

Dear Professor Roeggl,

Thank you for the expert comments and invitation to resubmit our paper titled "Association between population changes in use of e-cigarettes and changes in quit attempts, the success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services: a time-series analysis" to the BMJ. We found these comments helpful and have tried to address them as fully as possible in the paper. Details of our amendments are given below.

We look forward to hearing your response.

Yours Sincerely,

Emma Beard

Comments from the committee

1. The main concern is that the committee thought your paper was a rather difficult read as it currently stands, particularly around the area which describes where the data came from.

We have made a number of amendments on page 6 to the methods section to make it clearer where the data came from and where further details can be obtained. This includes an additional heading "Data Sources" and the following information: "Data came from two main sources: 1) the Smoking Toolkit Study (STS) and 2) NHS stop smoking services". Reviewer 2 requested this section included additional details on sampling which we are conscious may make this section more difficult to follow. We could add these additional details to the supplementary materials instead.

We have also been through the introduction and discussion sections carefully and reworded or deleted sections that made the paper hard to follow. For example, we have re-worded the main objectives and limitation sections.

2. We didn't find an ethics vote.

We have now included the following ethical approval statement on page 11 "Ethical approval for the STS was granted by the UCL Ethics Committee (ID 0498/001). Ethical approval was not required for use of data from Stop Smoking Services as the data are publically available."

3. What is the clinical relevance of the small increase in success of quit attempts?

We have added the following on page 15 which indicates the clinical relevance of the percentage increase in quit success, and add a citation to a paper that one of us has written on "If the link between change in e-cigarette use and smoking cessation rate is causal we would expect a rise in prevalence of e-cigarettes for smoking cessation from 35% to 45% in a 12 month period to increase the prevalence of successful quit attempts from 18.6% to 19.6% with other things being equal. This equates to around an extra 31,600 successful quitters per year assuming that 3.16 million smokers attempt to stop annually (i.e. an increase from $n=587760$ to $n=619360$ in smoking cessation)[17]. It would also mean that e-cigarettes have contributed an additional 47,100 to the numbers of short- to medium-term ex-smokers since the beginning of 2012 (an average of 16,000 per year). This is calculated on the basis of a 15.36% increase in current e-cigarette use since the beginning of 2012 to the beginning of 2015, which would be estimated to result in a 1.49% (15.36×0.097) increase in smoking cessation, equating to 47081 individuals out of 3.16 million. While these numbers are relatively small, they are broadly similar to previous estimates [21], and are clinically significant because of the huge health gains from stopping smoking: a 40 year-old smoker can expect to gain 9 life-years compared with a continuing smoker [46-48]. This number of additional long term quitters is unlikely to produce a detectable effect on smoking prevalence in the short-term but it might be picked up over a period of several years"

4. Your paper adds some interesting information but the conclusions are made a little strongly.

We have toned down our language in the final conclusion paragraph on page 15 .We have ensured that we do not assert a causal connection throughout the paper. If the editor can point out any specific instances, we would be happy to consider further amendments.

5. What about those smokers that used a variety of techniques to quit smoking?

We included the most popular evidence-based categories of cessation aid. We agree that another interesting question may be to assess the association between use of e-cigarettes and (comparatively rare) use of multiple treatments, but that would require another set of analyses which may be too much to include in one paper. We could include such analyses if the committee insists but it would require an amendment to our analysis plan.

6. The methods look complex but they are appropriate. We were glad to see a proper use of a times series model and one where the analysis plan was pre-registered with amendments fully documented.

We are pleased that the committee found the methods and analysis appropriate.

7. What does this add to West R et al. Estimating the population impact of e-cigarettes on smoking cessation in England. *Addiction* 2016; 111: 1118-9?

The letter by West et al published in *Addiction* was an indirect estimate of the number of long term quitters that may be attributable to the use of e-cigarettes in a given year. It was based on a number of well-established smoking cessation parameters (such as long-term relapse rates and effectiveness of prescription medications) and population statistics, combined with an estimated effect size for e-cigarettes. The estimated effect size for e-cigarettes was based on the two small RCTs and

our previous 'real world' effectiveness paper, which estimated the associations on an individual level between use of treatment and cessation outcomes. The current paper offers a comprehensive and direct method to consider the impact of e-cigarettes on a wider variety of outcomes using a time-series approach. It also extends the findings to assess the impact on other quitting activity: prevalence of quit attempts, use of Stop Smoking Services, use of NRT, and use of prescription medication (including varenicline and bupropion). Time-series analysis has the benefits of assessing associations while adjusting for the internal nature of the data (e.g. autocorrelation), seasonal and non-seasonal underlying trends and population level policies and interventions. We now introduce the paper by West et al in the introduction and compare the findings in the discussion (see above).

