Author's response to reviews

Title: Modifiable exposures to air pollutants related to asthma phenotypes in the first year of life in children of the EDEN mother-child cohort study

Authors:

Cailiang Zhou (zhou@u707.jussieu.fr)
Nour Baïz (baiz@u707.jussieu.fr)
Tuohong Zhang (tzhang@bimu.edu.cn)
Soutrik Banerjee (banerjee@u707.jussieu.fr)
Isabella Annesi-Maesano (isabella.annesi-maesano@inserm.fr)

Version: 2 Date: 12 April 2013

Author's response to reviews: see over
April 11, 2013

Dear BMC Public Health Editor,


Thank you for your consideration of our manuscript for publication in BMC Public Health.

We have revised the above manuscript according to the reviewer’s comments which have really contributed to improve the quality of our manuscript. We have marked in red the changes in the text.

We hope that you will find the amended version of our paper satisfactory for publication in your journal.

Dr Isabella Annesi-Maesano
Research Director French NIH/Head Department of Epidemiology of Allergic and Respiratory Diseases
Head EAACI Interest group Aerobiology and Air Pollution
Previous Head: Occupation and Epidemiology Assembly, European Respiratory Society
Previous Chair: Respiratory Diseases Section, IUATLD
POINT-BY-POINT REPLY

Reviewer: Denis Zmirou-Navier

Minor Essential Revisions:

1. While the associations between maternal smoking or exposure to traffic exhaust during pregnancy and asthma phenotypes, as very early outcomes (4 months), are grounded on an appropriate time sequence, the causal link is less evident for 8 or 12 months outcomes, given the strong relationships that exist between in utero and early month’s exposures.

We entirely agree with the reviewer on the fact that only exposure during pregnancy allows to establish a causality relationship as it precedes health outcomes and that the causal link is less evident for 8 or 12 months outcomes, given the strong relationships that exist between in utero and early month’s exposures. Therefore, to better understand the relationships of exposures to traffic and passive smoking to health outcomes by taking into account the correlation of observations within each subject, we included in the GEE model a time variable (=1 if at the age of 4 months, =2 if at the age of 8 months, =3 if at the age of 12 months) as an independent variable. The corresponding methods and results are amended in the text.

In the methods section, we added: “In order to study the relationships between the exposures, i.e., prenatal maternal smoking and in utero exposure to traffic-related air pollution, and each health outcome in the GEE model, we introduced a variable of time and tested the statistical significance of the presence of interactions between this time variable (=1 if at the age of 4 months, =2 if at the age of 8 months, =3 if at the age of 12 months) and each exposure, adjusting for confounders. As the interaction terms were not significant (P-value>0.05) in the models, they were consequently dropped. In the next step, we studied the
associations of all exposures together with each health outcome, including the time variable and confounders. This enabled to estimate the impact of time on the associations between the exposures and each health outcome.”

In the results section, we added: “There was no statistical significance ($P>0.05$) for the interaction term between exposure to the risk factors and time in the models. The aOR for time was 2.43 (95%CI: 2.28-2.60) for the model describing the relationships between in utero exposures and ever bronchiolitis.”

We also changed the aORs for exposures when appropriate.

2. Discussion, differences between in utero and first year exposure prevalence to traffic-related air pollution, page 12, line 267. Among the points to be clarified as far as this time sequence is concerned is the observation of surprising differences between in utero and first year exposure prevalence to traffic-related air pollution (28 and 21% respectively, line 186-188). This variation may be due to differences in the study sample (not all families accepted the one year interview) or to changes in places of residence. This also should be discussed.

We have added sentences in the discussion section as following:

“Lastly, the questions for assessing in utero and first year of life exposure to traffic-related air pollution were different (as showed in Table 1). This is because, after the survey time point of at birth, in order to take results from recent studies into account [46-47], we modified the questionnaire and assessed distances of the dwellings to major road, and in particular a 200 m circular buffer with which a risk of asthma had been associated. As a consequence, responses for in utero and first year of life exposure to traffic were not exactly comparable. In addition, the response rates varied from one survey to the other. Indeed, for
some mothers, it was difficult to figure out the exact circular buffer and there were more missing values for the variable of first year of life exposure to traffic-related air pollution than for the variable of in utero exposure to traffic-related air pollution. Notably, some mother-child pairs changed their residences after the birth of the child. However, in spite of these differences, the associations between asthma phenotypes and the exposure to traffic-related air pollution in utero life and in the first year of life are consistent.”

3. Limitation in the discussion section, page 13, line 300. The new sentence added line 300 is unclear: "Another limitation of our study is that no causality could be established but in the cases of prenatal maternal smoking and in utero life exposure to traffic-related air pollution that preceded the asthma outcomes."

This sentence has now been revised as follows:

“Another limitation of our study is that the exposure to risk factors was assessed simultaneously with asthma outcomes except for prenatal maternal smoking and in utero exposure to traffic-related air pollution. Therefore, the causal link implied by our study should be interpreted with caution.”

4. Discussion, page 13, line 309-10. To back their conclusion, the authors should more extensively justify in the discussion section how they could disentangle in utero and first year exposures. The sentence (line 309-10) "From the statistical point of view, the evolution of asthma phenotypes as well as effect modifiers and potential confounders were taken into account" is far too elusive for this important matter.

We have added in the discussion section sentences as following:

In the discussion: “In addition, we used different models to analyse the relationships between asthma outcomes and in utero and first year of life exposures respectively, taking
into account the temporal sequence in relation to asthma outcomes. We also considered the potential confounders and effect modifiers in the models to show the independent effects of exposures in utero life and in the first year of life.”

5. Idiomatic editing. The paper still needs extensive idiomatic editing (including for the one French term "Comission Nationale de l’Informatique et des Libertés" where "Commission" must replace Comission.

We have done the idiomatic editing carefully.

**Discretionary Revisions:**


We have added this important reference in the text in page 11, line 265 with details as following:

“In a previous case-control study in 5 French metropolitan areas, results indicated that traffic related pollutants might be associated with the incidence of asthma in children aged 0-3 years old [37].”