RESEARCH ARTICLE

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]

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Abstract

Background: Part of the evidence on harms and benefits of e-cigarettes concerns whether using e-cigarettes encourages smokers to quit. With limited results from controlled trials, and weaknesses in much epidemiological data, we addressed this using nationally representative prospective study data, with detailed accounting for factors associated with quitting.

Methods: Analyses used data for adults aged 25+ years from Waves 1 to 3 of the US PATH study. Separate analyses concerned follow-up from Waves 1 to 2, 2 to 3 and 1 to 3. The main analyses related baseline ever e-cigarette use (or e-product use at Wave 2) to having quit at follow-up, adjusting for predictors of quitting derived from 55 candidates. Sensitivity analyses omitted adults who had never used other products, linked quitting to current rather than ever e-cigarette use, used modified values of some predictors using later recorded data, or (in Wave 1 to 3 analysis only) also adjusted for quitting by Wave 2.

Results: In the main analyses, unadjusted odds ratios (ORs) of quitting 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 estimates reduced after adjustment, to 1.23 (0.94-1.61), 1.51 (1.24-1.85) and 1.39 (1.11-1.74). The final models, including between six and nine predictors, always included household income, everyday/someday smoking, wanting to smoke after waking and having tried quitting, with other variables included in specific analyses. Quitting rates remained elevated in e-cigarette users in all sensitivity analyses. ORs were increased where other product users were omitted. Adjusted ORs of quitting for current e-cigarette use were 1.41 (1.06-1.89), 1.30 (1.01-1.67) and 1.56 (1.21-2.00).

Conclusions: The results suggest e-cigarettes may assist adult

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smokers to quit, particularly in individuals not using other nicotine products, and who are current e-cigarette users.

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Introduction

Although it is believed that e-cigarettes cause far less harm to their users than do cigarettes (Nutt *et al.*, 2014), the introduction of e-cigarettes may theoretically have various adverse and beneficial effects (Lee *et al.*, 2019). Adverse effects would occur if the use of e-cigarettes encouraged initiation of smoking, if smokers intending to quit take up e-cigarettes instead, or if 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 smokers to materially reduce their cigarette consumption, or if use of e-cigarettes helps established smokers to quit. Here we present results relating to the last of these possibilities, the effect of e-cigarette use on quitting.

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; Masiero *et al.*, 2019), comparing e-cigarettes with nicotine replacement therapy (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, but this is not always the case (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. 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.*, 2019; 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, a recent review considered that the evidence is inconclusive due to the low quality of the research (Malas *et al.*, 2016). Problems involve the use of cross-sectional studies, the use of unrepresentative populations, 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 that report somewhat higher quit rates in those using e-cigarettes, (e.g. (Jackson *et al.*, 2019; Mantey *et al.*, 2017; Piper *et al.*, 2019; Snow *et al.*, 2018; Weaver *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.*, 2020; Flacco *et al.*, 2019; Grana *et al.*, 2014; Harrington *et al.*, 2015; 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 a study (Al Delaimy *et al.*, 2015) suggesting that e-cigarettes inhibits quitting.

Here we describe results from a prospective study aimed at avoiding such weaknesses. It is 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 two annual follow-ups (Waves 2 and 3). 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.

Methods

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 Wave 1 person-based weights. All analyses are limited to individuals aged 25 years or over at baseline.

Definition of smoking, e-cigarette use and predictor variables

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 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-cigs, e-pipes or e-hookahs) are also included, so the definition relates to e-product rather than e-cigarette use.

The main analysis for each period relates ever e-cigarette use at baseline to the probability of quitting, 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*.

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*.

Main analysis

For each period, the main 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 and 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 main 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.

Sensitivity analyses

While the main analyses relates 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 from the main analyses are on exactly how they are conducted. These are modifications of the main analyses:

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.

Missing values and other details

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 predictors 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 are given in the *Extended data*.

Software

Relevant data were transferred for analysis to a ROEELE database, and analysed using the ROEELE program (Release 59, Build 49). All these analyses could be run using the R-program, using the “lm” function including the “weights=” option for weighted linear regression, and for stepwise regression using the “step” function specifying “method=forward” and test=“F”.

Results

Main analysis

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 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 for 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 summarizes the results of the main analysis. 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. Interestingly, they were also less likely to quit if they had ever used pharmaceutical aids for quitting, i.e. Chantix, varenicline or bupropion (Wellbutrin, Zyban). Smokers were also less likely to quit if they were worse off and worse educated. Higher age (particularly above age 74 years) and higher BMI were also associated with a greater likelihood to quit.

Sensitivity analyses

Table 4 summarises the results of the sensitivity analyses, showing the estimated ORs in each case from the fully adjusted 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 confidence limits 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 analyses 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 minimize “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.

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
Smokers at baseline		6,503	6,847	6,490
Quit by follow-up		655 (10.1%)	633 (9.2%)	901 (13.9%)
<u>Demographics (A)</u>				
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
Current employment status	8	X1	X1	X1
<u>Aspects of smoking – general (B)</u>				
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
<u>Aspects of smoking – specifically related to quitting (C)</u>				
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

	Levels of variable ^a	Wave 1 to 2 quitting	Wave 2 to 3 quitting	Wave 1 to 3 quitting
<u>Smoking by family and friends (D)</u>				
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
<u>Awareness of hazards of smoking (E)</u>				
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
<u>Health status (F)</u>				
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
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
<u>Alcohol and drugs (G)</u>				
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
<u>Other (H)</u>				
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

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
Number in baseline in final regression	6,241	6,758	6,315
Number quitting	581 (9.3%)	616 (9.1%)	829 (13.1%)
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]

^aWhere 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 analyses.

	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)
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 bupropion (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)

Discussion

This report summarizes 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.

Other related analyses based on the PATH study have previously been published, all of which are consistent with e-cigarette use increasing the probability of quitting cigarettes.

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 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.

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). These results particularly seem quite similar to ours.

Strengths of our work include the use of a prospective study design based on a study population representative of the US, 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. We have also not studied persistent quitting, by relating Wave 1 e-cigarette use to quitting at both Waves 2 and 3. As our analyses were based on a pre-defined plan, and as data from Wave 4 are now available, we plan to address these issues in a further paper. This might, for example, relate Wave 1 e-cigarette use simultaneously to quitting at all subsequent waves, separating those who quit at all three waves, or at only one or two.

For the present, our results clearly suggest that among 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.

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/F4WA7> (Lee & Fry, 2020).

This project contains the following extended data file:

- Additional file_fuller details regarding the predictor variables used.docx

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

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 the various drafts of the paper.

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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 or 12 months at follow-up (see, Gilpin *et al.* 1997²). 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 in a 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 authors³⁻⁶.

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

Partly

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

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 Research¹.

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.* 1997²). 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 authors³⁻⁶.

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.

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