Author’s response to reviews

Title: Maternal occupational exposure and oral clefts in offspring

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Author’s response to reviews:

Reviewer #1:

Comment 1:

The authors of the manuscript mentioned above have respond to the majority of my comments. I agree with the modification done except for the statistical analysis. They authors in the methods indicate that they only variables associated significantly in univariate analysis. I persist that criteria to choose covariates to adjust for may be too restrictive and may lead to residual confounding especially tor the new control group (cf Tables One ). I suggest to include in the multivariate model all variable associated with a p value <0.2 in the univariate analysis (and then to add for the analyse with the non chromosomal malformed group smoking and alcohol during pregnancy and positive family history). At the opposite I am not sure that number of babies/foetus delivered or previous birth are covariates to consider since these covariates may be related to the exposures (I.E several concordant studies reported associations between solvents exposure and sponatenous abortion) and consequently are on the same pathway. Taking into account these last variables may overadjusted the estimates.

To finish in line with my previous comments, I feel much more confident in the analysis with second control group (which is for me better than chromosomal/genetic malformation group).

Answer:
We took into account the comment of the reviewer that all variables with a p-value <0.2 in the univariate analyses, can be included as confounders in the multivariate analyses and redid the analyses. The analyses with the chromosomal malformed control group did not change, because we already included all possible confounders with a p-value <0.2.

We redid the multivariate analysis with the non-chromosomal control group using the confounders we already included (child sex and previous births). In addition, we also included smoking (p-value = 0.47) and alcohol use (p-value = 0.16) during pregnancy and positive family history (p-value = 0.08), as recommended by the reviewer. The table in the supplement (Additional file 2 – Response to reviewers – table) shows crude odds ratios, odds ratio adjusted for child sex and previous births, and odds ratios adjusted for child sex, previous births, smoking and alcohol use during pregnancy and positive family history, respectively. Adding the new confounders did not change the results and conclusion.

Minor comment:

In the abstract First line of the results section : after non chromosomal it is possible to add 'malformed'.

Answer:

We added the word ‘malformed’ in the first line of the results section of the abstract.

Reviewer #2:

Thank you for the work that has gone into these revisions. I have a few minor comments on the revision, however these will not impact the conclusions or essential facts that are already presented, so these can be left to the authors' and editors discretion.

Comment 1:

Page 10, lines 251-255: although results were not statistically significant, stratifying exposure by low vs high was suggestive of a possible dose-response for some chemicals. That is an interesting finding and worth mentioning in the text, as it was in the response to reviewer comments.

Answer:

We rewrote the Result section about the low versus high exposure in according to the response to the reviewer: ‘For exposure categories with high prevalence in this study (‘other solvents’,
organic dust, and gases and fumes), additional analyses were performed for all three exposure intensity categories (no, low, and high). The number of high exposed cases was respectively 10, 11, and 4 cases. The aOR for cases with low exposure to ‘other solvents’ was 1.1 (95% CI 0.8-1.5), and increased to 1.5 (95% CI 0.8-3.0) for cases with high exposure (data not shown in table). For occupational exposure to organic dust the same trend is observed. The aOR increased from 1.3 (95% CI 1.1-1.6) for low exposure, to 1.7 (95% CI 0.9-3.2) for high exposure (data not shown in table). No trend of increased is observed OR for occupational exposure to gases and fumes. However, all ORs did not increase significantly.’ Page 10-11, lines 254-259.

Comment 2:

Page 12, lines 295-296: no other human studies have investigated metals and oral clefts. A number of animal studies have shown associations between cadmium, cobalt, and nickel and oral clefts.

Answer:

We decided to discuss only studies conducted in humans.

Comment 3:

Page 12, lines 309-310: using a JEM (versus expert rater review) would only avoid recall bias if non-malformed controls were used. There is no reason to think mothers of infants with oral clefts would provide more extensive job descriptions than mothers of infants with other sorts of birth defects. I suggest striking this sentence.

Answer:

At page 12, lines 309-310 (in the revised manuscript: page 13, lines 334-337) we compared the JEM with self-reported exposure and concluded that a JEM avoids recall bias. At page 13, lines 310-313 we compared the JEM with industrial hygienists.

Comment 4:

Page 13, lines 317-320: low sensitivity is also due, in part, to inherent variation in tasks (and consequently exposure) within individuals with the same job title. Most JEMs were also derived from either population-based (male and female workers) or all-male populations; previous research has shown that men and women with the same job title tend to perform somewhat different tasks. See, for example, Locke et al Occup Environ Med 2014;71(12):855-64.
Answer:

This is in general an interesting suggestion. However, the JEM we used is originally designed for chronic pulmonary airway diseases (COPD), and is population based (male and female workers).

Comment 5:

I'm still a little concerned about overadjustment, and not entirely confident of the authors' conceptualization of family history (first, because family history is often a predictor of the outcome or an effect modifier, but is unlikely to be a confounder-- how would genetic variants be causally related to exposure?-- and secondly, because I see it as analogous to adjusting cases for one genetic profile and controls for another) but that is not a reason to postpone publication. Competent researchers can disagree on the best manner of analyzing data, so long as the actions the authors took are clearly stated-- and they are in this manuscript. Since the crude and adjusted odds ratios are relatively similar, it is unlikely that these decisions make any difference one way or another.

Answer:

Thank you for your understanding. We agree with you that it would not affect the adjusted odds ratios substantially.