Author's response to reviews

Title: The association between ambient fine particulate matter and incident adenocarcinoma subtype of lung cancer.

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Responses to Reviewers’ comments

Reviewer(s)’ Comments:

Reviewer #1:

This manuscript explores whether the association between ambient fine particulate matter air pollution (PM2.5) and lung cancer is modified by non-melanoma skin cancer status. The authors report that participants with non-melanoma skin cancer experienced a reduced risk for PM2.5 associated lung cancer and that participants without non-melanoma skin cancer an increased risk. Comments include:

Thank you for your valuable feedback and thoughtful questions. Responding to them has improved our manuscript.

Abstract:

1. Would be nice to insert the years of the study period in the abstract

Response #1: We have inserted the study period in line 34.
2. Since the O3 adjustment doesn’t make any difference in HRs consider presenting the single pollutant PM2.5 result in abstract.

Response #2: We have deleted the ozone finding from the abstract.

3. Could the p value for interaction be provided in the abstract?

Response #3: We have modified the manuscript and, because of the low numbers with NMSC, have decided to present this as a sensitivity analysis instead of a test of interaction. Thus, we are no longer presenting the interaction between NMSC and PM2.5 on risk of lung AC even though the p-value for this interaction was < 0.001.

Methods:

4. Could the time period of participant enrollment be provided?

Response #4: We have added the period of enrollment, 2002-2011.

5. Is there any information about the occupation of study participants? And possible occupational-level confounders? Is there any information on working outside?

Response #5: The AHS-2 uses educational level as a measure of socio-economic status and this works well in our study population. We do have write-ins for occupation, but these have not been computerized so are not available for this paper. Unfortunately, to your question about working outside, the AHS-2 baseline questionnaire on time spent outdoors did not differentiate between leisure and work activities. Thus time spent outdoors is the combined time spent outside both in leisure and work activities.

6. Has an adjustment for ecological-level socio-demographic confounders been attempted?

Response #6: We have only used personal level socio-economic variables such as education and household income, to assess socio-demographic level. In addition to marital status and race, these have been found to characterize our population very well with regards to SES and socio-demographic confounders.

7. Could more information about the non-melanoma skin cancer be provided? Is it self-reported? Physician-diagnosed? Is there information regarding the timing of diagnosis? What is the mean age at diagnosis?

Response #7: The information on non-melanoma skin cancer is self-reported, physician diagnosed and the subjects report year of diagnosis as well. The question reads: “Has a physician ever told you that you had any form of cancer (including leukemia, lymphoma, myeloma and skin cancer)? If Yes, they are asked to write in the site of the cancer as well as the approximate year when it was first diagnosed. The average age at diagnosis for the NMSC was 57.2 year for past smokers and 58.2 for never smokers.
We have added in that the prevalent NMSC was self-reported physician diagnosed in line 94 of the manuscript.

8. Was an analysis with summer O3 attempted? Average summer and winter

Response #8: We used mean 24-hour ozone levels with no differentiation between summer and winter levels.

9. Did analysis examine potential non-linear effects of cigarette smoking on lung cancer risk?

Response #9: Since only 19% of our cohort had ever smoked and 55% of these had quit smoking more than 20 years ago, we use a nested smoking variable to adjust for smoking in our analyses. This nested variable included whether they had ever smoked, years since quit smoking (< 20 years or 20+ years) and number of cigarettes/day when smoking (< 8.5 and 8.5+)

Results:

10. Is physical activity recreational or total physical activity (including occupational?)

Response #10: The physical activity used in the manuscript is recreational physical activity. The AHS-2 also has information on physical activity at work, but this was not included in the current manuscript as it is not fully computerized yet?

11. Is hours per day spent outside leisure or occupational?

Response #11: There is no differentiation in our questionnaire on whether it is recreational or occupational. It is total time spent outdoors every day between 9 a.m and 5 p.m., differentiated by weekdays and weekends as well as by cooler (October-March) and warmer months (April-September).

12. Is seems it would be useful to examine participant characteristics by hours per day spent outdoors and by non-melanoma skin cancer status

Response #12: Yes, this would be a possibility. We have assessed hours spent outdoors per day by non-melanoma skin cancer diagnosis and the time spent outdoor was very similar between the two groups.

13. Table 2 insert single pollutant results for O3

Response #13: We have inserted the results for O3.

14. Would be nice to see HRs for never smokers only overall and for analysis of interactions
Response #14: We have now included results for sub-group analyses on smoking status (ever and never smokers) (Line 219-222 in the manuscript) even though the interaction was not significant (p=0.4241).

15. Results are based on only 22 lung cancer cases with NMSC - the limited sample size should also be considered more explicitly

Response #15: We agree that the low number of cases is marginal and creates uncertainty when testing for interaction. Even though the interaction term was significant (p<0.001), we have modified the manuscript to instead do sensitivity analysis where we exclude the 5,373 with prevalent NMSC to see if that changes the HR for the main effect (Table 2, model 4). Exclusion of prevalent NMSC is in line with what Raaschou-Nielsen et al (2011) did in their study of lung cancer incidence and long-term exposure to air pollution from traffic (ref#34).

16. Is there any information on changes in lifestyle over time? Perhaps participants with NMSC changed drastically their lifestyle and were more willing to quit smoking after diagnosis leading to reduced cancer risk? Is there information on the timing of diagnosis in relation to quitting smoking?

Response #16:

We do not have data on lifestyle change over time except for a few variables on diet.

