Reviewer's report

Title: Residential traffic exposure and pregnancy-related outcomes in mother and child: The Generation R Study

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Reviewer: Ulrike Gehring

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Summary
Van den Hooven and colleagues studied the association between maternal traffic exposure and fetal growth, preterm birth, and pregnancy complications in a prospective Dutch birth cohort study. Traffic exposure was defined as traffic density in a 150 m buffer around the mother’s home address and distance to major road. Neither pregnancy outcomes nor pregnancy complications were associated with traffic exposure.

General comments
1. This is an interesting paper. In particular the analysis between air pollution exposure and pregnancy complications is innovative.

2. The manuscript in its current state presents large amounts of data. Seven outcomes (4 pregnancy outcomes and 3 pregnancy complications) were linked to 3 exposure variables. The manuscript would benefit from focusing on a limited number of outcomes and exposures. My suggestion is to focus on two pregnancy outcomes describing fetal growth and pregnancy duration (for instance preterm birth and term birth weight). Cumulative traffic density and distance weighted traffic density within a 150 m radius around the participants’ homes were highly correlated (r=0.93). Therefore, one of these two variables can be left omitted without losing information.

3. Reducing the number of exposures and outcomes, would give the authors the possibility to present the results of the large number of sensitivity analyses they have done, but are not shown in the current version of the manuscript, e.g. the analyses in Dutch children and non-movers, and the analyses on the potential effect modification by socio-economic status. The paper would benefit a lot from showing the results of these analyses.

4. The number of women with pregnancy complications is small in this population, which raises the question of statistical power. Did the authors perform any power calculations? A discussion of statistical power needs to be added.

Major compulsory comments

Introduction

5. The authors review the types of exposure assessment that have been used in
studies on air pollution and pregnancy outcomes and underline the importance of taking into account the intra-urban variability of air pollution levels. Using indicator variables like (distance weighted) traffic densities is one way to approach this problem. However, this is only one possible approach, which has some limitations, which should be discussed in the discussion e.g. the fact that temporal variability of exposure is not accounted for. Recently, other approaches that take into account both the temporal and spatial variability of air pollution levels have been introduced in studies on air pollution and pregnancy outcomes (Slama et al. Environmental Health Perspectives 2007; Brauer et al. Environmental Health Perspectives 2008; Fanshawe et al. Environmetrics 2007; Aguilera et al. Environmental Health perspectives), which should be mentioned here.

Materials and methods

6. Page 7, line 1. It is not clear whether the complete address history of the mothers was included in the present analysis or whether exposure indicators were assessed for one specific address (e.g. birth address or address at recruitment). This needs clarification.

7. Page 7 f. calculation of distance-weighted traffic densities. This is difficult to follow. The authors refer to papers by Pearson et al. and Wilhelm and Ritz, but if I understand it correctly, the authors did neither exactly what Pearson did nor what Wilhelm and Ritz did in their publications. My suggestion is to skip the references, and to describe what was actually done.

8. Page 8f, birth and pregnancy outcomes. I agree that using the date of the last menstrual period for exposure assessment has limitations. Given the fact that ultrasound measurements were available for all children apart from the 3% of the population that was enrolled in late pregnancy, one option could be to limit the analyses to the 97% of the population for which gestational age was (consistently) determined by ultrasound measurements.

9. Page 9, birth and pregnancy outcomes. Swedish reference standards were used to define “small size for gestational age” although Dutch standards are available (www.perinatreg.nl/). Why did the authors decide to use the Swedish reference standards instead of the Dutch reference standards?

10. Page 10, covariates. Maternal BMI was defined as maternal BMI at intake, which was in mid or late pregnancy for one quart of the population. This means that for this part of the population, maternal BMI as defined here most likely is an overestimation of maternal pre-pregnancy BMI. The fact that the correlation between pre-pregnancy BMI and BMI at enrolment is high (r=0.97) does not convince me that BMI at enrolment is a good estimate of pre-pregnancy BMI. A high correlation can occur despite significant differences between pre-pregnancy BMI and BMI at intake.

Population for analysis

11. What was the reason that exposure indicators could not be calculated for 1% of the population?
Statistical analysis

12. All exposures were categorized. Later a number of sensitivity analyses were performed to examine the robustness of the results against the choice of the cut-offs. No results of these sensitivity analyses are shown, most likely to limit the number of tables. Nonparametric smoothers could be used to overcome the problem of the large number of sensitivity analyses. Smoothed curves could for instance be presented in an online supplement and justify the use of categorical exposure variables and the choice of the cut-offs.

13. How exactly was gestational age used in regression models? Linear term only, linear and quadratic term, categorical? How were maternal age and maternal BMI defined, continuous or categorical?

14. The associations between traffic-exposures and pregnancy outcomes are highly non-linear. This is evident from the tables. In my opinion, no trend-test is necessary to prove that. I advice to skip the trend-tests.

Results

15. Please add a table with the distribution of the main exposure variables.

16. Results of the sensitivity analyses need to be presented – either in an additional table or as part of the online supplement. I have concerns about the statistical power of the stratified analyses by maternal education. In particular the group of parents with low education is rather small (10%). This needs to be discussed.

17. Page 15, maternal socio-demographic risk factors for traffic exposure. This paragraph following the main and sensitivity analyses seems to be a bit misplaced and the objectives of these analyses are not entirely clear. It could be either skipped or extended to an analysis of the associations of all potential confounding variables and traffic exposures that could be used to explore the potential of these variables for being a confounder. The latter should be presented before the main results.

Discussion

18. With regard to pregnancy complications and the interaction between SES and traffic exposure a discussion of the (limited) statistical power needs to be added.

19. Page 19, 1st paragraph. It is correct that there are no previous studies on the association between traffic intensities and pregnancy outcomes in Europe. However, there are other European studies on air pollution and pregnancy outcomes using time-space exposure models (e.g. Slama et al. Environmental Health Perspectives 2007; Aguilera et al. Environmental Health Perspectives 2009) from areas with similar air pollution levels and mixtures, which should be discussed here.

20. Page 19, residential mobility. “Non-movers” were defined as women who did not move between 7 months before conception and five months of pregnancy. I personally would consider it more logical to define “non-movers” as those who
did not move home during the entire pregnancy. Is that possible and if yes, what are the results? Please include a table or with the results.

References

21. The list of references currently includes more than 50 papers, which is rather long for an original paper and should be restricted to the most relevant references.

Minor comments

• Abstract, conclusion. Mothers exposed to … please add “in this study”.
• Page 6, line 6. “briefly” should read “in brief”

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.