Author's response to reviews

Title: Short-term effects of ambient particulates and gaseous pollutants on the incidence of transient ischaemic attack and minor stroke: a case-crossover study

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Response to Reviews

Short-term effects of ambient particulates and gaseous pollutants on the incidence of transient ischaemic attack and minor stroke: a case-crossover study.

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We would like to thank all the reviewers for their constructive and insightful comments on our manuscript. We have carefully revised the manuscript according to your suggestions and outline our point by point responses below to indicate the changes we have made. In the manuscript, we have highlighted all revisions and changes with underlines to ease appraisal.

Reviewer: Julie Johnson

Major Compulsory Revisions

• A line or two discussing the clinical difference between TIA and ischemic stroke in the Introduction section is needed for those unfamiliar with stroke classification.

Response: We have provided definition of both terms as per your suggestion.

• References 4 and 5 specifically reported results on the short-term effects of ambient pollution on TIA and mild stroke. These results should be mentioned in the Introduction section and used to compare/contrast against this study’s results in the Discussion section.

Response: We have mentioned the two references in the Introduction and compared our results in the Discussion section.

• If the patient database does permit identification of recurrent strokes, it is advisable to remove them.

Response: Patients recruited into the NORTHSTAR study were done so on the basis of a qualifying, index TIA or minor stroke. Recurrent events during 3 month follow-up were monitored and recorded, but not used in these analyses.

• In the 1st paragraph of the Methods section, does “emergency unit” patients refer to those who presented to hospital emergency departments with stroke? Were “stroke unit” patients transferred from an ED? What needs to be clarified is: Could the same individual be included once as an ED patient and again as a stroke unit patient? Similarly, if a TIA patient has been admitted to a stroke unit, is it possible they could also be enrolled in a TIA clinic? Are the databases compatible in the sense that they would allow you to identify duplicate entries for the same individual? If so, and if there are duplicate entries, they should be removed.
Response: Patients were recruited from where they were first encountered by the research team. This was either from the TIA clinic, emergency department or the stroke unit. Recruitment was therefore not duplicated for any participant. This has been clarified in the methods section as highlighted by the reviewer.

- Was there only one monitoring station in each city? Was everyone in the city, regardless of their postal address assigned the same pollutant level on case and control days if their stroke admission date or onset date were the same? If so, this should be noted in the Discussion section as a considerable limitation due to the inability to capture the spatial variability of some pollutants.

Response: There was more than one air quality monitor in both cities and data from different monitors were retrieved for each pollutant and were pooled together to get an estimate of the daily averages for each city. In time series study as we describe here the critical variability that needs to be addressed [as we have done] is temporal rather than spatial. In any case, in the Discussion section, we have clearly emphasized the drawbacks of using central monitors as exposure parameter.

- The differences in mean and distribution of pollutant levels are commonly reported in this field, but as Kunzli and Schindler pointed out (J Epidemiol Community Health, 2005; 59:527-530), these are merely indications of the levels over the whole study time period, which is not the unit of comparison in case-crossover studies. What matters in the case-crossover study is the average and distribution of the differences between case and control periods. In the Discussion section of this study, the authors comment on the differences in baseline pollution between the 2 cities (which is interesting and could potentially be a valid reason for conducting separate analyses); however, it is imprecise and possibly incorrect to suggest, even indirectly, that this might be due to the higher baseline level of NO in Manchester. If the mean and distribution of the differences between case and control days are shown in the Results section and are, in fact, greater in Manchester than they are in Liverpool, then you have a stronger argument.

Response: We agree with the reviewer’s comment. We have reviewed the mean differences on case and control days in both cities and found that they are close to each other. Thus we have revised the original paragraph and removed the sentence that refers to the association of baseline NO in Manchester to TIA.

- Although the OR in lag 3 shown in Table 4 for PM10 was marginally non-significant, it is interesting and noteworthy that the percent increase in risk (12%) is actually twice that of NO (6%). Given a slightly larger sample size, one might see this become a more important finding. (According to Witte et al, the increase in sample size required to maintain sufficient power in analyses with additional comparisons is not as much as you might think {Stat Med, 2000;19:369-372})
Response: Thank you for the suggestion. We have emphasized this in the Result and Discussion sections.

• Exact p values used along with criteria for statistical significance at $\# = 0.05$ are not as informative as the point estimate of the OR and the 95% CI, which reflect the magnitude of association. In Table 4, the p values detract from the information presented and can mislead the reader. (See Chapter 10, Modern Epidemiology, 3rd Edition, Rothman, Greenland, Lash, 2008; Lippincott Williams and Wilkins)

Response: As per your suggestion we have removed p values from Table 4.

• The Discussion section statement “In the main model, a total of 48 regressions were performed and with a conventional 5% significance level, one would expect 2 to 3 effect estimates that would have occurred by chance” needs to be clarified.

Response: This sentence has now been clarified.