None of the subjects in this study were current smokers at enrollment and thus they were already non-smokers. The mean age at time of NMSC diagnosis was 55.7 years and the mean age at the time of quitting smoking was 36.5 years. Thus, as we expected, the subjects in this study quit smoking at an earlier age than the age at which they were diagnosed with NMSC.

17. Perhaps a DAG should be inserted for clarity?

Response #17: Since we are no longer treating NMSC as an effect modifier, the other confounders are well known and recognized as potential confounders. After discussion among ourselves, we therefore feel that there is no longer a need for inserting a DAG. However, if the reviewers or the editor want us to include a DAG with the traditional potential confounders, we will be happy to supply this.

Discussion:

18. Could more discussion be inserted regarding the manuscript of Hart et al. 2015

Response #18: We have included a paragraph discussing the Hart et al paper (2015) in lines 245-257.

19. There should be more discussion of O3 - findings here vs previous work and literature
Response #19: We have added more discussion on findings by others on the association between ambient ozone and lung AC as well as on the results of our previous paper (Beeson et al, 1998) in relation to the current paper in lines 323-334.

20. Suggest shorten discussion beginning on line 262 and instead provide more discussion of how existing studies (mortality and incidence) have treated NMSC in analysis (included vs excluded). A systematic comparison would be nice.

Response #20: We have shortened the discussion. With respect to inclusion/exclusion of NMSC, very few studies on lung AC and LC in general have specified what prevalent cancers they have excluded. The studies have either specifically mentioned that they did not exclude NMSC (2 out of 15 for AC, 5 out of 35 for LC) or they do not say whether they have excluded or not (13 out of 15 for AC, 29 out of 35 for LC). To our knowledge, only one study of the association between NOx ambient air pollution and LC specifically mention that they have excluded prevalent NMSC. We have included these findings in our Discussion, lines 280-288.

21. Typo page 14 = quite smoking should be quit smoking

Response #21: Thank you for pointing this out. It has now been corrected.

22. Could results throughout the manuscript be compared more with previous estimates based on non- or never smokers?

Response #22: We have added comments in lines 168-169 and 219-222 and 239-241.

Reviewer #2:

This is an interesting article examining the effect of environmental exposure (PM2.5) on adenocarcinoma (AC) in a wide cohort of non-smokers. The authors report an increased risk of 31% for AC for each 10 µg/m3 increment in ambient PM2.5 concentrations, which becomes statistically significant when the analysis is restricted to subjects who spent more than 1 h/day outdoors.

These results are interesting because they supplement the results reported by the same authors in a previous papers on lung cancer and air pollution (Gharibvand L. et al, Environ Health Perspect 2016) focusing on a specific subtype of lung cancer. Moreover, similar results were recently reported in the literature, showing that the effect of air pollution is particularly evident in AC.

Thank you for your response and constructive comments. We have tried to respond to each one and feel that our manuscript has improved.

1. However my biggest concern related to the results of this study regards the effect modification of PM2.5 when results are stratified for presence/absence of non-melanoma skin cancer (NMSC, on which instead the authors point their attention (also including this in the title).
In particular, the apparently protective effect of PM2.5 on AC among NMSC cases is quite worrying.

I think that this association, also based on small numbers (22 exposed to NMSC between cases), it is very difficult to explain, and that the discussion supported by the authors is not acceptable. They report in the discussion section (rows 283-290) "The increased HR of incident lung AC among persons without prevalent NMSC and the very low HR of incident lung AC among subjects with prevalent NMSC could potentially be explained by misclassification of air pollution estimates among subjects with prevalent NMSC. Since it is well known that sun exposure is a strong risk factor for NMSC, it may be reasonable to think that there is an element of reverse causation and that subjects who have been diagnosed with NMSC spend less time outdoors, at least during clear days, and thus are exposed to lower concentrations of the ambient air pollution at their place of residence than the recorded ambient levels". Reverse causation is not relevant here, because they NMSC is another exposure and not the outcome (the study outcome is always the AC), but in reality the result found could be explained by a variety of scenarios with completely different explanations (including collider bias, different patterns of interactions, etc) and it is therefore very difficult to explain.

Our response: We agree that this finding is challenging, especially given the low number of cases. After discussion among ourselves, we have therefore decided to take it out of the title and also to not deal with NMSC as a potential effect modifier, but rather deal with it in a sensitivity analysis.

2. Moreover, the authors should try to justify their choice of analysing NMSC (by the way: are these identified at baseline or ascertained during follow-up?) as an effect modifier a priori.

Our response: The NMSC were self-reported physician diagnosed at baseline (at enrollment into the parent AHS-2 study. The rationale for addressing the NMSC is, as we have explained in the manuscript, that several authors have found that NMSC increases the risk of non-skin cancers, including lung cancer. Thus it makes sense to see what effect including or excluding the NMSC has on the association between air pollution and lung cancer since both NMSC and ambient air pollution are related to spending time outdoors. However, given the small number of lung AC among the subjects with prevalent NMSC, we have found it more useful, in this manuscript, to instead do sensitivity analyses where we exclude the prevalent NMSC from the study population.

3. Their interpretations about the use of vitamin D or the avoidance of spending time outdoor because of a previous NMSC remain unconvincing and the proposed title is therefore inappropriate. The focus of the paper on this single debatable result should be avoided.

Our Response: We appreciate this candid response and agree that we put too much focus on this part of the manuscript. In response to the comments by both reviewer 1 and 2, we have therefore taken out the NMSC from the title and toned down the focus on this by using a sensitivity analysis where we exclude subjects with NMSC from our main model. We have therefore avoided the entire discussion on possible effect modification of NMSC.