Author’s response to reviews

Title: Particulate air pollution on cardiovascular mortality in the Tropics: Impact on the elderly

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Author’s response to reviews:

*Please see attached word document for the response as the tables and figures in the response to reviewers are better viewed in the attached document

Dear Editor,

We are grateful for the opportunity to revise our manuscript and would like to thank the reviewers for their constructive comments. We have responded to all the queries as listed below in a point-by-point manner and have highlighted the changes in the manuscript for easy reference. We hope that with this, our paper is now acceptable for publication.

Reviewer reports:

Both reviewers see merit in your paper, but also identify gaps in the analysis and discussion that you need to address. That will require additional analyses.
We have provided the additional analysis and updated the manuscript as per the points in the reviewer’s comments.

Reviewer 1:

The present study evaluates the association between air pollutants and all-cause mortality / cardiovascular mortality in Singapore, an equatorial Asian city showing a tropical climate. There are many strengths of this study. It is well written, with an adequate and properly described methodology, results that are correctly presented, and conclusions adequately derived from data. As the authors noted, there is a gap of studies examining the influence of air pollution on mortality in tropical settings (the majority of studies are from Europe and North America), while these relationships could be highly influenced by meteorological and other environmental factors that are highly dependent on local variables. In this sense, this study contributes with valuable information to fill this gap. My impression regarding this manuscript is positive; however, I have a number of suggestions and concerns.

1) Page 5. Sentence: "Stations which monitored roadside air quality by being located close to the traffic lanes were excluded from the study".

Comment: I don't understand the reasons for this exclusion. I could support this decision of excluding these stations if there are no people living near traffic lanes, or if this population was excluded from the analysis. But if mortality data included people living near these heavy traffic roads, they should be exposed to this air pollution, and these stations should be included in the analysis. Please clarify this point.

Only 4 stations were excluded from the analysis. These 4 stations were situated next to traffic lanes whose primary purpose was for the government agencies to monitor roadside air quality and vehicular emissions. These excluded stations are not situated next to residences/human activity and would not accurately reflect the daily exposure to air pollutants amongst the general population. This has been clarified in the manuscript.
2) Page 7. Sentence: "Co-pollutant (containing more than one pollutant) models were not built so as to avoid multicollinearity among variables".

Comment: I see in Table S1 that at least the O3 was not highly correlated with the other pollutants. In this context, maybe analyzing two-pollutant models would be appropriate. Moreover, as in other similar papers, I recommend presenting the results of two- or multi-pollutant models, and then discussing the implications of multicollinearity in the discussion section.

We thank the reviewer for the comment. We have performed further analysis to include two-pollutant models for PM10, PM2.5 and O3 (pollutants with significant effects in the single-day lag models). These results have been added to the manuscript and the tables are available in the Supplemenatry Appendix (Supplemenatry Table 2a,b,c).

3) I'm surprised that NO2 and O3 were not associated with all-cause mortality. In previous studies, even those carried out in cities with tropical climates from Thailand, Malaysia, Taiwan, and Brazil, these associations were significant in the majority of cases (see for example Bravo et al., 2016; Conceicao et al., 2001; Costa et al., 2017; Goggins et al., 2013; Gouveia et al., 2000; Guo et al., 2014; Tsai et al., 2003; Tsai et al., 2006; Wan Mahiyuddin et al., 2013; Yang et al., 2004; Vichit-Vadakan et al., 2010). Maybe the authors might suggest a hypothesis about why these gases are not showing a significant influence in mortality, taking into account their knowledge about the local environment. In this regard, I observed that the mean values of pollutant concentrations reported in this study are, in general, lower than those reported in the previously mentioned papers.

We thank the reviewer for the astute comment and agree that a plausible reason is that the values of these pollutants in Singapore are generally lower than those in the referenced papers. We have included these pointers in the discussion.

4) In the same line of the previous point, I don't understand the reason why the influence of NO2 and O3 on mortality was not assessed for elderly adults (>65 years).
We have performed the additional analysis of NO2 and O3 on mortality for the elderly. Please see table below.

