Reviewer's report

Title: Maternal exposure to air pollution before and during pregnancy related to changes in newborn’s cord blood lymphocyte subpopulations. The EDEN Study Cohort.

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Reviewer: Svetlana Glinianaia

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Manuscript “Maternal exposure to air pollution before and during pregnancy related to changes in newborn’s cord blood lymphocyte subpopulations. The EDEN Study Cohort.” by Nour Baïz, Rémy Siama, Marie-Christine Béné, Marie-Aline Charles, Marie-Nathalie Kolopp-Sarda, Antoine Magnan, Olivier Thiebaugeorges, Gilbert Faure and Isabella Annesi-Maesano

General comments

There is a growing body of evidence suggesting that exposure to ambient air pollution can have adverse effects on pregnancy outcomes.. This research is of great public health importance as the exposure to air pollution is widespread and birth outcomes are important determinants of future child and adult health. The epidemiological evidence is accumulating, although there is still inconsistency between the studies in relation to critical exposure windows during pregnancy and type of air pollutants that are harmful to fetal development. Only few studies examined the effect of ambient air pollution on the newborn’s immune system. This study investigates the impact of maternal exposure to air pollution before and during pregnancy on newborn’s immune system by measuring lymphocyte subsets in cord blood.

The abstract is concise and informative, and is a good summary of the main findings of the study. The introduction summarises the existing literature (however, see minor comments) and puts the current study into the context of evidence available to date.

The objective of the study and the study design are clearly defined. The methods are appropriate but need further clarification and explanation (see major and minor comments below). The results are satisfactorily interpreted (see minor comments).

The authors described the strengths of their study and also acknowledged the limitations in the Discussion.

Overall, the paper is clearly written (see some grammar and typos corrections below) and well presented.

Specific comments
Major Compulsory Revisions

Methods:
1) Lymphocyte immunophenotyping – p. 7
I recommend explaining and justifying why these specific lymphocyte subtypes were chosen to characterise the immune status. What is the advantage of using these indicators of immune status? Why, for example, didn’t authors choose to use general indicators of immune status, such as serum IgA, IgG and IgM levels? It will not be that obvious for readers of BMC Pregnancy and Childbirth.

2) Maternal exposure to air pollution – p. 8
The authors should give more details on the exposure assessment to ambient air pollution. They refer to one of the co-author’s paper (line 6) that used land-use regression for exposure estimation to ambient air pollution. Does it mean that in this study the same method was used? It is not clear from the description in the Methods whether the PM10 and NO2 levels measured by air monitoring stations located within less than 2km (results, p.11, line 1) from a maternal residential address were used for calculating the means for the study periods of exposure.

Minor essential revisions

1) Background, p. 4, sentence 3: I am not happy that the authors combined in one sentence the evidence available for environmental tobacco smoke (EST) and urban air pollution, as it does not give the reader a clear idea of the associations found between each of those environmental exposures and birth outcomes. It gives a reference to one study only for urban air pollution, which did not examined all the outcomes listed in that sentence. For example, Slama et al did not examine prematurity and postneonatal mortality in that study. Please change this.

2) Page 6, lines 22-24: Please give more information on how this sample of 370 women was formed. Was it a random collection of cord blood samples?

3) Methods: Terms ‘preterm birth’ used in Table 1 and ‘prematurity’ used on page 10, line 9 are not the equivalents so they should be defined and should not be used to replace each other. The definition of preterm birth (as well as that of low birth weight, LBW) is important to give, in particular, as they differ from the WHO definitions (see Table 1). According to the WHO definition, LBW is weight at birth of <2500g (not # 2500g) and preterm birth is birth at <37 completed weeks of gestation (not # 37 weeks) (see Results page 11, line 8).

4) Methods: Statistical analysis: p. 9, line 10. It is stated that for continuous variables means and standard errors were calculated, while in Tables 1-3 means and standard deviations are given.

5) Results: p. 11, line 4: The BETX was spelled out when used first time (p. 8, lines 9-10) so it does not need to be given here again.

6) Results: p. 11, line 5: Please add “…the total sample (n=2002), from which our…”.
7) Results, p. 12: it would be preferable to number Table 4 as Table 3 as their results are described first, and current Table 3 should be numbered Table 4 as it is presented later in the Results section.

8) Results p. 12, lines 12-14 and Table 3: I cannot see how from table 3 it can be concluded about temporal and intra-individual variations in exposure to air pollution. Also, based on the description of exposure assessment, I would not name these average levels of maternal exposure to ambient air pollution as individual maternal exposure in contrast to individual BETX assessment.

9) Results p. 12, lines 18-19: I suggest specifying during which trimesters of pregnancy CD8+ T-cell and NK cell percentages increased significantly with an increase in PM10 and NO2 concentrations, as this does not seem to be the case for each trimester (e.g. NK cell increased with an increase in PM10 in the first trimester).

10) Discussion, p. 14, line 6: PM10 and NO2 abbreviations are given in the methods on page 8, they do not need to be spelled out again.

Discretionary revisions:

1) Abstract, methods, line 8: I suggest moving ‘in 370 women’ to after …” was assessed…” so it would read: Exposure to background particulate matter less than 10 µm in diameter (PM10) and nitrogen dioxide (NO2) was assessed in 370 women three months before pregnancy and during each trimester using monitoring stations data.

2) Methods: I would recommend moving the Ethics statement subsection to the end of the Methods section as this is the usual practice in the scientific medical journals.

3) Results: p. 11, line 3: Change to “Table 1 presents… living within less that 2km…”

4) Table 3 (a) and (b): I would recommend aligning tables by the beginning of the table.

Typos:

1) Background, page 4, line 7: an extra comma needs to be removed after ‘impaired fetal growth [5],’; line 8: there is no need for a space before the comma after the word ‘prematurity’, but a space should be added after that comma before ‘postneonatal…’; line 12: a space should be added after the dot, before the new sentences starting with ‘Few studies…’

2) Methods: Statistical analysis: p. 9, line 12: Please change “ between each air pollutant and each lymphocyte phenotype…”.

3) Methods: Statistical analysis: p. 9, line 15-16: Please amend: “… lymphocyte percentages for a 10 mg/m3 increase in PM10 and NO2 …for a 1 mg/m3 increase in log-transformed benzene exposure.

4) Results: p. 11, line 6: “… study population was sampled”.

5) Table 2 footnote and Results, p.11, line 18: Chi-square test
6) Table 5 footnote: “…for each 10 mg/m3 increase in PM10 or NO2.”
7) Results p. 13, line 3 and title for Figure 2: “…increase in…”
8) Discussion, p.16, line 20: a full stop is missing at the end of the sentence.
9) Discussion, p.17, line 15: misclassification

**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