

Author's response to reviews

Title: Impact of ambient air pollution on gestational age is modified by season in Sydney, Australia

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Author's response to reviews: see over

13 May 2007

Dr D Ozonoff
The Editor
Environmental Health

Dear Dr Ozonoff

Re: Revisions to manuscript titled “Impact of ambient air pollution on gestational age is modified by season in Sydney, Australia”

Please find our responses to the major and minor essential revisions as suggested by the reviewers of our manuscript. We have highlighted our responses in the revised manuscript. We have also attached to this covering letter each of the major and minor essential revisions together with our responses.

We look forward to hearing from you. We will be happy to respond to any further comments from the Editors or the Reviewers.

Yours sincerely

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Responses to Reviewers comments for manuscript entitled “Impact of ambient air pollution on gestational age is modified by season in Sydney, Australia”

Reviewer 1 (CH)	
<i>Major essential revisions</i>	
<p>1. It is stated that there was a significant reduction in the risk of PTD if conception occurred in spring compared to summer. Due to the different lengths of gestation it would be beneficial to report if there was a significant association between PTD and season of birth. Season of conception assumes something occurred early in pregnancy to induce PTD at a later time, whereas season of birth assumes something closer to the time of delivery induced PTD.</p>	<p>We accept the Reviewer’s comments and we have conducted additional analyses for exposure in the first trimester and in the month prior to delivery where we have used season of birth instead of season of conception. There were only minimal differences in the beta coefficients and odds ratios for all six air pollutants in the two set of models. We believe that this is because both season of conception and season of birth may be adjusting for seasonal variation in a similar fashion.</p> <p>We have now stated this in the Discussion section – see first full paragraph on page 10.</p>
<p>2. As this is one of the few studies that have controlled for temperature and humidity, it would be interesting to know if these variables were significant in the models as the effect of temperature on PTD is worthy of brief discussion.</p>	<p>We made an error in the Methods section where we state that we adjusted for temperature and humidity in the multivariate logistic regression models. In the initial single variable logistic regression models, there were no significant effects of temperature and humidity on preterm delivery. Therefore temperature and humidity were not included in all subsequent multivariate models.</p> <p>This has been now stated in the Methods section – see page 4, last sentence.</p>
<p>3. In the main analyses PM10, O3 and SO2 showed an adverse association with PTD, however, this was only for the 5km exposures with most of these effects being protective for the Sydney exposures – there is no major discussion as to why this may have occurred, especially for O3 and SO2</p>	<p>We have added a paragraph in the Discussion section – see last sentence on page 9 and continuing onto page 10.</p>

<p>because the effects are so high.</p>	
<p>4. For the 5km exposures O3 during month one of gestation showed a 60% increase in the risk of PTD (for a one unit increase in O3) – this is extremely high compared to all other studies and it needs some discussion. Furthermore, it is interesting to note that when averaged over trimester one the effect becomes protective. With such a large effect for O3 during month one you would expect the effect to persist when averaged over trimester one (therefore I assume there must have been very strong protective effects specifically for months 2 and 3 for the result to go towards the null when averaged over trimester one). Given the result presented, you would therefore assume that the timing of the effect associated with O3 exposure is very specific to month one of gestation, this should be discussed. Is there a biological mechanism that could be related to this outcome?</p>	<p>A number of biological mechanisms have been canvassed regarding the effects of air pollution but we are not aware of a biological mechanism/s acting specifically in the first month of pregnancy. We have already discussed possible biological mechanisms in the manuscript (paragraph 2 on page 11).</p> <p>We have added a further sentence regarding the timing of adverse events during gestation – see second full paragraph on page 11.</p>
<p>5. SO2 levels are low for Sydney when compared to more industrialized cities, so it would be interesting to note why the 5km effects for SO2 in Sydney are so large compared to previous studies. The effect for SO2 among those conceived during autumn is extremely high and there is no discussion as to why. Furthermore, SO2 during trimester one is a protective factor for all of Sydney in Table 4, however, in Table 5 it becomes a strong adverse effect across almost all seasons (except summer). Is this really SO2 or some other associated factor? More discussion on this is warranted.</p>	<p>In epidemiological studies of the effects of air pollution, where measurements from air quality monitoring stations are used as a proxy for personal exposures, it can be difficult to assign health effects to a particular air pollutant. In metropolitan Sydney, vehicular traffic is the primary source of SO2. It is conceivable that SO2 is a marker for traffic related air pollutants in our study and therefore effects attributed to SO2 are in reality due to other traffic related air pollutants.</p> <p>We have now stated this more clearly in the Discussion section – see first paragraph on page 12.</p>
<p>Minor essential revisions</p>	
<p>1. Metropolitan Sydney needs to be defined. For example, did the sample include births to women who resided within a particular geographical distance from the centre of</p>	<p>Metropolitan Sydney comprised the geographical areas as defined by the NSW Health Department. Three local government areas were excluded as they</p>

