Author's response to reviews

Title: Environmental Tobacco Smoke Exposure and Diabetes in Adult Never-Smokers.

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Author's response to reviews: see over
Dear Editor,

Re: MS: 4344155001336148 - Environmental Tobacco Smoke Exposure and Diabetes in Adult Never-Smokers - Response to Reviewers.

Reviewer #1
1. Abstract: No information regarding the final sample size and # of diabetes cases among never smokers.

Response: We have updated the abstract with the final sample size and number of diabetes cases among never smokers.

2. The Introduction section was poorly organized and thus confusing. For example, the last sentence in the first paragraph came from nowhere, and did not integrate the contents before/after it.

Response: We have moved this last sentence to lines 69-71 of the revised manuscript. It integrates better with the rest of the second paragraph.

3. The authors did not emphasize the necessity of investigating the associations of interest among never smokers, whereas in the Abstract they did so. If never-smokers are of interest, the authors shall clearly state so in the introduction.

Response: Thanks for pointing this out. We have emphasized this in lines 78-87 of the revised manuscript.

4. It’s unclear how the sample size ended up with 6392 from a total of 8047.

Response: 8047 participants took part in the follow-up study. We ended up with 6392 participants due to lacking data among subjects who only completed the short questionnaire. We indirectly accounted for the effect of these missing data by doing analyses involving inverse probability weighting as part of sensitivity analyses. Additional file, Table A1 shows the baseline characteristics of SAPALDIA cohort participants based on whether they were included in the present analysis or not. While most characteristics were significantly different, the proportion of diabetes cases was the same in both groups.

5. Define RBG at line 103.

Response: It is already defined in line 105 of the revised manuscript.

6. It is interesting to know how many never smokers at 1st follow-up reported smoking at baseline. This is evidence for the validity of self-reported smoking status.

Response: In our definition of never smokers we excluded persons having reported former or current smoking at baseline. The responses were fairly accurate. In fact, none of the never-smokers at follow-up reported smoking at baseline. We had added this as a validity of self-reported smoking status in lines 308-310 of the revised manuscript.

7. It’s unclear exactly how ETS was defined in the current study. What is the
question(s) for assessing ETS status? Was this question(s) validated?

**Response:** Participants were asked if they were regularly exposed to cigarette smoke from other people in the last 12 months preceding the survey. This is a validated question and has also been used in other ETS studies.[1-4]

8. It’s unclear how the interaction terms were constructed and how the interaction tests were performed (LRT)?

**Response:** For each potential effect modifier, we ran two models. The model from which we got the p-values involved the entire sample and included an interaction term between ETS and the respective effect modifier. The other model, providing the sub-group specific estimates, was stratified into the subgroups of the effect modifier. We have clarified these in lines 179-182 of the revised manuscript.

9. Table 2, Line 540: Unadjusted model includes smoking status. It’s unclear in this stratified analysis, whether the authors further adjusted for smoking history in each stratum?

**Response:** We appreciate this observation. We did not further adjust for smoking history in each stratum. This sentence is wrong, thus we have removed it. We adjusted for smoking pack-years instead, for current and ex-smokers.

10. Table 4: it’s very confusing what the OR (95% CI) for “Interaction” meant? The authors stated that “The association between ETS and DM in never smokers was highly strengthened by older age and COPD [Table 4]. Associations were also strengthened (albeit less strongly) by female sex, obesity, physical inactivity, hypertension, high serum triglyceride and low serum HDL, and post-menopausal status in women [Table 4].” However, the 95 CIs overlap between strata, making it hard to understand how the interactions are significant. Actually, it may be very helpful if the authors can justify using a mixed logistic regression model rather than the ordinary logistic regression model.

**Response:** We have now presented the p-values of the interaction terms in the revised manuscript. As mentioned earlier, the sub-group specific estimates and the p-values of interaction terms were from separate models. We performed all analyses using mixed logistic regression model. Moreover, a slight overlap of confidence intervals for different subgroups is still compatible with a statistically significant difference.

11. In the dose-response analysis, the authors should evaluate whether the dose-response curve is linear or non-linear. In addition, why >=3hr ETS at home is different from >=3hr ETS at somewhere else in terms of the “dose” of ETS?

**Response:** We reported a non-linear dose-response relationship because we tested this with categories of reported hours of ETS exposure. In some cases, the observed dose-response relation might be compatible with the assumption of a linear relation, in others not. We explored this further by using LR-test to compare the categorized ETS model with another model with ordinal ETS variable (with one degree of freedom). In both settings of ETS exposure (home and elsewhere) the p-values of LR-test were non-significant, thus we cannot exclude a linear relationship. We have additionally presented the results of analyses
Due to varying smoking regulations across countries, exposures to ETS tend to be more consistent in some settings than others. Previous papers have tried to disentangle effects of ETS at home and outside home. We did this to assess differences in effects by settings of exposure and allow comparison of findings across studies. We have explained these in lines 123-125 of the revised manuscript.

