Author’s response to reviews

Title: Early-life exposure to PM2.5 and Risk of Asthma Clinical Encounters among Children in Massachusetts: A Case-Crossover Analysis

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Author’s response to reviews:

Dear Editors,

We appreciate the opportunity to address reviewer comments. Please see our point by point responses below. The revisions recommended by the reviewers have improved the manuscript’s clarity. We have conducted additional analyses as requested and feel the paper is ready for your review.

Best regards,

Roxana Khalili, MS
Reviewer #1: The present manuscript concerns an important topic related to the effect of PM2.5 low levels on asthma clinical encounters. The manuscript is of interest but some aspects have to be taken into account.

Major revisions:

- Statistical analyses, page 6, lines 130-131: The authors reported that "referent days were randomly selected 7 days before or after the clinical event"; maybe the referent days are too close to the clinical event; the authors should consider a possible long term effect of the exposure to PM2.5.

Response: Since we are only estimating short-term effects of asthma exacerbation (rather than asthma development) in this study, a referent date of the 7th day before or after the clinical encounter is likely beyond the biologically plausible window of effect. We believe our referent date of exposure is long enough to exceed the lags of 0, 1 and 2 days where a child would have symptoms severe enough to seek care in an emergency setting. Other studies that have used a case-crossover study design to analyze the relationship between short-term PM2.5 exposure and asthma outcomes have used similar lags, and many that have looked at longer lag periods have found no associations between PM2.5 exposure and asthma outcomes (Fan et al., 2015, Strickland et al., 2016). In addition, our referent selection is close enough to the index date to allow our referents to be restricted to the same season as the index dates.

- Have the authors tried to choose the referent day at the same weekdays within the same month and year as the day of the event?

Response: Our referent date was 7 days before or after the clinical encounter so they were always on the same day of the week. However, instead of the time-stratified design suggested by the reviewer, we are using a semi-symmetric bi-directional referent design. The two are very similar as both avoid overlap bias, but instead of taking all referents within each arbitrarily defined stratum such as calendar month, the semi-symmetric bi-directional design randomly chooses a referent using a fixed time interval either before or after the index date (event). (Janes et al., 2005)

- The authors reported that "Changes in residency were not problematic because the index date and the referent date were only 7 days apart". But, at page 5, lines 98-99, the authors reported that "Children who did not have the same zip code at the time of their clinical encounter and at birth were excluded from the study". Thus, changes in residence are not a problem related to the choose of the referent date, 7 days apart.
Response: The age range of the children in our study is 0-9 years which is why many of them (especially the older years) may have moved from their time of birth to the time of their clinical encounter. Therefore, because PM2.5 concentrations were assigned based on residential location at birth, we excluded the children whose zip codes did not match the time of their clinical encounter to avoid exposure misclassification. The manuscript has been changed to read “Changes in residency between clinical encounter and referent date were unlikely to be problematic because the index date and the referent date were only 7 days apart”. (page 7, lines 147-148)

We expect that very few children moved during the 7-day period between the clinical encounter and the referent day. The manuscript has been changed to read “We excluded children who did not have the same zip code at the time of their clinical encounter and at birth because the PM2.5 concentration at their residence at birth was unlikely to be representative of their PM2.5 exposure at the time of their clinical encounter”. (page 5, lines 103-105)

- Statistical analyses, page 6, line 133: have the authors tried to analyze a cumulative exposure (lag 0-2)?

Response: Per the reviewer’s suggestion we performed an analysis with a cumulative exposure equally weighted across lags 0-2 and observed similar results from our individual lag analyses (OR: 0.98; 95% CI: 0.96, 1.00).

- Statistical analyses, page 7, lines 146-147: this sentence is not clear; could the authors specify what means the ”fully adjusted model”?  

Response: The fully adjusted model includes temperature, humidity, barometric pressure and a holiday indicator. Lines 143-147 were modified to read “Variables that were controlled for, and included in the fully adjusted model, were those that had short-term changes…” (page 7, lines 150-151).

- Have the authors run a model adjusting for all the variables instead of stratifying for them?

Response: In a case-crossover study design, one cannot adjust for time invariant variables such as sex and race, because each case also serves as her/his own control and therefore time invariant variables are always matched. Although this design is ideal for controlling for time invariant confounders, it is not possible to add them to the model or estimate their independent effects. One can only stratify for time invariant variables, as we have done here to investigate potential effect modification.
What is the meaning of the interaction term? Does it analyze the effect modification of the variables reported in Table 3?

Response: Yes, the p-values in Table 3 are for tests of the null hypotheses that each interaction term is zero (i.e., no effect modification by that risk factor). The ORs presented in Table 3 are from stratifying on each risk factor, and the p-values we present are for the interaction term of each risk factor and PM2.5 that was added to the fully adjusted model to test for effect modification. This has been added to the legend in Table 3 with a footnote that now reads “p-value presented is from the interaction term of each risk factor and PM2.5 added to the fully adjusted model”, and specified that the asterisk is for “statistical significance (p<0.05) for interaction term”

Statistical analyses: A 5 µg/m³ increase was used in the analyses; considering that the mean PM2.5 concentration is 8.8 µg/m³ and the median is 7.8 µg/m³, an increase of 5 µg/m³ could hide the PM2.5 effect. Have the authors tried to use the interquartile range or a smaller increase?