Comments from reviewer one

1. The title needs double-checking, it reads association between... on...

Thank you, we have now modified the title to: "Association between population changes in use of e-cigarettes and changes in quit attempts, the success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services: a time-series analysis"

2. What is already known paragraph: I find it a bit odd to refer to a specific systematic review here and would suggest referring to concerns about this in general. Otherwise, a reference would be needed here

We have now changed this to "Concerns have been raised that the increase in population use of e-cigarettes may be undermining smoking cessation. If this is true, then e-cigarettes may have a negative impact on public health."

3. What this study adds: The sentence about the TPD is too vague to be meaningful. It could possibly be clarified why these findings are important when considering the TPD, but I would suggest removing the sentence as it does not seem to be based directly on the study findings. Also, there is little or no discussion of the TPD in the main body of the manuscript so this appears like an afterthought.

We have now decided to delete the sentence on the TPD.

4. Introduction: The first sentence needs some references

We have now added references to the first sentence

5. Aim 1 is nearly unreadable, please consider splitting this sentence or rephrasing to make clearer.

We have changed this to read: "The associations between the success rates of those who made a quit attempt in the past 12 months and: a) prevalence of use of e-cigarettes among current smokers b) prevalence of use of e-cigarettes during a quit attempt"

6. Aim 2: As in the title, this talks about associations on something. Also outcome 'attempts' – would this be proportion making an attempt, number of attempts or something else? Please define

We have changed this to read: "The association between the proportion of past-year smokers who attempted to quit smoking and prevalence of use of e-cigarettes among current smokers"

7. Aim 3: as above - 'association on'; and is it really necessary to repeat the words 'quit attempt' eight times within this sentence? It is tautological to say 'during a quit attempt among those who made a quit attempt'

We have now changed this to read: "The associations between the percentage of last-year quit attempts involving the use of e-cigarettes and a) the percentage that used licensed medications (any prescription medication, specifically NRT on prescription, and NRT bought over the counter), and b) the number of smokers who set a quit date with the English Stop-Smoking Services."

8. page 6, line 19 and 44: Why was 0.1% chosen, presumably this was the figure when data were first collected?

Other studies show use around this period was relatively negligible. The model requires non-zero values. Therefore we arbitrarily and a priori selected 0.1%: "Data were first collected in 2011 and prior to this use was assumed to be stable at 0.1% of smokers based on studies that indicate use before this period was negligible [25 26]."

9. It would be useful to have response options for the question on aids used during quit attempts and to give all outcome variables labels.

A full list of the response options are given in the pre-registered analysis plan (<https://osf.io/fbj2/>) and the names of all variables can be found in the R syntax code (<https://osf.io/yqaxm/>). Links to both of these are given in the paper. We have now also added this in the supplementary material. We are conscious that the committee wanted the readability of the paper to be improved and do not want to add too much further detail here.

10. "Price of cigarettes was correlated 0.99 with time and was thereby taken into account by use of differencing to make the series stationary" This sentence will be completely opaque to most readers and should either be explained or moved to the supplementary appendix.

We have changed this to read: "Price of cigarettes increased linearly over time with a correlation of 0.99. Therefore any impact

of price on outcome measures could not be distinguished from a linear change over time for which we were already accounting by 'differencing' the time-series (using the difference between successive values of the outcome variables rather than the values themselves)."

11. Analysis: I appreciate the appendix, but some explanation of ARIMAX modelling would be helpful here, e.g. 'first differenced and seasonally differenced'.