Minor Essential Revisions

• Reference 2 is not a study of short-term effect. Reference 9 is specifically looking at effects on stroke recurrence, which is based on a defined population (more susceptible to stroke) that is different than a first-stroke population and should be removed.

Response: Thank you for the comment. We have removed the two references.

• The first sentence of the 3rd paragraph in the Introduction section does not read smoothly. Perhaps, if consistent with the intention of the original sentence, the following would be better: “There have been a number of studies that have suggested an association between ambient air pollutants and stroke morbidity and mortality, while others have suggested this association does not exist”. More importantly, there are more recent studies in less-polluted regions than the studies included in the citations listed. For example, Ren et al. (Env Health, 2010;9:3) and O’Donnell et al. (Epidemiol, 2011; 22:422-431).

Response: We thank the reviewer for this suggestion. Based on the suggestion, new information and references have been added to the manuscript.

• What is meant by “accident and emergency and stroke units” in the first paragraph in the Methods section? Why would accident patients be included in this study? Is this confusion simply due to the label – if so, please clarify.

Response: We have explained this point in more detail as suggested. In the United Kingdom the term “Accident and Emergency” refers to the “Emergency Room” department which accepts patients whether they are accident victims or emergency medical cases. No accident victims were included in the study.
• Diagnostic criteria or clinical guidelines used by the stroke neurologists to classify TIA in the study would be informative in the Methods section.

Response: We have provided definition used to characterize the study outcome.

• Caution against citing studies of long-term effects in the Discussion section. The present study is one of short-term effects. There are physiological and epidemiological differences between long and short term effects. These studies, therefore, should not be pooled without distinguishing them.

Response: We have removed studies that deal with long term effects of air pollution.

• There are inconsistencies in the formatting used in the reference list.

Response: We have followed consistent formatting guidelines of the journal.

Discretionary Revisions
• If the authors are aware of reasons for why air pollution effects on TIA has been apparently ignored in the scientific literature (relative to acute ischemic strokes), the reasons might be of value to the reader of the Introduction section.

Response: We are not aware of any reason why this issue was not specifically investigated by others. Like the reviewer we too felt that knowledge gaps needed to be addressed and hence we conducted this study.

Reviewer: Marc Saez

Major compulsory revisions
1.- Page 6. 'Environmental air quality data were obtained (...) and ozone' In which monitoring stations? Where are they located? Are there missing data? What percentage of missing data? How are missing data handled? Please detail

Response: Thank you for your suggestion. We have provided more information about the environmental air quality data in the Methods section.

2.- Page 6. 'Data on meteorological confounders (temperature and relative humidity) were obtained from the UK Meteorological Office database [21]' In which monitoring stations? Where are they located? Are there missing data? What percentage of missing data? How are missing data handled? Please detail

Response: We have added more information on meteorological parameters in the Methods section.

3.- Page 6. 'Four exposure lags were evaluated (...)’ Why four and not seven lags, for example? What was the reason to choose just four? Please detail. In results, only the third lag resulted statistically significant, but why not other lags beyond the four? Authors should try more lags in a new version.
Response: We chose the lags *a priori* based on the literature which we have cited in this manuscript. Although there are some differences, most short term effect air pollution studies on cardiovascular outcome, including stroke have investigated lags of up-to three days. This is based on the knowledge that most such effects are acute, occurring on lag 0 or 1. We have thus restricted our analysis to lag of 3 days before the onset of TIA to ensure comparability with other published literature in this area.

4.- Pages 6 and 7. 'The analysis was conducted using a case-crossover design [22]'. Although it is true that the particular design is explained (a bit) in page 7 ('For reported data of onset of each TIA (...) and day of the week [23].') and it seems that is bidirectional, what particular type of case-crossover design is applied? Why? What are their advantages over their alternatives? Please take a look of Figueiras et al. Epidemiology. 2005; 6(2):239-246 or Carracedo-Martínez et al. Environ Health Perspect. 2010; 118(8):1173-1182.

Response: Our design followed a time stratified asymmetric case crossover approach and the advantage of this method over other methods is explained in the text.

5.- Page 7. '(...) the effect of two pollutants was explored' Why not three or even more pollutants. From the results section it seems that there is an interaction between NO, NO2 and PM10. But because the three-interaction was not tested we do not know if there exists any (for instance between NO2, PM10 and CO, seems likely)

Response: We had carefully considered these matters when designing the study and the final judgements can be very finely balanced. We considered it important to avoid Type I errors in particular. Due to common source and correlation between the pollutants, interpretation of multi-pollutant models in which more than two pollutants are included in the model is challenging. It has been shown that there is considerable sensitivity of estimates when more than two pollutants are included in the model and inferences about the individual effects of pollutants in models with many pollutants is difficult and at times may lead to misinterpretation [1, 2]. This issue has been identified as a priority research area by National Research council[3]

Minor essential revisions
1.- Page 9. Results section
Please provide median and quantile, besides of mean and standard deviations (maybe the distributions were not very symmetrical in all cases).

