Author's response to reviews

Title: A study protocol to evaluate the relationship between outdoor air pollution and pregnancy outcomes

Authors:

Manuel C Ribeiro (manuel.ribeiro@ist.utl.pt)
Maria J Pereira (maria.pereira@ist.utl.pt)
Amilcar Soares (asoares@ist.utl.pt)
Cristina Branquinho (cmbranquinho@fc.ul.pt)
Sofia Augusto (s.augusto@fc.ul.pt)
Susana Fonseca (susanafonseca@yahoo.com)
Joaquim G Nave (joaquim.g.nave@gmail.com)
Antonio B Tavares (antonio.tavares@insa.min-saude.pt)
Carlos M Dias (Carlos.Dias@insa.min-saude.pt)
Ana Silva (ana.silva@alentejolitoral.min-saude.pt)
Ismael Selemane (ismael@csgrandola.min-saude.pt)
Joaquin de Toro (jdetoro@cssantiago.min-saude.pt)
Mario J Santos (lince@cssantiago.min-saude.pt)
Fernanda Santos (fernanda.santos@alentejolitoral.min-saude.pt)

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Author's response to reviews: see over
“A study protocol to evaluate the relationship between outdoor air pollution and pregnancy outcomes”, Manuel C Ribeiro et al.

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Dear Natalie Pafitis,
Editorial Team for BioMed Central,
Thank you very much for your kind email dated July 28th 2010. We also want to thank the reviewer for his comments on our work. We included the revised version of the manuscript incorporating the suggestions by the Editorial Committee and the reviewer. Changes in revised manuscript are highlighted in yellow. We believe we have addressed all those suggestions, as discussed below on a point-by-point basis.

Comments by the Editorial Team

1. **Provide the email addresses of all authors within your title page.**
   Email addresses of all authors within the title page are provided in revised version.

2. **Include a 'Competing interests' section between the Conclusions and Authors' contributions.**
   The “Competing interests” section is included and the sentence 'The authors declare that they have no competing interests' is added.

3. **Include an Authors' contributions section before the Acknowledgements and Reference list.**
   An “Authors' contributions” section is included in revised version.

4. **Provide a power calculation within the methods section of your manuscript, used to determine the sample size of your study.**
   We added a “Statistical Power” sub-section within the methods section, with details on power calculations performed.

Major compulsory revisions pointed by Reviewer

1. **Introduce an extensive discussion on the pros and cons of the exposure assessment approach, in particular in reference to the temporal and spatial resolution issues exposed above.**
   We introduced a discussion section with the pros and cons of the exposure assessment approach. In the same section we also included temporal and spatial resolution issues. Four references are added and cited in the text.

2. **p 13: Regarding confounding factors, no information seems to be collected on occupation and associated exposures (both chemical [usage of pesticides in agriculture; working at petroleum plan ...] and physical risk factors: standing position etc) nor on personal smoking. Please comment.**
We modified last paragraph of Health Data section (Materials) to stress that pregnant are asked for their occupational and associated exposures, and personal exposure to tobacco (passive or active smoking in each trimester of pregnancy). We also add these items in Table 2.

3. Also add a short section about possible selection bias linked to participation acceptance and its likely impact on risk estimates.
We add a “Selection Bias” section to stress the possibility of participation bias. We also state how we expect to assess possible differences between participants and non-participants.

Minor essential revisions pointed by Reviewer

Methods section:

4. Page 10, the authors state that the choice of the Lichen sampling spots avoided “sites with local disturbances, particularly main roads or other facilities like farms or small factories”. This might result in underestimation of the local-short distance pollution variability, which is much greater than long term- and wide scale average differences. Add a comment.
We had a comment in Methods Section (Material-Exposure data) of reviewed version stating that: “These criteria may result in underestimation of the local-short distance pollution variability. However, we consider that the spatial resolution adopted is adequate to capture main air pollution spatial patterns.”. In the same paragraph we modified the text to stress that spatial resolution has shown in the past to be quite effective in capturing the deposition of most pollutants: “This spatial resolution is based in previous studies (16; 17; 21; 24) developed in the region using different approaches - LDV, accumulation of pollutants in lichens and diffusion tubes - where the sampling grid resolution has shown to be quite effective in capturing the deposition of most pollutants.”.

5. Page 13: it is said that information on “residential proximity to air pollution sources” is collected through questionnaires. Now air pollution is already assumed to be captured by the lichen index. Comment on whether this might or not produce a redundant information.
We collect information on residential proximity to air pollution sources as additional information on potential source of local pollution variability, which is not considered in our sampling design. This information might be redundant in cases where residential proximity to air pollution sources does not produce local pollution variability. To stress the role of this information in the study we add the following text in brackets “(collected as additional information that takes into account local pollution variability)” next to “residential proximity to air pollution sources”.

6. P 13, the section on the statistical analysis (logistic regression) is unclear.
To address this, the second paragraph of the Methods Section was changed to: “Both pregnancy outcomes are binomial data, therefore they’re modeled via logistic regression.
Exposures extracted from each simulated map are used as input data for model fitting, in order to estimate LDV exposure odds ratios while adjusting for other risk factors (see Table 2) such as tobacco smoke (passive or active), residential proximity to air pollution sources (collected as additional information that takes into account local pollution variability), social and economic status, diet, disease family history, drugs or vaccines during pregnancy or complications during pregnancy.

For each simulation we fit a logistic regression and we get an odds ratio for LDV exposure. From the set of all simulations we can build an empirical distribution of LDV exposure odds ratio. This enables us to 1) assess a point and a confidence interval estimate for LDV odds ratio and 2) measure how the risk of pregnancy outcome varies with simulated LDV exposures.”

Discretionary revisions pointed by Reviewer

7. Page 5: what do the authors mean about the air quality sampling sites being sit at "much higher altitude?". They are typically between 2 to 4 meters high. This did not disqualify them to assess population exposure in hundreds of published studies.

We agree with the reviewer. We removed this statement from the revised version.

8. The outcomes relate only to babies born; the authors might want to add a word about the fact that still births are not included, thus underestimating the possible impact of air pollution.

We understand the reviewer point of view. However, still births are an outcome with very few observations in the study region. According to the national official statistics only 8 cases of still births are registered in this region in 2007-2009 period. Any analysis of this outcome would have no statistical power.

9. Page 10: what does “the same type of land management” implicate in terms of sampling criteria?

We replaced “the same type of land management” for “the same type of landscape, namely cork-oak woodlands under constant low-intensity land-use”. The aim of this sampling criterion was to avoid the variability due to different land-uses between sites that were not related to air pollution.

10. P 13, What information is collected about diet as a possible confounder or effect modifier (remove the term “effect modifier” at the entry of this paragraph and substitute by the more neutral term of “other risk factors”)?

We collect data concerning the following food items consumption during pregnancy: meat, fish, seafood, milk, vegetables, fruit, cake, coffee and wine. We substituted in the text the term “effect modifier” by “other risk factors”.

11. The last section, before a short conclusion, might describe where the study currently stands, in order to provide the reader with a sense of how the proposed protocol will indeed be undertaken.
The last paragraph of Discussion Section gives a short description on where the study currently stands.

We believe that we have addressed all the suggestions and criticisms rose. We hope that the improved revised manuscript is now acceptable for publication in BMC Public Health.

Sincerely,
On behalf of all co-authors
M C Ribeiro