Percentage change (95% confidence interval)

<table>
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<th>Lags 0-5</th>
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<tbody>
<tr>
<td>Non Accidental Mortality</td>
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<tr>
<td>&lt;65 O3</td>
<td>-0.235 (-1.073, 0.610)</td>
<td>-0.563 (-1.601, 0.487)</td>
<td>-0.845 (-2.213, 0.543)</td>
</tr>
<tr>
<td>NO2</td>
<td>-0.563 (-2.336, 1.241)</td>
<td>-1.536 (-3.722, 0.701)</td>
<td>-2.320 (-4.595, 0.009)</td>
</tr>
<tr>
<td>&gt;65 O3</td>
<td>0.292 (-0.319, 0.907)</td>
<td>-0.724 (-1.547, 0.106)</td>
<td>-1.464 (-2.684, -0.228)</td>
</tr>
<tr>
<td>NO2</td>
<td>-1.213 (-2.570, 0.164)</td>
<td>-2.617 (-4.562, -0.632)</td>
<td>-0.409 (-3.117, 2.376)</td>
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Cardiovascular Mortality

<table>
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<tbody>
<tr>
<td>&lt;65 O3</td>
<td>-0.496 (-1.903, 0.931)</td>
<td>-0.626 (-2.395, 1.175)</td>
<td>-1.763 (-3.986, 0.512)</td>
</tr>
<tr>
<td>NO2</td>
<td>-1.595 (-4.583, 1.487)</td>
<td>-2.362 (-5.965, 1.380)</td>
<td>-3.761 (-7.145, -0.252)</td>
</tr>
<tr>
<td>&gt;65 O3</td>
<td>0.978 (0.036, 1.928)</td>
<td>-0.712 (-1.921, 0.511)</td>
<td>-2.079 (-3.733, -0.397)</td>
</tr>
<tr>
<td>NO2</td>
<td>-1.829 (-3.817, 0.200)</td>
<td>-4.399 (-6.952, -1.776)</td>
<td>-1.708 (-4.774, 1.456)</td>
</tr>
</tbody>
</table>

In single pollutant models, ozone had no association with cardiovascular mortality and only significant association with overall mortality at Lag 1 (there was no association at Lag 0.2,3). Furthermore, this did not remain significant in the two pollutant models adjusting for PM10 and PM2.5. NO2 had no significant association with both types of mortality. In such a scenario, we have chosen not to further stratify by age as any significant association may arise by chance and the primary focus of the manuscript is on particulate air pollution. The results of the further analysis are appended in the table above. We have for now chosen not to include this table in the manuscript but would be glad to do so if the reviewer and editors find it useful.

5) The number of air monitoring stations should be reported; if possible, reporting the number of days with missing data in at least one station would be important too.
We thank the reviewer for the comment. We have included the number of air monitoring stations as well as the completeness of data for each pollutant and each station in the manuscript.

6) Table 2. The association between O3 and all-cause mortality (Lag 1) was also significant, but the authors did not take into account this result.

We have added the significant association between O3 and all-cause mortality at Lag 1 into the manuscript. However, this association was not significant at Lag 0,2,3 and additionally, did not remain significant in the two pollutant models adjusting for PM10 and PM2.5 as we responded to the comment 4) previously. As such, we feel that the strength of this association may not be worthy to report. This has been elaborated in the manuscript.

7) Page 7. Sentence: "Residual autocorrelation and partial autocorrelation charts for the core models were performed and shown in Supplementary Figure S5".

Comment: these ACFs and PACFs graphics were mentioned in the methodology, and were shown in the appendix, but they were not referred to again in the text. Please mention in the text the interpretation or the use that was given to these graphics.

We have added the use of these graphics in the manuscript.

8) Page 13. Another possible limitation of this study is the lack of concentration-response function analyses.

We have added this in the limitations.

9) Pollutant units are missing from Table 1.

We have amended Table 1 to include the units.
Reviewer 2

This paper reports the results of a long-term time-series analysis using daily mortality counts and air pollution exposure from Singapore. Results from the statistical analysis consist of single day effect estimates as well as cumulative estimates using distributed lag nonlinear models. Quasi-Poisson models regarding terms for confounders such as seasonality, trend, day-of-the-week, holidays, periods of known epidemics, were applied. As in many studies of similar design the main findings were significant excessive risks of non-accidental and cardiovascular causes in the elderly group associated with particulate matter concentrations (PM2.5 and PM10). The estimated effects were of similar magnitude to those in similar studies carried out in Europe, Asia, North and South America. There was evidence of mortality displacement in the analysis of cardiovascular mortality.

I think the data handling and the statistical analysis conducted in the paper are sound and up to date. The presentation of results is clear and illustrates the main parts of the analysis.

Major comments:

1. The authors emphasize that there are few similar studies carried out in equatorial countries. However, the article discussion could benefit a great deal if they compared their research and results also with studies carried out in tropical countries, even though the study cities were not so near the Equator, such as the ESCALA project.

We thank the reviewer for the comment. We have included the above pointers and study in the discussion.