We have extended the analysis section in the paper to provide a fuller description of ARIMAX modelling and have described what differencing means: "The analysis plan was registered on the Open Science Framework prior to data analysis (<https://osf.io/fbgj2/>). All data were analysed in R version 3.2.1 using Autoregressive Integrated Moving Average with Exogeneous Input (ARIMAX) modelling. ARIMAX is an extension of autoregressive integrated moving average analysis (ARIMA), which produces forecasts based upon prior values in the time series (Autoregressive terms; AR) and the errors made by previous predictions (Moving Average terms; MA). Such models have been used to explore the impact of tobacco price and mass media campaigns on smoking prevalence [1 2]. We followed a standard ARIMAX modelling approach[3], which is detailed in Supplementary Appendix 1. The series were first log-transformed to stabilise the variance, and if required, 'first differenced' and 'seasonally differenced'. First differencing involves calculating the change between one observation and the next, while seasonal differencing involves calculating the change between one year and the next. The autocorrelation and partial autocorrelation functions were then examined in order to determine the seasonal and non-seasonal MA and AR terms. To identify the most appropriate transfer function for the continuous explanatory variables the sample cross-correlation function was checked and models with varying lags compared using the AIC. Coefficients can be interpreted as estimates of the percentage change in the outcome of interest for every percentage increase in use of e-cigarettes and mass media and absolute impact of tobacco control policies. Strobe guidelines were followed throughout [4]."

12. Sample characteristics: The stop smoking services do not report the number of smokers but the number of quit attempts made with them

We have changed the title of table one to reflect this. Thank you for spotting the error.

13. In terms of writing style, it would be better not to start most paragraphs in the results with 'Table x shows...' or 'Figure x shows...'. At least in some places describing the finding and then referring to the table/figure would flow better

We have made these changes throughout the results section

14. Briefly define in one place what determines that a result is inconclusive

We now define this in the discussion with the following sentence added to the limitations "Sixthly, caution should be taken when interpreting null effects and readers should not assume it represents no association [38]. Instead, we can only conclude in the presence of a p value > 0.05 that the data are inconclusive as to whether an association exists [39]; albeit this study was powered to detect relatively small associations."

15. Discussion: page 12, line 32: which policies?

We have now extended this sentence to read: "First, estimates of the impact of some of the tobacco control policies were implausibly large and confidence intervals wide, particularly for the increase in age-of-sale, suggesting caution when drawing conclusions about these."

16. To address concerns about population impact, a brief mention of e.g. prevalence of e-cigarette use among never smokers would also be helpful.

We have added the following to the discussions limitations: "Finally, for a full assessment of the impact of e-cigarettes on public health future studies should assess the impact on use among never smokers. Although previous studies report a rise in recent years in experimentation by never smokers, regular use in the UK is currently rare at below 1% [5-8]"

17. The formatting of tables 2 to 4 is disgraceful even though this is only review stage. Please reformat so that the font size is reasonable and they don't extend beyond the page margins.

After looking at these again they were very hard to read and have re-formatted them accordingly.

Comments from reviewer two

1. It may help the reader if the sampling strategy is explained some more. For example, how many households were contacted monthly or quarterly? My understanding is that random location sampling involves quota-based sampling and response rates do not apply to this method. This may need to be mentioned.

See earlier response.

2. The finding related to the decline in rates of quit attempts over years may need some discussion.

We have included the following paragraph in the limitations of the discussion section: "Consideration is also needed as to what

may have contributed to the slowing down in the rates of attempts to quit smoking identified over the course of the study. Previous studies suggest a possible effect of reduced spending on mass media campaigns [21], the possibility that smokers may be becoming inured to smoking cessation messaging [42] and the financial crisis and austerity within Europe [43]. We did not find a clear impact of any of our measures on quit attempts over the period studied."

3. Page 5, second paragraph, question #3, a-c, it may not be necessary to mention "among those who made a quit attempt."

We have now deleted this.

4. Page 11, last paragraph, there is a typo.

Thank you for noticing this, we have changed it to "... e-cigarettes during a quit attempt among."

5. Please distinguish between over-the-counter NRT and prescription NRT with examples. The negative relationship between e-cig use and prescription NRT use, but not the other NRT use, may need some discussion.

We have included the following definition of over-the-counter on page 10 "In England, over-the-counter medications, or the self-medication market, refers to all products which can be brought in shops (including supermarkets) and pharmacies without a prescription". We have also added the following which discusses the results further to the discussion "The finding of an association with use of prescribed NRT but not over-the-counter NRT is difficult to explain. One possibility is that health professionals are discussing the options with patients who are then choosing to use e-cigarettes, perhaps having already tried NRT. This issue requires further research."