetse et al., 2019), though it was in others (Benmarhnia et al., 2018; Watkins et al., 2019). Those who used e-cigarettes at baseline may not at that time have used them intending to quit, but may have found during follow-up that they could meet their nicotine needs without smoking cigarettes. Our analyses compared quit rates

between e-cigarette users and non-users to try to answer the simpler, and highly relevant, question 'are e-cigarette users more likely to quit?' We prefer to present results based on the whole population of baseline smokers, thus using a larger sample size than if we restricted attention to quit attempters, and to try to avoid bias by taking into account a range of predictor variables related to quitting.

However we will add a second paragraph in the methods section as follows.

'Some studies of data from Waves 1 to 3 of the PATH study (Benmarhnia et al., 2018; Pierce et al., 2020a; Watkins et al., 2019) have limited analyses to quit attempters, but others (Berry et al., 2019; Kalkhoran et al., 2019; Verplaetse et al., 2019) have not. Although such a limitation more closely mimics randomized control trials (Pierce et al., 2020b) we prefer not to do so, and to avoid bias by adjusting for aspects of quitting in analyses. Our approach uses a larger sample size and provides results that are more representative of the whole population of baseline smokers'.

As already noted, we intend to carry out some additional analyses limited to quit attempters in the paper being prepared based on data from Waves 1 to 4, though we do note for the reviewers' information that a preliminary analysis we conducted, based on data from Waves 1 and 2 and limiting attention to those who at Wave 2 had ever made a quit attempt, produced an adjusted odds ratio of 1.20 (95%CI 0.91-1.57) which is very similar to the estimate we give in Table 2 of our paper of 1.23 (0.94-1.61).

The methods are not at all clear about the outcome measure used in this analysis. In their section outlining their main analyses, the authors use the term "quitting during follow-up". What does this mean? A logical interpretation is that a quit attempt was made in the year prior to the follow-up survey. However, the authors have not addressed the quit attempt data in the methods. Do they use a point prevalence of former smoking at the follow-up survey? If so, how can this be described as successful smoking cessation? This is one of the most critical points in the paper. Most other papers discussing successful quitting require abstinence for either 6 of 12 months at follow-up (see, Gilpin *et al*. 1997[2]). This is particularly important in an observational study when a person quit at follow-up could have quit only for the day before the survey, for example.

We certainly thought that we had made it clear enough in the methods that we were defining smoking status as at each Wave, and defining quitting based on being a current established smoker at baseline and a former established smoker at follow-up. While we agree that some former smokers may only have quit for a relatively short time, we believe that our method still provides meaningful results. However, we will extend the first sentence of the old fourth paragraph of the methods to read 'The main analysis for each period relates ever e-cigarette use at baseline to the probability of being an established former smoker at follow-up (referred to subsequently as either "quitting" or "quitting during follow-up"), with adjustment for predictor variables measured at baseline.'

Again, for the reviewers' information, we repeated our Wave 1 to 2 analysis, redefining quitting as having quit for at least 30 days. This produced an adjusted estimate of 1.26

(95%CI 0.93-1.70) which is very similar to the estimate we give in Table 2 of our paper of 1.23 (0.94-1.61).

The potential confounders in this analysis include those variables that are associated with use of e-cigarettes as well as variables that are associated with successful cessation. The authors omit any discussion of variables associated with the probability of a smoker using an e-cigarette, thus seriously confounding their analyses. At least in a supplement, there should be a summary table of these predictors outlining how they are associated with e-cigarette use.

We will extend the fifth paragraph of the methods section to read as follows:

'The specific predictor variables are listed in the Results section, with fuller details of their definition given in the *Extended data.* While the variables were chosen as being suggested by the literature as being related to smoking, the *Extended data* also provides information, based on Wave 1, of their association with ever e-cigarette use. As shown there, ever use was highly significantly ($p < 0.001$) more frequent in the young and in females, and after adjustment for age and sex, was also highly significantly related to a range of the predictor variables considered, being less frequent in Hispanics and Blacks, and more frequent in those with more income or education, those who ever use other tobacco products, those who have a perceived greater need for tobacco, those who have tried to quit more often, those who plan to quit, those who find it hard to stop smoking and those who have used quitting aids. Users were also clearly more likely to have significant problems more recently with sleeping, anxiety and distress, to see a doctor more often, to use the internet often, and to use various different types of drugs (but not cocaine or crack). At most weak relationships were seen with smoking by family and friends, awareness of the hazards of smoking, use of alcohol, body mass index, or self-perception of physical health or quality of life. Little relationship was also seen between ever e-cigarette use and daily cigarette consumption, a finding which was reported earlier (Lee et al., 2020), where it was suggested that it was explained by smokers taking up e-cigarettes having higher consumption initially, reduced by partial replacement of cigarettes by e-cigarettes.'

