Author’s response to reviews

Title: Systematic review and meta-analysis of case-crossover and time-series studies of short term outdoor nitrogen dioxide exposure and ischemic heart disease morbidity

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Author’s response to reviews:

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Dr. Jordi Sunyer
Associate Editor
Environmental Health

Dear Dr. Sunyer

Thank you very much for your favourable decision on our manuscript. We also thank the reviewer for his/her positive comments and helpful suggestions. Itemized responses are provided below. In responding to the reviewer’s comments, we also took the opportunity to once again ensure that we had not missed any primary studies, and in fact identified one additional time-series study which provided results for NO2 only in supplementary materials. Inclusion of these results did not materially affect our findings. We also converted Table 3 (Summary of risk of
bias ratings) to a heat map figure (new Figure 2) to reduce the text-heaviness of the original table.

Sincerely,

Dave Stieb

Reviewer #1: Overall, this systematic review is well written and summarizes results of the associations between NO2 and ischemic heart disease. I only have some minor comments.

Introduction: There is already one review on the effects of NO2 on IHD (ref #9). Why do we need a second review? I am not saying it is not needed, but it would be good to justify. The results of both reviews are compared and discussed in the discussion sections, and the added value of the review presented in this manuscript is highlighted. However, it would be nice to read about the added value of this review and meta-analyses already in the introduction: what did the previous review not cover that the current review will add?

- We identified one additional systematic review and have added the rationale in the introduction that previous systematic reviews considered only studies published up to 2011 (nearly 10 years ago), provided only limited evaluation of sources of heterogeneity, and did not examine whether the magnitude of effect differed between single and multi-pollutant models. One review did not conduct a formal evaluation of study quality/risk of bias.

Methods: In the results section it is mentioned that the review is part of a broader review including cardiovascular and respiratory health effects of NO2. The reference provided indicates that it is registered in PROSPERO. This should be explained in the methods section. When looking at the search terms provided at the additional file 1, one realizes that the search includes respiratory and cardiovascular terms. Thus, there was one common search. How did you select the articles to be included in this specific review on IHD? Also, the registration in the PROSPERO dataset should be mentioned in the methods.

- We have moved this text to the methods section under literature search, adding that “Studies were selected for the present review if reported outcomes matched the inclusion criteria specified above.” Inclusion criteria described earlier in the paragraph indicate that outcomes of IHD (including myocardial infarction (MI) and angina pectoris (AP)) were included. We have also added a sentence at the end of the methods section regarding PROSPERO registration and the registration number.

Results:
In the first paragraph, providing percentages next to the n of papers would help contextualize.

- We have added this.

It would be good to mention the lags included in the analyses. On what exposure lags are the results of the meta-analyses based?

- We indicate in the data extraction section of methods that, “When single pollutant results were presented for multiple lag times, we extracted the most highly statistically significant result (regardless of the direction of the association), or that reported by the authors as their primary finding. Results from multi-pollutant models that resulted in the greatest reduction in magnitude of effect compared to single pollutant results were selected in order to bracket the magnitude of effect from each study.” All forest plots specify the lag time in the label for each effect estimate e.g. “Evans 2017 Rochester, US STEMI HA lag 0-2”.

"Risk estimates", I prefer to call them effect/association estimates. Risk is for incidence proportions and therefore RR. You also report OR here.

- We have changed our terminology to “effect estimates”.

The authors specify that they finally included 66 studies in the meta-analyses. How many case-crossovers and how many time-series?

- Adding one time-series study as mentioned at the outset, the total number is now 67. We have added that this includes 28 case-crossover and 39 time-series studies.

Discussion: First sentence: "based on an analysis of 85 case-crossover and time-series studies, we found that short term exposure…” According to the results section and the flowchart, only 66 studies were included in the meta-analyses. Please, correct this.

- We have corrected this.

Figure 1: in line with my comment on the methods, it would be nice to show here how the data for this specific study on IHD is collected. What are the numbers included in the identification part of the flowchart? Are they based on all search terms described in the additional file 1? When does the study on IHD start? Also, when records and full articles are excluded, is it possible to show n of excluded records by reason (or groups of reasons if too many different reasons) for exclusion?

- We have added details to the flow chart including the number of case-crossover/time-series studies of respiratory morbidity or cohort studies of mortality, as well as reasons for exclusion. Note that the original flowchart (without reasons for exclusion) was based on the default DistillerSR output, which ascribes more of the exclusions to the full text review stage.