Author’s response to reviews

Title: Prenatal exposure to cooking gas and respiratory health in infants is modified by tobacco smoke exposure and diet. Results from the INMA birth cohort study.

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Version: 2 Date: 30 August 2013

Author’s response to reviews: see over
To the Editor of
Environmental Health

Valencia, Spain, 22/august/2013

We enclose our original manuscript entitled “Prenatal exposure to cooking gas and respiratory health in infants is modified by tobacco smoke exposure and diet. Results from the INMA birth cohort study.” by Ana Esplugues et al. Following the reviewers’ and editor’s comments, changes have been made in our manuscript. Below we present an answer (in blue and in italics) to each referee’s comment along with an indication of the changes made. In the manuscript, new text is highlighted in yellow, and deleted text is crossed out in the text (e.g. deleted text).

We sincerely thank the editor and the reviewers for the helpful comments and suggestions that contributed to the improvement of the manuscript.

Sincerely yours,

Ana Esplugues on behalf of the authors
Date: August, 22nd 2013

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1 Reviewer’s report

Title:

Prenatal exposure to cooking gas and respiratory health in infants is modified by tobacco smoke exposure and diet.

Version: 1 Date: 27 June 2013

Reviewer: Deborah Jarvis

Reviewer’s report:

This report describes results from a prospective study of infant health in the first year and examines the relationship of gas cooking with symptoms. Overall no associations are seen but there is some evidence that wheezing with use of gas for cooking is modified by maternal smoking in pregnancy, and otitis with gas may be modified by maternal intake of fruit/vegetables (10 interactions reported, 2 with p<0.05). These results are compatible with some of the hypotheses regarding health effects of indoor gas appliances – but results are very preliminary (although the gas/smoking interaction on wheeze is strong p<0.002), and require replication in future studies.

Major Compulsory Revisions

Please state whether FFQ has been used to derive intake of antioxidants and whether these have been tested as possible effect modifiers (and results)

In this study we used a semiquantitative FFQ to assess the usual dietary intake of 100 food items and beverages during the first and third trimesters. Participants were asked to report the frequency of consumption of 10 fruit items (oranges; orange juice; bananas; apples or pears; peaches, nectarines, or apricots; watermelon or melon; grapes; prunes or plums; kiwis; and olives) and 12 vegetable items (spinach; cabbage, cauliflower or broccoli; lettuce or endive; tomatoes; onions; carrots or squash; green beans; eggplant, zucchini, or cucumber; green, red, or yellow peppers; artichokes; asparagus; and garlic) during 2 different periods: the first trimester (10–13 wk) and third trimester (28–32 wk). Fruit and vegetable are rich in antioxidants, so we assumed this fact, we didn't transform dietary intake of fruit and vegetable into antioxidants intake. Reported intakes in the questionnaire were converted to estimate daily frequencies of fruits and vegetables.

We tested fruit and vegetable consumption as an effect modification of exposure to gas cooking and outcomes. When we stratified by fruit and vegetable intake (<518 gr, median) we found a significant relationship between gas cookers and otitis among infants whose mothers consumed low intakes of fruits and vegetables during the first trimester of pregnancy (see page 10 and Table 3).

Please state proportions using bottled gas and test/briefly report that effects same for mains and bottled gas (if they are). There is limited evidence that pollutants from bottled gas appliance may be different to that from mains.

The use of different types of gas (bottle gas primarily butane and propane in very low concentration, and network gas, primarily metane) varied depending on the
region. Valencia is the region with major proportion of use of bottle gas. We added this proportions in the table A bellow

Table A: Use proportion of different types of gas in each region.

<table>
<thead>
<tr>
<th>Type of cooking gas</th>
<th>Asturias</th>
<th>Gipuzkoa</th>
<th>Sabadell</th>
<th>Valencia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N  %</td>
<td>N  %</td>
<td>N  %</td>
<td>N  %</td>
</tr>
<tr>
<td>Network gas</td>
<td>27 11.8</td>
<td>62 11.8</td>
<td>309 56.8</td>
<td>235 33.4</td>
</tr>
<tr>
<td>Bottle gas (butane)</td>
<td>16  7.02</td>
<td>20  3.8</td>
<td>24  4.41</td>
<td>219 31.1</td>
</tr>
<tr>
<td>Electric</td>
<td>185 81.1</td>
<td>440 83.5</td>
<td>206 37.9</td>
<td>245 34.8</td>
</tr>
<tr>
<td>Other</td>
<td>0  0</td>
<td>5  0.95</td>
<td>5  0.92</td>
<td>5  0.71</td>
</tr>
</tbody>
</table>

We made the analysis in the manuscript with the exposure variable with two categories: “electric or gas” considering butane and network gas together because we hadn’t observed differences in results (see table B bellow) and the proportion of use of butane is very small in Gipuzkoa.

