Author’s response to reviews

Title: Pesticide exposure assessed through agricultural crop proximity and risk of amyotrophic lateral sclerosis

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Dr. Philippe Grandjean – Editor in Chief, Environmental Health

2nd revision of manuscript ENHE-D-17-00049 (“Pesticide exposure assessed through agricultural crop proximity and risk of amyotrophic lateral sclerosis”: response to the Editor and the Reviewers

We wish to thank once again the Editor and the Reviewers of Environmental Health for the comprehensive review of our manuscript. We have rerun the analyses and done our best to address the remaining concern of the Editor and the Reviewer, and we believe that the revision satisfies their remark and requirement. We have also updated the literature through July the 1st, eventually adding to the references Vinceti et al. 2017, Cassereau et al. 2017 and Krewski et al. 2017.

Reviewer #1:

Editor's comments: We agree with the reviewer in regard to the overmatching issue. Short of rematching, I encourage you to add a proper discussion of this concern. We normally allow up to two revisions, but in this case we will ask for a third and last revision before an editorial decision is made.

Reviewer #1: I continue to believe that there was a potential for significant bias due to overmatching, my comments follows: issue of overmatching always comes to mind, eg. why was the control not chosen at random from the four provinces of study area instead of being matched precisely to the same province? This may have resulted in overmatching on the exposure of interest, proximity to agricultural exposure to pesticides? I am not sure what you do about this at this point but it should be discussed in the weaknesses and strengths section.

I indicated that there was really nothing to be done as once you have matched on province there is no way to undo this short of choosing a new control group. that being said. I believe this
significant bias needs to be directly stated in the strengths and weaknesses section or it will be open to criticism within the environmental epi community. The authors indicate that they considered the proportion of tillable land was similar between provinces as well as the rates of ALS but they have not specifically stated that the there is a potential for overmatching when a case is directly matched to a control from the same place which may directly nullify any difference in exposure, It doesn't mean this happened but there needs to be an admission that overmatching could have occurred, I would recommend this should be placed in the strengths and weaknesses section before publication could go forward.

We have addressed this remaining issue with some new analyses using Episheet. If overmatching occurred, it would mean that the analysis was affected by nonconfounders that were associated with exposure, leading to completely concordant matched sets. No bias would result with the proper matched analysis, but precision would be lost. However, we found that after matching, the crude analysis that ignores the matching and the stratified analysis that takes the matching into account resulted in the same estimate to three decimal places (see screenshot in the word attachment). Thus, collectively the matching factors were not correlated with the exposure (which follows from these two estimates being the same), and there could not have been any overmatching. We have mentioned this finding in the latest draft of the text, with this sentence:

"Conversely, there was evidence that the variables we used in the study for control sampling and data analyses were not important confounders. In fact, when we computed with the Episheet software a pooled OR of the matched sets conditioned on the matching factors the result was 0.92, and the crude result was also 0.92, indicating that collectively all the matching factors were uncorrelated with exposure and were therefore not confounders in this study."

We are confident that our methodological approach and our addition adequately address the issue raised by the Reviewer.

We are most grateful to the Environmental Health for this new opportunity to submit a revision of our manuscript.

Kind regards,

Marco Vinceti, Tommaso Filippini, Kenneth J. Rothman and Lauren Wise – on behalf of all coauthors