Author's response to reviews

**Title:** Highway proximity associated with cardiovascular disease risk: the influence of individual-level confounders and exposure misclassification.

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**Author's response to reviews:** see over
Reviewer:

Sandrah Eckel

Reviewer’s report:

The authors were very responsive to my last set of comments. I appreciate that I could see the track changes in this version. The refined presentation of statistical methods and investigation of the effects of continuous exposure variables (allowing for non-linear relationships via GAM) have added to the paper. I have a few last minor comments, but I do not need to see this manuscript again. It seems suitable for publication, if the other reviewer and editors agree.

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Minor essential revisions:

1. I appreciate the authors’ responsiveness to my comment that they were overemphasizing the impact of “rarely included confounders” since there was no clear demonstration of novel or major impacts from controlling for these additional confounders, but it seems a bit over-zealous to remove so much text regarding confounding. Confounding is, of course, an important issue. To ensure the reader that confounders are considered carefully, I recommend reversing the deletion of confounding in the following places:

   - abstract, background: line 3
   - intro, background, end of 2nd paragraph
   - last paragraph of intro, keep: “and consideration of a large number of potential confounders.”
   - first line discussion, keep: “and considering a large number of potential confounders”
   - conclusion paragraph, retain the line on individual-level confounding

We have accepted and made all of these revisions. They are marked in red in the manuscript.

2. My comment about cutting Figure 2 must have been a typo, I think you were correct that I was thinking about replacing Table 3 with supplemental Table 4. I do recommend this change unless you have a strong justification otherwise. Readers will be more interested in the impacts of refined geocoding methods in confounder adjusted models rather than in crude models.

   Have switched these tables.

3. The geocoding method used to produce the first sentence of the results section of the abstract should be stated.

   We have identified that the orthophoto corrected geocoding method was used to produce the values presented in the first line of the Results section of the abstract.
We have added the red text, which corrects this issue in the abstract.

**Using the orthophoto corrected geocoding, in a** fully adjusted model, hsCRP and IL-6 differed by distance category relative to urban background…

4. Top of p. 11. Do you mean that “Estimates were predominantly biased towards the null...” rather than just the 95% CI?

We agree this wording was not idea and have changed the wording, see red below:

We reran the unadjusted and adjusted hsCRP and IL-6 models using the parcel matched, StreetMap USA and TIGER address geocoding and found predominantly that there were changes in associations toward the null for the StreetMap USA and TIGER addresses. The effect of geocoding error on directionality of effect for model β-estimates was not systematic. The confidence intervals (95%) **changed in non-uniform ways**, resulting in some spurious results (Table 3 & Table S4). Distance bin misclassification was examined for the TIGER and Parcel geocoding methodologies by comparing to the ortho-photo corrected residential locations. TIGER geocoding had more false negatives and less sensitivity than parcel geocoding in all distance bins (Additional File 5:Table S5).