Reviewer #2
Major Compulsory Revisions
1. Pg 5, ln 96 - The authors use a number of variables to define DM with some of these being self-reported. How valid is it to use self-report. Will there be under- or over-reporting? How might this affect the results?

Response: To collect information on disease history by interview or questionnaire is standard in large surveys due to reasons of cost. It is important to ensure that respondents are aware of their anonymity and in a relaxed environment to improve the quality of their responses. These we ensured during our data collection, even though we expect some under-reporting. If under-reporting was less among those with ETS-exposure than among those without, the association between diabetes and ETS-exposure would be over-estimated. Fortunately, we had some internal validity in that self-reports correlated well with objective measures. The observed associations did not vary substantially when we used different definitions for the identification of diabetes cases. We have added a comment to the discussion about the potential influence of under- or over-reporting as well as under-diagnosis of diabetes.

2. Pg 5, ln 95 – I am not clear about the definition of diabetes. The diagnosis of diabetes was ascertained from a series of questions at the first follow-up. Was such information also available at baseline? If so, an analysis of the incident cases could be more useful in terms of assigning causality.

Response: Diabetes was only defined at follow-up. Baseline investigation mainly focused on respiratory outcomes. This was why we could not explore incidence of diabetes and we have discussed this as part of the limitations to our study. We added this information to lines to lines 99-100 (Methods) of the revised manuscript.

3. Pg 5, ln 108 – the definition of smoking status needs clarification. I assume that if participants were current smokers at first follow-up and either former smokers or never smokers at baseline, then they were current smokers. Similarly, if participants were former smokers at first follow-up then they were classified as former smokers regardless of the status at baseline.

Response: This is exactly how we defined smoking status and we now state that more clearly in lines 112-115 of the revised manuscript.

4. Pg 6, ln 119 - Why was ETS exposure categorised into 0, <3 and >=3 hours. What was the reason for this? How accurately does self-report reflect actual exposure?

Response: This categorization was done because about 50% of those who reported ETS exposure reported 3 or more hours/day. Also this categorization has been used in previous
SAPALDIA publications, thus ensures internal comparability within the SAPALDIA study. We have stated the above reasons in lines 127-129 of the revised manuscript. Self-reports do not accurately reflect actual exposure but when we compared mean exhaled carbon monoxide (an indicator for recent exposure to tobacco smoke) in never-smokers across groups of ETS exposure we found a positive trend. We have shown this table in the appendix (Table A6). We therefore assume some validity in these reports. Previous studies [5, 6] have also shown positive correlation between self-reported ETS and salivary cotinine measures. Our observed positive trend in carbon monoxide concentration of exhaled air is thus consistent with the results of these validation studies.

5. Pg 6, ln 125 - I would like to see physical activity, consumption of fruit and vegetable and alcohol consumption better defined. For example, for physical activity, is this referring to mild, moderate or vigorous physical activity? Does alcohol consumption refer to standard drinks? For the consumption of fruit and vegetables, does the question indicate the amount to be eaten eg. three servings per day, etc. It would be useful if the authors provided the questions used in the questionnaire either in the paper or as an appendix.

Response: Physical activity referred to number of hours per week of vigorous activity. Consumption of alcohol, fruits and vegetables referred to the frequency of consumption per week. Specifically, vigorous physical activity was assessed by “how many hours a week do you usually so much that you get out of breath or sweat?” Alcohol consumption: “how often each day do you normally drink alcohol including beer, wine, liquors and spirits?” Raw vegetables: “how many days each week do you eat any raw vegetables, salad or do you drink vegetable juice?” Citrus fruits: “how many days each week do you eat any citrus fruit or drink citrus fruit juice?” Other fruits: “how many days each week do you eat other fruits (except citrus fruits)?” We have explained these questions in detailed in lines 137-141 of the revised manuscript.

6. P6 6, ln 130 – the authors go to some trouble to provide information on the quality of the air pollution measurements. However, the effect of air pollution on outcomes is not discussed in the paper at all. Why was the 2010 dispersion models used to estimate home outdoor exposure for baseline and follow-up? What is the rationale for adjusting for PM10?

