Author's response to reviews

Title: Long-term Exposure to Traffic-related Air Pollution and Type 2 Diabetes Prevalence in a Cross-sectional Screening-study in the Netherlands

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

Thank you for giving us the opportunity to revise our paper. Below is our response to the Reviewers’ comments. The comments are presented in italic and our responses are presented in normal font below each Reviewer’s comment.

We uploaded the revised manuscript and an additional ‘track-changes’ version in which the revisions have been marked for ease of cross-referencing. The ‘track-changes’ document was uploaded in the ‘Additional Material files’ box at the website. We also uploaded the revised smooth plots (Figure 2 and in the Supplemental Material).

On behalf of all the authors, I thank you for considering our revised manuscript and hope you will find it to be suitable for publication in Environmental Health.

Yours sincerely,

Marieke Dijkema
Reviewer 1:
Dijkema and colleagues studied the association between prevalence of type 2 diabetes and long-term exposure to type 2 diabetes in a cross-sectional screening study including approximately 8000 subjects (50 to 75 years old).

Major comments
1. Traffic related pollutants decay exponentially with increasing distance from roads traffic. Therefore, using log distance in the smoothed analysis might reflect the exposure better.
   Answer: We agree with the reviewer that log transformation of distance to the road would do more justice to the physical dispersion of air pollution by distance of a road. Therefore, we converted the x-axis of the smooth plots to a log-scale. We furthermore added some text on this to the results section. No further changes to tables or figures were done as we display OR’s per quartile of exposure.

2. BMI is a major risk factor for type II diabetes. The authors adjust in sensitivity analysis for BMI. Effect-modification by BMI on the air pollution diabetes prevalence should also be addressed.
   Answer: We tested for exposure-BMI interaction, and added this to the methods section. No statistically significant interaction was observed, which is now mentioned in the results.

Minor
1. Abstract last sentence of result section add p-for interaction
   Answer: Patterns observed in the total population and described above seemed more pronounced among women than among men. In regression analysis with exposure-gender interaction terms, however, the interaction was not statistically significant. We added the notion that interaction was non-significant to the abstract.

2. I wonder whether to stop the smoothing at percentile 95th or 90th and 5th 10th would give more accurate measurements.
   Answer: Reducing the span of the data by leaving out the min. and max. 5 or 10 percent would just reduce the size of the plot (x-axis). Confidence intervals at the ends of the plot would widen, but the pattern for the majority of the plot would not change. We believe that showing the full data range is most honestly representing the data of this study.

Reviewer 2:
I think the topic of the study is interesting and important and I do, moreover, think the paper is very well-written. The conclusions drawn by the authors are in my opinion nuanced. The study have, of course, some limitations, but I think the authors discuss them in a systematic and skilled way.

Editorial Team:
We would appreciate a more detailed justification for this study, including the biological plausibility for an association.
The choice of air pollution marker and its associated imprecision needs further consideration. The Conclusions need to consider the confidence interval, i.e., how large an effect that can be reasonably excluded.
Could there be (residual) confounding with BMI (or physical exercise), such that proximity to heavily travelled roads with public transportation might lead to both higher BMI and higher exposure to air pollution?
   Answer: Text on the biological plausibility was added to the introduction: “At present, there is little data supporting this hypothesis. Recently, Sun et al. [4] demonstrated increased adiposity inflammation and whole-body insulin resistance in mice exposed to particulate matter air pollution. A study by Kramer et al. [3] further supported the plausibility of oxidative stress and inflammation as a biological mechanism for the relation between air pollution and type 2 diabetes, by showing that women with high C3c blood levels (a marker for subclinical inflammation) were more susceptible for particulate matter related excess risk of diabetes than were women with low C3c levels.”
We added the following text to the methods section, explaining the choice of air pollution markers we made: “Exposure to traffic-related air pollution was defined by four different variables that have been demonstrated to be valid indicators of exposure [16-19]: modelled NO$_2$-concentration, distance to the nearest main road, traffic flow at the nearest main road and traffic within a 250 m circular buffer. NO$_2$ is considered an indicator of the complex mix of various gaseous and particulate components originating from both traffic combustion and wear of road and vehicles.” Exposure in the study area, and associated imprecision (misclassification, value of the different indicators, etc) was discussed extensively in the Discussion section. This discussion included comparison with other studies and the power of this study, which is also reflected in the confidence intervals. Acknowledging all aforementioned, we came to our carefully worded conclusions.

As shown from the sensitivity analysis shown in Supplemental Material, Table II, BMI was not an important confounder for the association between traffic related air pollution and diabetes prevalence in this population. Off course we can not completely rule out residual confounding, this was added to the Discussion section. Confounding by physical inactivity trough public transportation, as suggested, seems quite unlikely as the availability of bus-connections is fairly limited (about 6 lines, departing every hour or less) and consequently this means of transportation is not very popular in this (semi-)rural area.

It is important that your files are correctly formatted. We note in particular the following discrepancies: The title should preferably include the study design, for example “A versus B in the treatment of C: a randomized controlled trial X is a risk factor for Y: a case control study”. On the title page, each institutional addresses should begin its own line and the semi-colons removed; the phrase §Corresponding author should replace the existing contact information and the symbol placed after the superscript number(s); and the authors’ email addresses should be listed under the heading Email addresses as author’s initials: email address e.g. JS:joe.shmoe@university.edu. Only the first letter of the headings should be capitalized e.g. Abstract. All underlining should be changed to normal font. The first heading in the text should read Background, not Introduction. After the Discussion section, insert the heading Conclusions stating clearly the main conclusions of the research and giving a clear explanation of their importance and relevance (and avoid expressions like ‘In conclusion...’). After the Conclusions the following sections should follow: List of abbreviations, Competing interests, Authors’ contributions and Acknowledgements. The List of Abbreviations should be organized as abbreviation: term separating the pairs with semi-colons and in sentence format. The proper wording for the Competing interests and the final sentence of the Authors’ contributions can be found in the Instructions for authors. All authors up to 30 names should be listed in the references. In the tables, all horizontal lines should be visible.

Answer: We adjusted the formatting of the manuscript following your comments, the title was adjusted to “Long-term Exposure to Traffic-related Air Pollution and Type 2 Diabetes Prevalence in a Cross-section Screening-study in the Netherlands”. Moreover, the Conclusion section was adjusted as follows: “This study did not find consistent associations between type 2 diabetes prevalence and exposure to traffic related air pollution, though there were some indications for a relation with traffic in a 250m buffer. Our study adds to the limited number of studies on air pollution as a risk factor for type 2 diabetes [2-5]. In contrast with previous epidemiological studies [2,3,5] we did not find consistent associations, though despite the limited exposure in the population studied, some indications for a relation were observed.”

All further comments concerned formatting of the manuscript, we adapted all as requested.