Reviewer’s report

Title: Long-term exposure to air pollution and ischemic stroke risk: a register-based case-control study in Southern Sweden

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Reviewer: Victor Van Hee

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Oudin et al present a large two-phase case-control study examining the relationship between residential exposure to oxides of nitrogen and ischemic stroke risk in southern Sweden. This is a well-written, thoroughly analyzed study specifically designed to address the question regarding low level exposures to oxides of nitrogen and ischemic stroke risk. Given that relatively few studies have addressed this question, and given the size of the population and size/completeness of the stroke registry data, this study is important and interesting. This reviewer also appreciates the use of the relatively uncommon ‘two-phase’ design, which addresses potential confounding by important risk factors.

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.

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?

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.

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.'

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.

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."

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 that others, this section should be more specific (as in the discussion), describing specifically which air pollutants (PM10, PM2.5, NOx, etc) have been implicated in which studies. This is particularly important given the null results of the study, which suggest that low-level NOx 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.

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.

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.

Minor Essential Revisions
None

Discretionary revisions
None

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.