We will also, in due course, add to the Extended data a section describing and presenting the output from which the above results are summarized.

Analytic Plan: The analysis plan lays out a stepwise forward selection logistic regression, adjusted for selected covariates. What is unclear is how the authors use step 5 & 6 of their analytic plan in drawing their inferences.

Our inferences are drawn from the results of the step 5 and 6 analyses which, reassuringly, produced the same models. The results in Table 2 compare unadjusted odds ratios with those adjusted for the final (step 5/6) models shown in Table 3.

There is a problem with the use of study weights. For their Wave 2 to Wave 3 analysis, it would seem that the appropriate weights would be the Wave 2 weights,

In fact we did use Wave 2 weights for the Wave 2 to Wave 3 analysis. We will correct the end of the second sentence of the first paragraph of the Methods section to read

', and take account of the person-based weights of the baseline population'.

A figure laying out the different analyses with samples sizes (including loss to follow-up) would be very helpful to the reader.

Results: The unadjusted quitting rates by ever use of e-cigarettes should be presented in a table in the results section.

Also, the authors should report the percentage of subjects excluded in the multiple regressions.

We already present in Tables 1 and 2 sample sizes in each of the main analyses. We will add information on the proportion of the baseline population that were not followed up, but do not think that this merits a figure. We will also extend Table 2 to include additional lines to cover the other points made by the reviewers. Thus the revised tables will start with the following lines:
Table 1.
Table 2.

Any reworking of this manuscript should discuss the four recent analyses that address e-cigarettes and smoking using the PATH data. All these papers use appropriate analytic procedures and arrive at opposite conclusions to those of the authors[3 - 6].

Of the four references which the reviewers cite, two (Dai and Leventhal, 2019; Everard et al., 2020) relate to relapse, which is outside the scope of the paper, and not quitting, and one of these (Dai and Leventhal, 2019) in any case states that 'Baseline e-cigarette use was not associated with smoking relapse at follow-up after covariate adjustment.' We do not propose to cite these two references, as our paper concerns quitting.

One of the other two references the reviewers cite (Pierce et al., 2020a), not published at the time our paper was prepared, describes analyses based on Waves 1 to 3 of the PATH study. We have, in the discussion in paragraphs 3 to 7, already summarized findings from five other analyses based on the PATH study which are consistent with e-cigarette use increasing the probability of quitting cigarettes. To take into account this paper, and to provide further detail in the discussion, we propose to make the following two changes.

First, we will extend the second paragraph of the discussion to read as follows:

'Six other related analyses based on the first three Waves 1 of the PATH study have previously been published. The first five analyses summarized below (Benmarhnia et al., 2018; Berry et al., 2019; Kalkhoran et al., 2019; Verplaetse et al., 2019; Watkins et al., 2019) are consistent with e-cigarette use increasing the probability of quitting

cigarettes, despite variation in whether Wave 3 data has been used or not, whether analyses are restricted to those attempting quitting at baseline, the definition of abstinence used, the confounding variables adjusted for, and other analytical details. However, the final analysis (Pierce et al., 2020a) only reported a small and non-significant increase in quitting related to e-cigarette use.'

Second, we will add a new paragraph about the latest study at the end of the paragraphs describing the results of the first five analyses as follows:

'A third analysis based on data from Waves 1, 2 and 3 (Pierce et al., 2020a) restricted attention to adult (ages 18+) smokers identified at Wave 1 who reported a quit attempt before Wave 2 and completed Wave 3. 12 month abstinence at Wave 3 among e-cigarette users was slightly but non-significantly reduced as compared both to users of pharmacotherapy to quit or no product.'

The other reference cited by the reviewers (Chen et al., 2020) refers to analyses based on Waves 1 to 4 of the PATH study. Partly because our analyses relate to Waves 1 to 3, and partly because we are currently developing analyses based on Waves 1 to 4 for a further publication, we strongly prefer not to consider analyses that include Wave 4 data in our discussion.

We will also add two extra sentences at the end of the penultimate paragraph of our discussion section, which refers to the planned further paper, as follows:

'That paper might also consider different definitions of quitting, such as at least 30 day quitting, and investigate the effect of restricting attention to those attempting quitting at baseline. It will also describe and comment on other publications that have used data up to Wave 4'.

Is the work clearly and accurately presented and does it cite the current literature?
Partly
It was never intended to consider literature based on analyses using PATH Wave 4 data, or considering relapse, and the huge literature on e-cigarettes from other studies is covered in fair detail.
< >Is the study design appropriate and is the work technically sound?Are sufficient details of methods and analysis provided to allow replication by others?If applicable, is the statistical analysis and its interpretation appropriate? Are all the source data underlying the results available to ensure full reproducibility?Are the conclusions drawn adequately supported by the results?
We confirm that we have read this submission and believe that we have an appropriate level of expertise to state that we do not consider it to be of an acceptable scientific standard, for reasons outlined above.
We hope that our submission, when the revisions described are made, will now be considered of an acceptable scientific standard.