Response: Two dispersion models were used to assign PM10 estimates, a dispersion model based on data from 1990 for baseline and a dispersion model based on data from 2000 for follow-up. Annual estimates between both measurements were extrapolated using air pollution trends obtained from monitoring stations nearest to participants’ residences. We have clarified this in lines 147-153 of the revised manuscript. Studies including ours [7] have previously found an association between air pollution and diabetes. We cannot entirely exclude the role of ambient air pollution as a potential confounder; therefore, we included it in the analysis. This rationale for adjusting for PM10 has been clarified in lines 143-146 of the revised manuscript. We have discussed effects of air pollution on outcomes in lines 296-298 of the revised manuscript.

7. Pg 7, ln 136 – BMI category <=25 also includes underweight. Does including underweight subjects lead to any potential bias?

Response: Thanks for pointing this out. We agree that this might lead to some bias, but fortunately, we have only 85 underweight participants (2.8% of “normal weights”), thus
any bias due to this would be very small. We repeated the analysis excluding these people and the estimates for normal weights was not substantially changed (initial estimate: 1.15 [0.42, 3.19]; revised estimate: 1.18 [0.42, 3.26]). Also, estimates for the overall ETS effect in never-smokers was also stable when we excluded the underweights (initial estimate: 1.50 [1.00, 2.26]; revised estimate: 1.50 [0.99, 2.26]).

8. Pg 8, ln 180-182 – it is not clear to me that Table 1 gives the ETS exposure rates by the variables listed in the Table. It seems to me that the table presents the column percentages rather than row percentages.

Response: Yes, Table 1 presents column percentages instead of ETS exposure rates by the listed variables. We presented the column percentages to allow us compare prevalence of each variable (within each category) with that of other categories.

9. In Table 4, I do not understand why the ORs for interaction terms are presented.

Response: We wanted to show more of the actual estimates than just the p-values. We have now presented the p-values of the difference between the two groups, considering that it makes for an easier understanding.

10. Pg 224, ln 225 – the authors say that there was a positive non-linear dose relationship for ETS exposure at home. The data suggest there may be a threshold effect. In any case, I think it is difficult comment on a dose-response relationship with only three data points.

Response: We have further explored this dose-response relationship by doing analyses with hours of ETS exposure (ordinal variable with one degree of freedom). There was a positive relationship between hours of ETS exposure and diabetes, with borderline significance. Also comparing this model with the categorical hours of ETS exposure yielded non-significant p-values, thus, we cannot exclude a linear relationship. We have acknowledged the three data point issue and better explained the dose-response concept based on these new results in lines 248-254 of the revised manuscript.

11. Tables 3 and 4 – why are the results for hypertension presented in these two tables? As I understand it, the full model does not include hypertension.

Response: We previously included hypertension in Table 3 to show that it does not substantially affect the ETS and DM relationship, given that some readers may argue it is a confounder. For Table 4, we merely tested for the presence of any effect modification by hypertension. But for consistency, we have moved hypertension, which may be in the pathway from ETS to diabetes, to Additional file, Table A2.

Minor Essential Revisions
1. Pg 5, ln 88 – is there a reference for SAPALDIA.

Response: Yes there is, and this reference has been added.

2. Pg 8, ln 168 – what does ‘complementary’ diabetes mean?
Response: By ‘complementary’ diabetes we meant the diabetes cases identified by other criteria used in the diabetes definition that were not of interest in a particular analysis. We tested association between ETS and diabetes based on diabetes defined by each of the 4 criteria. For instance when we focused on self-reported diabetes, we excluded diabetes cases identified by medication use or blood test, and the excluded cases were referred to as ‘complementary’ diabetes. We agree that this term is confusing and have re-worded that line as shown in lines 186-188 of the revised manuscript.

3. Pg 8, ln 180-182 – the authors need to be more specific about ‘lower social status’, ‘less healthy lifestyles’.

Response: We have edited this to “lower educational level, lower neighbourhood socio-economic index and lower physical activity” as shown in lines 201-202 of the revised manuscript.

4. Pg 8, ln 182 - I am also not sure what is meant by “...ETS exposure was higher ......diabetes rates”. This needs clarification.

Response: We have clarified this sentence accordingly. “In never-smokers, ETS exposure was higher in females, younger participants, and participants with lower educational level, lower neighbourhood socio-economic index, lower physical activity, low HDL, higher hs-CRP and higher diabetes rates (Table 1)”. This is shown in lines 200-203 of the revised manuscript.

5. I assume ETS <3 hours/day is actually ETS 0 to <3 hours/day.

Response: Yes it is, and we have edited this definition where appropriate in the revised manuscript.

6. Add T1DM and SE to the abbreviation list.

Response: We have added them to the abbreviation list
References


