Author's response to reviews

Title: Long-term exposure to air pollution and hospital admissions for ischemic stroke. A register-based case-control study using modelled NOx as exposure proxy.

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

We hereby resubmit the manuscript *Long-term exposure to air pollution and ischemic stroke risk: a register-based case-control study in Southern Sweden*, (the title has changed, see below).

We think that the comments of the reviewer were initiated and insightful, and they have lead to improvement of the paper. Below, we have addressed the comments, one by one.

We also did some not listed language corrections and other minor changes to the manuscript.

Sincerely,
Anna Oudin, Emilie Stroh, Ulf Strömberg, Kristina Jakobsson, Jonas Björk

*All references to pages and sections refer to the modified manuscript, if not otherwise stated.*

**Reviewer: Victor Van Hee**

Major compulsory revisions

1. NOx concentrations fall off rapidly over the first 100 meters from major roadways. The writers should comment on how the use of NOx modeling on a 500 meter grid, without regard to microscale effects, might affect the results. This kind of misclassification could either bias health effects estimates towards the null (if classical measurement error is present) or significantly reduce precision and power (if Berkson error holds). In either case, the null results are less convincing because of potential measurement error.

We agree with the reviewer and modified the manuscript accordingly. We have extended the description of our choice of spatial resolution in “Exposure assessment” (“Exposure assessment” Page 7, the last section). We have extended the section on exposure misclassification by modelling error (Page 12, section 3-Page 14, section 1).

2. The choice of outcome --only ischemic stroke hospital admissions --could lead to an underestimation of the impact of NOx on ischemic stroke if NOx has a larger impact on rapidly fatal stroke than stroke events that are not immediately fatal. This choice on the part of the investigators was reasonable, given the reduced quality of the data on fatal events, but more attention should be given to the issue of not rapidly fatal events versus rapidly fatal events in the discussion
and the background. Do the results of this study differ from prior studies of pollutants and stroke because of this different case definition? Recognizing that case ascertainment may not be accurate for individuals that die rapidly out of hospital, please estimate the proportion / number of rapidly fatal strokes in this population for clarification --how might the number of hospital admissions compare in magnitude to rapidly fatal stroke (which occur prior to hospital admission) in this population?

Yes, we think that our results differ to others with respect to the outcome, which in previous studies has been mortality (Three studies), or mortality and cerebrovascular events (One study). In that study, the results are strongest for mortality, similar to the Rosenlund study. We added a discussion at Page 16, third section regarding this. We added a section (Page 5, first section) where we give an estimate on the (rather small) proportion of fatal stroke without medical examination in our study area.

3. To evaluate this issue specifically, the investigators could estimate the numbers of cases that died rapidly after hospital admission. If the pollution-associated risk of more rapidly fatal stroke is higher than the risk of survivable events, then the lack of cases who died prior to hospital admission is a very important concern. The investigators should (if possible) look for effect modification by survival time to help address this potential issue.

We performed a subanalysis where we restricted the analysis to include only the (relatively few) cases who were registered as deceased within 30 days after the stroke, yielding similar estimates as the main analysis. Page 5, section 4, Page 11, section 4 and Page 16, section 3.

4. Results which suggest significant protective effects of NOx in certain groups (such as in participants born 1923-1940 and in rural areas) are a bit concerning. I find it difficult to believe that NOx would be protective in any group, given the literature. I also tend to disagree that there is no evidence of effect modification in these groups (p = 0.1, almost significant). Could these results have come about from biased exposure estimates or residual confounding? The fact that the effect of residing in an urban area shows 'no significant effect modification (p=0.09)' does not suggest to me that 'the effect estimates in this study were not influenced by such a misclassification.'
As the reviewer states, literature does not support a protective effect by long-term exposure of NO\textsubscript{x} on ischemic stroke risk, nor is it likely that such an association exists. We agree with the reviewer that a p-value of 0.10 does not rule out potential effect modification and have removed the sentence from previous Page 11, end of section 2 accordingly.

Our best explanation is that these effect estimates below unity are chance findings. We added a section on Page 15 (section 2) where we discuss the seemingly protective effect in rural areas. To further improve our exploring of potential error sources, we performed a biased sampling analysis on Page 10, section 3, and Page 14, section 4 instead of a crude adjustment for geographical area, which was removed from previous Page 12, end of first section.