References
Benmarhnia, T., Pierce, J.P., Leas, E., White, M.M., Strong, D.R., Noble, M.L., Trinidad, D.R.,

2018. Can e-cigarettes and pharmaceutical aids increase smoking cessation and reduce cigarette consumption? Findings from a nationally representative cohort of American smokers. Am. J. Epidemiol. 187, 11, 2397-2404. DOI:10.1093/aje/kwy129.

Berry, K.M., Reynolds, L.M., Collins, J.M., Siegel, M.B., Fetterman, J.L., Hamburg, N.M., Bhatnagar, A., Benjamin, E.J., Stokes, A., 2019. E-cigarette initiation and associated changes in smoking cessation and reduction: the Population Assessment of Tobacco and Health Study, 2013-2015. Tob. Control. 28, 1, 42-49. DOI:10.1136/tobaccocontrol-2017-054108.

Chen, R., Pierce, J.P., Leas, E.C., White, M.M., Kealey, S., Strong, D.R., Trinidad, D.R., Benmarhnia, T., Messer, K., 2020. E-cigarette use to aid long-term smoking cessation in the US: Prospective evidence from the PATH Cohort Study. Am. J. Epidemiol. Published online ahead of print July 27, 2020 (doi: 10.1093/aje/kwaa161). DOI:10.1093/aje/kwaa161. Erratum appears in Am J Epidemiol. 2020 Sep 12;kwaa193. doi: 10.1093/aje/kwaa193.

Dai, H., Leventhal, A.M., 2019. Association of electronic cigarette vaping and subsequent smoking relapse among former smokers. Drug Alcohol Depend. 199, 10-17. DOI:10.1016/j.drugalcdep.2019.01.043.

Everard, C.D., Silveira, M.L., Kimmel, H.L., Marshall, D., Blanco, C., Compton, W.M., 2020. Association of electronic nicotine delivery system use with cigarette smoking relapse among former smokers in the United States. JAMA Netw. Open. 3, 6, e204813. DOI:10.1001/jamanetworkopen.2020.4813.

Halpern, S.D., Harhay, M.O., Saulsgiver, K., Brophy, C., Troxel, A.B., Volpp, K.G., 2018. A pragmatic trial of e-cigarettes, incentives, and drugs for smoking cessation. N. Engl. J. Med. 378, 24, 2302-2310. DOI:10.1056/NEJMsa1715757.

Kalkhoran, S., Chang, Y., Rigotti, N.A., 2019. E-cigarettes and smoking cessation in smokers with chronic conditions. Am. J. Prev. Med. 57, 6, 786-791. DOI:10.1016/j.amepre.2019.08.017.

Lee, P., Fry, J., Forey, B., Coombs, K.J., Thornton, A.J., 2020. Cigarette consumption in adult dual users of cigarettes and e-cigarettes: a review of the evidence, including new results from the PATH study [version 1; peer review: awaiting peer review] F1000Res. 9, 630. DOI:10.12688/f1000research.24589.1.

Malas, M., van der Tempel, J., Schwartz, R., Minichiello, A., Lightfoot, C., Noormohamed, A., Andrews, J., Zawertailo, L., Ferrence, R., 2016. Electronic cigarettes for smoking cessation: A systematic review. Nicotine Tob. Res. 18, 10, 1926-1936. DOI:10.1093/ntr/ntw119.

Pierce, J.P., et al., 2020a. Role of e-cigarettes and pharmacotherapy during attempts to quit cigarette smoking: The PATH Study 2013-16. PLoS One. 15, 9, e0237938. DOI:10.1371/journal.pone.0237938.

Pierce, J.P., Messer, K., Leas, E.C., Kealey, S., White, M.M., Benmarhnia, T., 2020b. A source of bias in studies of e-cigarettes and smoking cessation. Nicotine Tob. Res. 22, 5, 861-862. DOI:10.1093/ntr/ntz143.

Verplaetse, T.L., Moore, K.E., Pittman, B.P., Roberts, W., Oberleitner, L.M., Peltier, M.K.R., Hacker, R., Cosgrove, K.P., McKee, S.A., 2019. Intersection of e-cigarette use and gender on transitions in cigarette smoking status: Findings across Waves 1 and 2 of the Population Assessment of Tobacco and Health Study. Nicotine Tob. Res. 21, 10, 1423-1428. DOI:10.1093/ntr/nty187.

Watkins, S.L., Thrul, J., Max, W., Ling, P.M., 2019. Real-world effectiveness of smoking cessation strategies for young and older adults: Findings from a nationally representative cohort. Nicotine Tob. Res. 22, 9, 1560-1568. DOI:10.1093/ntr/ntz223.

Competing Interests: None other than already stated in the paper.