Author's response to reviews

Title: Adult asthma and traffic exposure at residential address, workplace address, and self-reported daily time outdoor in traffic: A two-stage case-control study.

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Response to reviewer 1, Joachim Heinrich

1. There was a question on use of asthma medication in the second survey. We have now inserted a table showing how many of those with asthma symptoms last 12 months who also reported that they were using asthma medication (table 3). We also analysed asthma medication as an outcome variable (as described in the statistical analysis section) and found that use of asthma medication was associated with living close to traffic (last result section). Since the confidence intervals were wide we choose to not report this as a main outcome in the abstract, but rather as an additional analysis. We did not investigate effect modification between traffic and use of asthma medication on asthma symptoms, because of the general lack of power for stratified analysis.

We inserted a sentence in the discussion discussing that the use of regular asthma medication may decrease the visible effects of traffic on asthma symptoms.

2. The study did not have a cluster-design (in the sense that not only some geographical areas were selected). It had a stratified sampling where all strata were included, but where a disproportional high number were selected from sparsely populated strata. The reason for this was that the original purpose for the first public health survey was not to estimate effects from traffic, but to make stable prevalence estimates for a large number of outcomes also for smaller communities.

However, this turned out to be a disadvantage in the second survey, which was focused on traffic exposure, since there were a disproportional large number of people not exposed to traffic. The study population in second survey however was randomly sampled from the study population in the first survey, without being matched on geographical strata, only frequency matched on sex.
To analyse the first or second survey in any way conditional on geographical strata is not possible, because of the non-comparable ranges of traffic exposure between the geographical strata.

We inserted box-plots (figure 2) describing this skewed exposure distribution between the communities, which make it hard to fully exclude that the results are due to urban-rural confounding. Since the exposures are not comparable we can unfortunately also not adjust for urban-rural to avoid residual confounding. We have added a discussion on this in the manuscript, and think a very high priority in future studies is to ensure a study design with large power and comparable exposure ranges in relevant subgroups (e.g. within different cities or socio-economic strata) to be able to exclude that the results are due to confounding.

4. No previous epidemiological studies in adult asthma at least, has made any attempt to use GIS for 24h-exposure on respiratory disease, and we now rewrote this sentence. We found two studies on asthma in children who has used modelled exposure both at home-address and school-address (but not time spent in traffic) and included references for these.

5. Yes, the national road database is very extensive and also covers busy roads within the bigger communities.

6. Yes, asthma symptoms and asthma prevalence are two completely different outcomes, and we now point this out in the discussion. We also discuss that since a large part of asthma begin in childhood, retrospective exposure for asthma prevalence may be poorly estimated in a cross-sectional study. However, we also point out that migrational bias will most likely decrease the effect estimates.

Response to reviewer 2, Jenny Selander

1. We wrongly stated that the geocooding procedure is better at residential address. Actually the geocoding procedure was better at workplace adress due to manual geocoding at exact workplace address in contrast to applying the centre of the real estate as was made for residential address.

We have now written more clearly about this in the geocoding section and in the discussion. We discuss that even if the geocoding technique itself is better at workplace address, there may be other reasons for larger exposure misclassification at workplace address, such as people not working at the factual adress. We also discussed potential problems with residential address, such as people living in family-housing in urban areas or at vast land areas in more rural areas. Geocoding/misclassification problems however, can generally be expected to give conservative estimates, provided that they are not differential to disease (something we can't exclude, but don't find likely).
2. We included a flow-chart (figure 1) to give a better overview of the selection process.

The major selection of participants took place in the first step, among those who chose to not answer the first survey. Due to confidentiality issues we could not make use of any information to analyse who didn't want to participate in the first survey. However, other studies have found that it's mainly those with low socio-economic status and/or immigrants, who choose to not participate. It is hard to estimate how this could have affected the study, except that these population groups are likely to have a large burden of chronic respiratory disease due to other factors than traffic, and the relative effect of traffic may then seem larger if these groups are excluded.

When it comes to the selection of those who agreed to further participate, we now briefly describe this in the results section. Those with high exposure to traffic at residential address were more willing to participate in further studies, especially among asthmatics. This could of course have biased the estimate. However it is very complex to analyse if this group have some other population characteristic which is later adjusted for, so it does not affect the effect estimates in the end.

The further loss of participants until a selection of only 1488 persons, were based on the availability of complete exposure information and is less likely to have biased the exposure estimates.

The criteria for calculation of total exposure was that the following information was available on the participant: geocoded exposure to outdoor NOx at both residential and workplace address, as well as self-reported time spent in traffic and self-reported percentage working of full-time, for those who reported that their current occupation was work.

The inclusion criteria for total exposure was previously mentioned in the results section, and we have now moved it to the methods section.

In the description section in results, we now also describe the percentage of full-time work for those who had reported this. Since only those who were currently working reported percentage of full-time work, current employment was an inclusion criteria for total traffic exposure calculation, and subjects fully unemployed, housewives or on sick-leave are not included.

This could of course have affected the results if people who got ill due to exposure to traffic at workplace address, therefore got excluded from the analysis. Unfortunately we don't have information about previous traffic exposure at work, so this problem cannot be addressed in the study - but if it has affected the study it probably diminished the true effects. We now discuss this kind of potential migrational bias in the manuscript, although mainly in relation to residential address.

4. The NOx exposure at work refers only to outdoor NOx at work. We tried to make this more clear by changing the vocabulary from NOx at work, to NOx at
workplace adress, when describing the calculation of total exposure. There is unfortunately not enough power for stratified analyses between traffic and occupational exposure to gases/dust/fumes. We have tried to better describe the JEM and other work-exposure questions in the statistical analysis section. Occupational exposure was finally adjusted for as stated in table 1 - using the question on how often the subjects were exposed to hazardous substances at work - but not by self-reported more specific exposure to dust or gases or fumes as separate entities, and not by probabilistic assessment by the Job-Exposure-Matrix.

5. This could be an important source of diminished association. We have added that migrational bias could dilute the results into the discussion section.