5. Was there evidence of effect modification by birth country in this study? This is an important question that should be addressed because it gets at individual susceptibilities based on ethnicity.

We followed the reviewer's recommendations and analyzed effect modification by birth country on Page 11, last section. We saw no evidence for effect modification by birth country in our material.

6. The title, although accurate, could be more specific. Because the effect of oxides of nitrogen may differ from the effect on stroke risk of other pollutants, the title should be modified to describe the specific air pollutants analyzed in this study. "Air pollution" should be modified to indicate "oxides of nitrogen" or (less specific) "traffic-related air pollution."

We agree with the reviewer that the title should benefit from being more specific. We changed the title into “Long-term exposure to air pollution and hospital admissions for ischemic stroke. A register-based case-control study using modelled NO\textsubscript{x} exposure proxy”.

7. The background section describes prior studies rather generally, as demonstrating possible effects of general 'air pollution' on stroke. Because air pollution is a complex mixture, and certain components may be more important than others, this section should be more specific (as in the discussion), describing specifically which air pollutants (PM10, PM2.5, NO\textsubscript{x}, etc) have been implicated in which studies. This is particularly important given the null results of the study, which suggest that low-level NO\textsubscript{x} does not impact stroke risk. "Low levels" should also be defined numerically, with brief reference to the specific higher
levels seen in the studies implicating NOx.

We agree with the reviewer that we should be more specific when discussing air pollution and that “low levels” should be defined. We have modified the background section, to further clarify what substances in air pollution explored by previous studied on long-term exposure to air pollution (Page 3, section 2) and defined “low levels” (Page 4, end of first section).

However, we chose not to specify the air pollutants in the studies of short-term exposure to air pollution since the number of pollutants in short-term studies often are numerous and correlated with each other- making inference of the effect of a single pollutant sometimes precarious.

8. The title and abstract should both specify "hospital admissions" for ischemic stroke. Without that clarification, the assumption is that this paper readily generalizes to rapidly fatal stroke.

We changed the title, see point 6 and added information on hospital admissions being the outcome to the abstract and the title.

9. The investigators indicate that 78% of a 'large sub-sample' of the second-phase subjects did not change residential address over 10 years. Please clarify the exact size of this subsample. This proportion may not be generalizable to the entire group, as the authors state. The investigators should comment on possible selection bias in this subsample of individuals with this data. Why did only a subsample of individuals have this data, and how was it obtained? Even if this number is generalizable, it suggests that perhaps 20% of the individuals studied may suffer from misclassification of exposure. This raises the issue of measurement error leading to biased (towards the null) or less precise estimates.

Comment on these issues in the discussion.

We have further clarified how we reached the estimate of 78 % at Page 8, last section. It is most likely that this has led to misclassification of exposure, and bias towards the null. We further commented on this in the Discussion, (Page 12, section 3-Page 14, section 1) in “Strengths and limitations”.

It would have been desirable to perform a sub-analysis without the estimated 20 % (roughly) that have changed residential address the previous 10 year. However, the information on residential history was, as mentioned in the manuscript, only available for a
sub-sample of the cases and for the second-phase controls. Therefore, such a sub-analysis would only be possible for the already biased second-phase estimate, thus we decided not to.

Minor Essential Revisions
None

Reviewer: Francesco Forastiere

(numbers to comments given by Oudin and colleagues)

1) Since the results are non positive, the authors have a great responsibility to assure that all the important methodological aspects are covered.

We certainly agree, and we modified the manuscript in order this suggestion, see Answer 1, 4 and 9 for the specific questions of Reviewer 2.

2) My suggestion is to discuss how the exclusion of out-of hospital deaths may have influenced the results. Findings from Rosenlund et al in Sweden indicates a greater risk for fatal myocardial infarction.

We modified the manuscript according to this suggestion, see answer 2 and 3 above.

3) The authors may wish to better discuss the issue regarding the non optimal representation of the study base.

We assume that the selective participation of the second-phase controls (from the public health survey) is what the reviewer refers to? Please correct us if we were wrong. We extended the mentioning the selective participation at page 15, end of first section.