2. In the methods section it is mentioned that during parts of the year the smoke caused by biomass burning contributes to the air pollution levels. Biomass burning air pollution is rather different in chemical composition than vehicle and industrial air pollution. I wonder if that mix of air pollution sources could have been exploited in the time series analysis as an effect modifier, for instance stratifying the analysis according to dry and wet seasons, or even including some sort of term to account for the yearly month-long episode of biomass burning.
Unfortunately, the period, duration and intensity of the “haze” episodes in our country varied significantly from year to year. The overall effect of all the air pollutants are routinely recorded by the measuring stations even during the “haze” periods and any rise in the different air pollutants would be detected and analysed in our study. It was also not our intent to distinguish air pollution effects generated by domestic sources or transboundary haze arising from biomass burning as we aimed to study overall ambient air pollution effects on population health.

3. It has been mentioned also that other age groups and/or groups of causes were not investigated due to Singapore's population size. That can be discussed based on theoretical and applied statistical grounds. For instance, in the present study the average of daily deaths for non-accidental causes in the elderly is about thirty, whilst for cardiovascular causes is about eleven. These are considered counts of moderate size. Smaller counts on average can be analyzed using the same methods. Therefore, if there is interest in exploiting the groups of even more elderly people and/or more restricted groups of causes in Singapore for the same period, that should be fine.

We have further performed analysis in more granular age groups- namely age 65-79 and ≥80 years old. The results are shown in the table below. We have reported as a subset analysis of the findings in the very elderly ≥80 years old in the manuscript.
Table: Distributed lag models for association between air pollutant models and mortality by age group (per 10ug/m3 increase in PM10 and PM2.5).

Percentage change ( 95% confidence interval)

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<tr>
<td>Non Accidental Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>PM10 0.105 (-0.641, 0.856) -0.726 (-1.659, 0.216) -1.214 (-2.442, 0.029)</td>
<td>PM2.5 -0.073 (-1.039, 0.903) -1.045 (-2.246, 0.171) -1.694 (-3.220, -0.143)</td>
</tr>
<tr>
<td>65 - 79</td>
<td>PM10 0.676 (-0.004, 1.362) 0.496 (-0.415, 1.415) 0.201 (-1.143, 1.563)</td>
<td>PM2.5 0.791 (-0.097, 1.686) 0.672 (-0.521, 1.879) 0.357 (-1.372, 2.116)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>PM10 0.749 (0.095, 1.408) -0.044 (-0.943, 0.862) -0.517 (-1.862, 0.848)</td>
<td>PM2.5 0.955 (0.105, 1.812) -0.194 (-1.371, -0.997) -0.630 (-2.366, 1.137)</td>
</tr>
<tr>
<td>Cardiovascular Mortality</td>
<td></td>
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<tr>
<td>&lt;65</td>
<td>PM10 -0.706 (-2.038, 0.645) -0.885 (-2.466, 0.721) -1.456 (-3.411, 0.539)</td>
<td>PM2.5 -1.145 (-2.872, 0.613) -1.302 (-3.332, 0.771) -2.015 (-4.417, 0.447)</td>
</tr>
<tr>
<td>65 - 79</td>
<td>PM10 1.134 (-0.028, 2.310) -0.480 (-1.919, 0.979) -2.824 (-4.726, -0.885)</td>
<td>PM2.5 1.282 (-0.230, 2.817) -0.748 (-2.603, 1.142) -3.652 (-5.999, -1.246)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>PM10 0.940 (-0.139, 2.031) -0.755 (-2.176, 0.688) -2.060 (-3.987, -0.094)</td>
<td>PM2.5 1.271 (-0.126, 2.688) -1.256 (-3.103, 0.627) -2.424 (-4.845, 0.058)</td>
</tr>
</tbody>
</table>

4. It was mentioned in the methods section that there were missing values in the air pollution network dataset, but there is no information about how many sites were regarded in the exposure assessment nor the amount of missing data points overall as well as per site. Furthermore, depending on the amount of imputation that has been carried out some sort of sensitivity analysis as regards the effect estimates should be proposed.
We thank the reviewer for the comment. We have included in the manuscript a description about the completeness of the data. To allay the reviewer’s concern about how the imputation may affect the effect estimates, we calculated the arithmetic mean from the observed values available for each day and pollutant and compared these values with our imputed values. We also calculated the Pearson’s correlation coefficient for each pollutant. The imputed values are highly correlated with the observed values hence we foresee the impact on the effect estimates to be minimal.

5. In Figures 1a and 1b the displayed patterns for the group "below 65" suggest protective effects, specially for PM2.5. Yet, these findings have not been discussed.

We thank the reviewer for the comment and have included the findings in the results and discussion of the manuscript.

The manuscript has been strengthened by the revisions suggested by the reviewers. We sincerely hope that the revised manuscript would now be suitable for publication.

Regards,

Dr Jonathan Yap

On behalf of all the co-authors