Response: The results in Table 3 and the values throughout the text have been changed to reflect the ORs for an IQR increase in PM2.5. Note that the IQR is 5.9 µg/m³. Scale changes in exposure do not affect statistical significance, so all hypothesis tests have the same conclusion.

Statistical analyses: the analyses in the subgroup of children 5-9 yrs were reported in the supplemental material. The results are quite different from the ones on the whole sample and they are reported in the Results and Discussion sections. Why did the authors not insert the tables in the main manuscript? Moreover, have the authors analyzed the subgroups of age 0-4 yrs?

The analyses seem to suggest a different susceptibility according to age, that it is currently not considered in the analyses.

Response: In the analyses of children 5-9 years of age, cases are not just children who present with clinically severe asthma for the first time in their lives after the age of 5. Approximately 40% of the children 5-9 years of age already had a clinical encounter related to asthma or wheeze previously. We decided to do a sensitivity analysis with this age group because these older cases are more severe cases of poorly managed or difficult to control asthma. Because diagnosis can usually be more accurate at 5 years and older we felt that this would be a better group to conduct the sensitivity analysis with than the younger group. The majority of our cases are younger, decreasing in number as age increases, so we didn’t feel that it was necessary to also do an
analysis with ages 0-4. Several studies have analyzed different age ranges of asthma cases but with severe cases that lead them to seek care in an inpatient setting many include younger ages in their analyses (Delfino et al., 2014; Fan et al., 2015; Strickland et al., 2016). We decided to put the analysis of 5-9-year-olds in the supplemental materials because we feel that they are still interesting findings, but are not necessary for understanding the manuscript’s main results.

Minor revisions:

- Background, page 4, lines 83-88: in this paragraph, the authors reported a summary of the analyses, instead it should be better to clearly report the 2 aims of the manuscript.

Response: We have made the suggested edit in the manuscript by clearly reporting the two aims: “The aims of the study were to investigate the associations between early-life short-term PM2.5 exposure and the risk of asthma or wheeze exacerbation, and to determine if there was any effect modification. To do this, we employed a case-crossover study design with short-term exposure lags using data on clinical encounters among all children 0-9 years of age in Massachusetts (MA) obtained from the innovative Pregnancy to Early Life Longitudinal (PELL) cohort record linkage system.” (page 4, line 88-93)

- Exposure assessment, page 5: the clinical encounters were collected between January 2001 and September 2009. I suppose that the daily PM2.5 concentration was modeled for the same period, in order to link the event happened in a specific period with the PM2.5 concentration of the same period. If so, please, specify it.

Response: Yes, that is correct. This has been edited. (page 5, line 116: “PM2.5 concentrations were modeled spatiotemporally using satellite remote sensing, meteorological and land use data for the same duration as the study period”.)

- Statistical analyses, page 6, lines 138-139: have the authors controlled also for the “influence epidemics”? They could be an important factor related to the asthma exacerbations.

Response: We did not control for possible influenza epidemics in this study. However, of the 33,387 asthma cases used in our analyses, only 274 cases (0.8%) also had an ICD-9 code for influenza, so we believe confounding by influenza would be negligible in this study.

- Results, page 7, line 152: please, add "during pregnancy" after "were non-smokers".
Response: We have made the requested change.

- Table 3, legend: please, specify that the p-value is referred to the interaction terms.

Response: We have made the requested change.

Reviewer #2: Using data from the PELL system the authors conducted a case-crossover analysis on the short-term effect of PM2.5 exposure on asthma related clinical encounters. It is an interesting study with well-established methodology. Statistical analysis techniques used are appropriate for the study design.

- My main concern is that I find the title and conclusions somewhat misleading, as they focus on a single finding (effect modification by LBW born children) whereas the study examines a much wider range of factors. The authors shall not selectively focus on findings based only on statistical significance.

Response: The title has been changed to “Early-life exposure to PM2.5 and Risk of Asthma Clinical Encounters among Children in Massachusetts: A Case-Crossover Analysis” in order to reflect a more general description of the study.

Minor comments:

Study population:

- The authors should consider the inclusion of a flow chart describing the study population.

Response: A flow chart has been added as Figure 1 in the manuscript.

- The final number of study participants is not presented.

Response: We included the final number of participants in Methods Section describing the study population on page 5, lines 106-107.
- How did the authors treat participants with missing information on potential effect modifiers?

Response: Participants with missing information were excluded from those analyses. The number missing for each characteristic is listed in Table 1. Relatively few participants (0.1%-0.5%) had missing data so we did not find it necessary to do multiple imputations or apply other more sophisticated missing data methods. This has been added to the text on page 8, line 170.

- Results: lines 159-161: This information shall be included in study population

Response: The 10% of study sample with missing PM2.5 estimates has been added to the study population section as requested. However, to clarify, this was not an exclusion criteria when choosing our cases. They were missing values after assigning PM2.5 exposures and therefore excluded from the analysis.

- Discussion: The authors should comment on the limitations that arise from the study design as no individual characteristics of the participants that may play a significant role on asthma onset are examined.

Response: We agree with the reviewer and text has been added to the last paragraph of the discussion to reflect this point (pages 13-14, lines 303-305).