<p>Sydney, or within particular government areas within Sydney? What defines 'metropolitan'?</p>	<p>were not adequately served by ambient air quality monitoring stations.</p> <p>This has now been stated in the last paragraph on page 3.</p>
<p>2. The exposure assessment was also based on data from a monitoring site within 5km of the mothers' residential postcode. For the postcode to be included, was the centroid of the postcode 5km from the monitoring site, or was the postcode included if the boundary of the postcode was within 5km of a monitoring site. I ask this because there could be large postal areas in the outer regions of a city – which also relates to comment number 1.</p>	<p>Postcode areas were included in the 5 km radius of an air quality monitoring station if more than 50% of the postcode was within the 5 km radius.</p> <p>This has now been stated in the second last paragraph on page 4.</p>
<p>3. The third trimester is sometimes referred to as 'third trimester' and sometimes referred to as '3 months preceding birth' - use one or the other to make it consistent.</p>	<p>This has been corrected. It is now referred to as 'three months preceding birth'.</p>
<p>4. Add 'meteorological variables' as one of the factors adjusted for in the footnote of Table 4.</p>	<p>Meteorological variables were not included in the multivariate logistic regression models. Therefore, we have not made any changes to the footnotes of Tables 4 and 5.</p>
<p>5. Table 5. – There is a significant protective effect for SO₂ in summer that is not highlighted (e.g. **). Were meteorological variables included in the analyses when stratified by season of conception?</p>	<p>Asterisks have now been added for the SO₂ effect.</p> <p>Meteorological variables were not included in the multivariate logistic regression models. Therefore, we have not added to the footnotes of Table 5.</p>
<p>6. When presenting odds ratios from other studies (p12) for comparison purposes I feel it is important to state the unit increase in the pollutant that the authors have used in the model, otherwise the size of the effect estimates being discussed can be slightly deceiving.</p>	<p>We have added the unit increase when quoting odds ratios from other studies in the Discussion section.</p>
<p>Reviewer 2 (MB)</p>	
<p>Major essential revisions</p>	

<p>1. The main problem of this study, as of most studies where multiple comparisons are done, are the inconsistencies in the results of different models. Some associations were significantly positive, some significantly negative, and some non-significant. Although the authors gently touched this problem in the discussion, I am not sure that they addressed it explicitly. Firstly, given the large number of comparisons, some kind of formal correction (of the statistical level to be considered as significant) might help. Alternatively, the authors should reach, informally, a more balanced view on the positive, negative and non-significant results.</p>	<p>We have already stated in the Discussion section the issues around large number of comparisons. In such cases it is not unusual to find some inconsistent results. However, we do accept the Reviewer's comments about reaching a more balanced view. We have therefore reviewed the manuscript and made changes so as to present a more balanced view on the effects of air pollution on preterm delivery in the Discussion section and in the Abstract.</p> <p>Please see Conclusion section in the Abstract (page 2), the second paragraph on page 12 in the Discussion section and the Conclusion section on page 12.</p>
<p>2. Second, the authors understandably concentrate on the positive ("harmful") associations, and not on the inverse ("protective") ones. In my view, the overall balance of the positive and negative associations indicates an absence of a meaningful (i.e. reasonably strong) association in either direction, rather than a presence of a harmful one, possibly due to very low levels of pollution in this setting. I think that the overall interpretation should take this into account, both in the main text and in the abstract.</p>	<p>This comment relates to the comment above. We agree with the Reviewer's comments and have now presented a more balanced view on the effects of air pollution on preterm delivery in the Discussion section and in the Abstract.</p> <p>Please see Conclusion section in the Abstract (page 2), the second paragraph on page 12 in the Discussion section and the Conclusion section on page 12.</p>
<p><i>Minor essential revisions</i></p>	
<p>1. I agree with using pollutants as continuous variables in the analyses. In my view, the statistical analysis is appropriate. However, it would be helpful for the reader to express the effects in some meaningful units (e.g. per range corresponding to top vs. bottom quintiles or per 1 SD). This becomes even more important in the discussion when the results are compared to other studies. At present, results of different studies, as shown in the discussion, are not comparable.</p>	<p>We have now added units in the Discussion section when quoting odds ratios from the literature (see also Reviewer 1, Minor essential revision #6).</p>