Response: We have added median and quantiles of measured pollutants in Table 2

Reviewer: Maria Jose Medrano

Major Compulsory Revisions:
1. The study is restricted to TIA and minor stroke, the less severe forms of cerebrovascular disease, probably because of data availability. I wonder if inclusion of fully established stroke cases would have clarified the results in one sense or the other. As the data set used did not
include these cases, the alternative would have been using other data sources to focus also on stroke, i.e. hospital discharge data. I suggest the authors should add this analysis or alternatively, comment on this in the discussion.

Response: The aim of our study was to specifically investigate effects of ambient air pollution on TIA and minor (non-disabling) stroke, many of whom were outpatients. The clinical relevance of this group is their risk of stroke, yet the effects of air pollution on TIA and minor stroke are less-well studied than for stroke, as described in the introduction and discussion sections. Regarding inclusion of fully established stroke cases, as we have mentioned in the discussion section, results from earlier studies on stroke are not conclusive. Some studies have shown an association between ambient air pollutants and stroke, while others suggested associations did not exist. These may be due to numerous reasons, including outcome and exposure misclassification among others.

We have no access to hospital discharge data to conduct the suggested analysis. Routinely available administrative data on stroke has several drawbacks including incompleteness of records, occurrence of coding errors and inaccuracy, which could result in outcome misclassification [4, 5]. In our study the diagnosis of each TIA case was made and confirmed by stroke physicians and this will minimize the possibility of outcome misclassification.

2. As the authors say, sample size is small so statistical power can be compromised and this could be the reason for the non-significant results. This problem is aggravated by the case-crossover design which is less efficient statistically than Poisson time series analysis. At the same time, cases are separated in two groups accordingly to the two different geographical location of the cases. I suggest combining the two groups and to include geographical site as a covariable in the models, or alternatively explain the rationale for not doing it.

Response: We have carried out a combined analysis of the data and we found that the results were similar. However in view of the difference in the distribution and constituents of air pollutants in the two cities, we have retained separate analysis so as to avoid criticism from the readers that we might have pooled two heterogenous groups.

3. The authors should explain why they have not considered all pollutants jointly in a model to assess their independent effects.

Response: Please refer to the response given to Reviewer Marc Saez under major compulsory revision point 5.

4. The authors should comment on the contradictory results for NO, which apparently increased risk in Manchester and decreased it in Liverpool. Could these results be just artifacts?

Response: We have discussed this point in the Discussion section. Although the health effect of NO has not been widely reported in literature, it is a major primary pollutant which is oxidized to ozone and NO₂. The persistence of effect of NO in single and multipollutant
models indicates that NO might either be responsible for the observed effect or it is acting as a surrogate for some unmeasured pollutants. Thus we believe this effect should not necessarily be discounted as an artefact but should be noted and subsequently further investigated.

Minor revisions:
1. In my opinion, not correcting for multiple comparisons is not so important in this study.

**Response:** We have removed the sentence.

2. Table 4. Omit symbol ¶ for p<0.05 in table and in footnote.

**Response:** We have removed the symbol and the p values as suggested by you and another reviewer.

**Reviewer: Adolfo Figueiras**

1. How the models were built? That criteria used to include variables and their lags in the model?

**Response:** The effect of each ambient air pollutant on TIA was assessed separately at different lags (lag 0 to lag3) and we have adjusted for important known confounders (temperature, relative humidity, influenza count, and public holidays). We first built a baseline model by incorporating these confounder variables without including the air pollutants. To account for the non-linear effect of temperature and humidity we used cubic splines with 3 degrees of freedom. After modeling each pollutant individually, a two-pollutant model was fitted to estimate the independent effect of each pollutant at lag 3 where significant association was observed with NO.

2. Analyzed how the effect of atmospheric variables? It is well known that the relationship between temperature and morbidity and mortality follows a U-shaped. What statistical model applied? Splines ?

**Response:** We have added more information regarding how meteorological variables were modeled in the Methods section.

3. Is it evaluated the statistical power of the study?

**Response:** The study was originally designed for another purpose (as indeed we have stated in the paper) and we have used all data that were available and as such we did not do power analysis at the outset for air pollution purpose. We considered this appropriate as the first paper (so far as we have been able to determine) to address TIA as a specific outcome in relation to air pollution exposure.
4. Have you done a sensitivity analysis by analyzing the models using another type of CCO design or events to Poisson time series (Environ Health Perspect 118:1173-1182 (2010))?

Response: Thank you for your suggestion. To check the robustness of the estimated effects we undertook sensitivity analysis by using bidirectional referent selection scheme. This information is included in the Methods and Result section. However, we have not done the analysis using Poisson time series model.

We hope the revised version of the manuscript meets your approval and thank you again for your consideration of our manuscript.

5. Department of Health, Committee on the Medical Effects of Air Pollutants (COMEAP), UK Cardiovascular disease and air pollution In.; 2006.