Table B: Adjusted association of exposure to network gas and bottle gas for cooking during pregnancy and respiratory problems during 1st year of life in a birth cohort. Spain

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>(95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRTI</td>
<td>0.99</td>
<td>0.78</td>
<td>1.26</td>
</tr>
<tr>
<td></td>
<td>0.95</td>
<td>0.68</td>
<td>1.33</td>
</tr>
<tr>
<td>Wheezing</td>
<td>0.89</td>
<td>0.70</td>
<td>1.13</td>
</tr>
<tr>
<td></td>
<td>0.98</td>
<td>0.69</td>
<td>1.37</td>
</tr>
<tr>
<td>Cough</td>
<td>0.91</td>
<td>0.65</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>0.87</td>
<td>0.53</td>
<td>1.41</td>
</tr>
<tr>
<td>Otitis</td>
<td>1.09</td>
<td>0.85</td>
<td>1.38</td>
</tr>
<tr>
<td></td>
<td>1.02</td>
<td>0.73</td>
<td>1.43</td>
</tr>
<tr>
<td>Chestiness</td>
<td>0.93</td>
<td>0.74</td>
<td>1.17</td>
</tr>
<tr>
<td></td>
<td>1.01</td>
<td>0.74</td>
<td>1.38</td>
</tr>
</tbody>
</table>

*Adjusted variables: (LRTI) region, country of origin, parity, smoke during pregnancy, season of birth, parents allergic antecedents, sex, gestational age, cleaning frequency, day-care attendance, pets, child age at questionnaire administration; (wheezing) region, social class, parity, smoke during pregnancy, global passive tobacco exposure at pregnancy, parents allergic antecedents, sex, breastfeeding, day-care attendance, pets, child age at questionnaire administration ; (cough) region, social class, weeks of gestation, day-care attendance, child age at questionnaire administration ; (otitis) region, educational level, home passive tobacco exposure at pregnancy, parents allergic antecedents, sex, day-care attendance, pets, child age at questionnaire administration ; (chestiness) region, mother's age, parity, smoke during pregnancy, sex, day-care attendance, pets, child age at questionnaire administration.

The discussion 3rd paragraph addresses effect modification by diet on otitis/gas cooking. Much of the discussion is about the potential effects of the diet on lung anti-oxidant defence. Evidence that acute otitis is accompanied by low oxidant levels/oxidative stress is given - but this is not quite the same as saying that low antioxidant levels lead to more otitis. I think this paragraph could be restructured to explain the proposed biological mechanisms more fully.

*Following reviewer comments we had rewrite this paragraph explaining the proposed biological mechanism more in depth.*
Final two sentences of last paragraph on page 13 don’t really make sense. I think the point is being made that ‘exposure’ to gas derived UFP is occurring throughout the house.... (?).... and that therefore getting fixated on exposure measures that are kitchen based is inappropriate (?). The sentence – ‘By being aware of this lack of accuracy ....’ is contradictory when it states ‘misclassification bias is non-differential’. By definition bias is differential (??). .....perhaps authors mean ‘misclassification of exposure is non-differential’ (?)

Following reviewer comments we had rewrite this sentence as misclassification of exposure is non-differential.

Minor Essential Revisions

Introduction – author states that WHO say that having a gas cooker leads to an increase of 28ug/m3 in indoor NO2. In the document quoted the WHO are merely quoting another study, - the original derivation of this figure came from the Hasselblad meta-analysis many years ago when he combined gas as a proxy

Following reviewer comments we have cited also the original meta-analysis of Hasselblad.
2 Reviewer’s report

Title: Prenatal exposure to cooking gas and respiratory health in infants is modified by tobacco smoke exposure and diet.