<p>2. A related point: when reporting the results on meteorological, infant and maternal factors, the authors should report the units.</p>	<p>We have reviewed the manuscript and added the units where the units have not been reported. For the air pollutants, we have stated in the Methods section that the odds ratios were calculated for a one unit increase in the air pollutant concentration. This is also stated in the footnotes to Tables 4 and 5.</p>
<p>3. It would be useful to report the heterogeneity between season-specific ORs, e.g. by adding an extra column to table 5.</p>	<p>Season of conception was found to be an effect modifier in this model and hence the analysis was conducted separately for each season. We believe that a test of heterogeneity across the season-specific ORs would provide no additional information as we have already identified that season is an effect modifier. If readers wish to compare the results across seasons, they could compare the 95% confidence interval for each OR and if the intervals do not overlap then there is a significant difference between the seasons.</p>
<p>Reviewer 3 (</p>	
<p>1. Abstract: Last sentence in the results section should be clarified. Ozone levels in the 1st trimester of pregnancy might be associated with increased risk for preterm delivery for all Sydney, however, decreased risk for preterm birth for within 5km. In case of ozone, winter was not related with increased risk for preterm delivery.</p>	<p>The abstract has been modified to reflect this comment and also comments made by Reviewer 2 (Major essential revision #2).</p>
<p>2. Background: The aim of the study is not clear. It should be clarified.</p>	<p>The test has been changed to clarify the aims of the study. Please see paragraph 3 on page 3.</p>
<p>3. Methods: 3.1 Authors used season of conception as one of confounding factors. I wonder how they could obtain the different results when using the season of delivery rather than using that of conception.</p>	<p>Please see our response to Reviewer 1's first comment. We have now stated this in the Discussion section – see first paragraph on page 10.</p>
<p>3.2 It would be helpful to give a full account</p>	<p>Single and two pollutant regression models</p>

<p>of the aim, advantage and framework of the “two-pollutant model”.</p>	<p>have been widely used in epidemiological studies of the effects of air pollution on health outcomes over the last 15 years. There is also consensus that the interpretation of these multi-pollutant models can be very difficult. That is why we have not concentrated on presenting the results of the two-pollutant models.</p> <p>We accept the Reviewer’s comment and give further description of the two-pollutant model – see paragraph 1 on page 5.</p>
<p>3.3 It should be mentioned which software was used for the statistical analysis.</p>	<p>We used SAS v8 statistical software (SAS Institute Inc., Cary, NC, USA) for all our analyses.</p> <p>This is now mentioned in the Methods section – see first full paragraph on page 4.</p>
<p>4. Results: 4.1 Page 8, 5th line from the bottom: There might be an error that PM10 had “both increased risks” for all Sydney and for within 5km.</p>	<p>We agree that we made an error and that this paragraph is confusing.</p> <p>We have revised this paragraph so that it reads better – see first full paragraph on page 7.</p>
<p>4.2 Table 3: It would be helpful to test for correlation coefficient and add corresponding p-values.</p>	<p>We have done this and p-values have been added to Table 3.</p>
<p>4.3 Table 4: In case of ozone and SO2 in the first trimester, it should be mentioned the reason of the inconsistency of OR values for all Sydney and for within 5km.</p>	<p>See also comments by Reviewer 1 (Major essential revision #3).</p> <p>We have added a paragraph in the Discussion section – see last sentence on page 9 and continuing onto page 10.</p>
<p>4.4 Table 5: In case of SO2 in autumn, it should be mentioned the reason why OR value was pretty higher in autumn than in other seasons. In the table, OR for SO2 in autumn might be significantly related to decreased risk for preterm birth (“*” need to be indicated in the table).</p>	<p>Asterisks have been added to the SO2 result.</p>

<p>4.2 It should be clarified that how they could get the different results between one- and two-pollutant models were obtained. It should be mentioned the advantage of using two-pollutant model.</p>	<p>Although we report our results for two pollutant models, we have not focused on the two-pollutant models in the Discussion as the interpretation can be difficult because of collinearity between air pollutants and air pollutants acting as surrogates for other known or unknown air pollutants. Therefore, theoretically two-pollutant models should have the advantage over single pollutant models in that effect estimation for one pollutant is adjusted for the second air pollutant. However, this is not often the case as the interpretation of the point estimates in two-pollutant models is not straightforward.</p> <p>See also our response to #3.2 for Reviewer 3.</p> <p>We have added a paragraph in the Discussion section discussing our results of the two-pollutant models - see first full paragraph on page 11.</p>
<p>5. Discussion: Page 10, 5th line from the top: “preceding pregnancy” might be changed to “preceding delivery”.</p>	<p>This has been done.</p>
<p>6. Conclusion: The conclusion of the paper could be written more clearly</p>	<p>We have now done this.</p> <p>Please see Conclusions section on page 12.</p>