Version: 1

Date: 11 July 2013

Reviewer: Tanya Turnovska

Reviewer’s report: The author must respond to these before a decision on publication can be reached:

1. The positive subordination between gas cooking at home during pregnancy and respiratory problems in children during their first year of life is pointed out, but the survey data refer only to gas cooking during pregnancy (1st and 3rd trimester, page 7). The more realistic possibility, namely that respiratory problems during the first year of child’s life are due to ongoing pollution caused by gas cooking is excluded in practice. Even if we assume that in this case NO2 is marked as gas pollution indicator, the impact of the remaining pollutants may not be ignored. In my opinion, the work will be much more persuasive if it included even a limited number of real measurements.

We included cooking during pregnancy (3rd trimester). As we indicated in page 14, “due to the high proportion of homes that maintain the same type of cooking range from pregnancy to the first year (91.2%), only 3.3% changed from electric to gas and 5.5% changed from gas to electric, it is impossible to distinguish if the relationship found is related only to prenatal exposure or only to postnatal exposure or both”.

In a subsample of 352 child of the Valencia cohort NO2 and BTEX were measured indoor and outdoor during 15 days (Esplugues A, 2010 a, b and 2011)*. We found relation between the square root of the indoor NO2 levels observed and the use of a nonelectric cooking range that led to higher exposure levels; in the case of natural gas, the increase was 0.51 (95% CI: 0.26, 0.77), while for butane gas, it was 0.59 (95% CI: 0.33, 0.86), and for propane gas, it was 0.67 (95% CI: 0.23, 1.57). With this data we had studied the relation with respiratory health and our results indicate that exposure to outdoor, but not indoor, NO2 during the first year of life increases the risk of persistent cough. (Esplugues A, 2011). Regarding to BTEX we obtain an unexpected finding. During the study period, homes with an electric cooking range had higher BTEX concentrations than homes in which gas was used to cook. Although this relationship is the opposite of that expected, it is similar to that reported between toluene and the use of electric heating as opposed to gas heating in the NHANES study carried out in the United States (Symanski et al., 2009). Now is ongoing a new manuscript that analyze the relation of BTEX with respiratory health, but unfortunately only for this subsample of the Valencia cohort. In this sense the present study with a sample of 2003 children in different regions in Spain have the advantage of reduced random error.


2. The residential environment is specified only as “urban” or “rural”, but there are no data reflecting air pollution monitoring in support of this statement. Why the possibility that rural regions may also be polluted is excluded? Even if they do not have their own sources of pollution they may be influenced by the transfer of air pollutants.

We have not excluded rural region, in fact, due to their different exposure levels that we obtained in previous studies (Estarlich M, 2011)*, we introduced this variable in the adjusted model. Also, use of gas cooking is different depending of type of zone.


3. It is claimed that deteriorated respiratory health in children during the first year is related to the lower consumption of fruits and vegetables by the mother during her pregnancy, but there are no data on the consumption of fruit/vegetable juices and purees by the child during his/her first year - influence which is more likely to have the strongest impact on the obtained results.

We have not available this data, but we consider that might be a high correlation between pregnancy consumption and consumption by the child in their first year.

Furthermore, what makes a strong impression is the significant difference between the relative shares of the exposed persons residing in various regions (table 1). I think that it will be more correct if statistical analyses show comparative results among the regions having a low relative share of gas application at home or if they are focused only on the regions where exposure exceeds 60%.

As we indicated in “results” page 10 “all results by cohort showed no significant heterogeneity ($I^2<50\%$), and because this we used a multivariate analysis with fixed effects for analyze the relationship between exposure variables and respiratory health outcomes. Nevertheless we included here (fig 1 to 5 bellow) results from metaanalysis where the reviewer could see result for each cohort. There are no significant differences between more and less exposure regions.

Fig 1: Association of exposure to gas cooker during pregnancy and LRTI during first year.
Fig 2: Association of exposure to gas cooker during pregnancy and wheezing during first year.
Fig 3: Association of exposure to gas cooker during pregnancy and cough during first year.

Fig 4: Association of exposure to gas cooker during pregnancy and chestiness during first year.
Fig 5: Association of exposure to gas cooker during pregnancy and otitis during first year.

<table>
<thead>
<tr>
<th>Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asturias</td>
</tr>
<tr>
<td>Gipuzkoa</td>
</tr>
<tr>
<td>Sabadell</td>
</tr>
<tr>
<td>Valencia</td>
</tr>
<tr>
<td>I-V Overall</td>
</tr>
<tr>
<td>D+L Overall</td>
</tr>
</tbody>
</table>

Level of interest:
An article of importance in its field

Quality of written English:
Acceptable

Statistical review:
Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests' below