

From: jack mandel [<mailto:jackmandel@yahoo.com>]
Sent: Sunday, November 15, 2015 12:42 PM
To: Breckenridge Charles USGR; Colin Berry; Ellen Chang; SielkenAssoc@aol.com
Subject: Fw: Major Revisions requested EJEP-D-14-00578R2

----- Forwarded Message -----

From: European Journal of Epidemiology (EJEP) <em@editorialmanager.com>
To: Jack S. Mandel <jackmandel@yahoo.com>
Sent: Sunday, November 15, 2015 6:55 AM
Subject: Major Revisions requested EJEP-D-14-00578R2

Dear Dr Mandel,

We have received the reports from our advisors on your revised manuscript, "Association Between Parkinson's Disease and Cigarette Smoking, Rural Living, Well-Water Consumption, Farming and Pesticide Use", which you submitted to the European Journal of Epidemiology.

As you will see, in particular reviewer #4 is not satisfied with your revision. I would like you to address his/her points. I feel that your manuscript could be reconsidered for publication should you be prepared to incorporate major revisions. When preparing your revised manuscript, you are asked to carefully consider the reviewer comments which are attached, and submit a list of responses to the comments.

Please submit your response as separate submission item.

Please note: When uploading your revised files, please make sure only to submit your editable source files (i. E. Word, tex).

In order to submit your revised manuscript, please access the following web site:

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Your username is: Jmandel

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http://ejep.edmgr.com/Default.aspx?pg=accountFinder.aspx&firstname=Jack&lastname=Mandel&email_address=jmandel@exponent.com;jckmandel@yahoo.com

We look forward to receiving your revised manuscript before 15 Jan 2016

With kind regards,
Albert Hofman
Editor in Chief
European Journal of Epidemiology

COMMENTS TO THE AUTHOR:

Reviewer #3: In general, the authors have addressed my previous comments in this revision. I have just the following remaining concerns:

1. In the abstract, the authors report the results as "There was a consistent inverse (negative) association between current cigarette smoking and PD risk. In contrast, associations between PD and rural living, well-water consumption, farming, and use of pesticides, herbicides, insecticides, fungicides, or paraquat were less consistent when assessed quantitatively or qualitatively." This section does not accurately reflect the main results of the study. The authors need to mention that there were significant positive associations between pesticides, herbicides, insecticides, as well as paraquat and PD.
2. In the end of each section in the Results, the authors comment on the plausibility for each of the examined exposures. As judgement of plausibility is more a matter of interpretation rather than an objective result, I would suggest moving these sections to the discussion.

Reviewer #4: - The introduction could be considerably shortened, as it addresses many characteristics (eg, genes) that are beyond the scope of the paper.

- The rationale for comparing the association between pesticides and PD to the association between smoking and PD seems far from clear and rather artificial: these are very different types of exposure and the potential biases involved very different. For pesticides, the main issue is exposure assessment, while for smoking, issues such as reverse causation, confounding by genes or personality are the main ones. I don't see the point of combining these two exposures in the same paper, and the authors should choose whether they want to discuss the association of PD with pesticides or with smoking. The authors conclusion is that "The weight of the evidence does not establish a causal relationship for any variable reviewed", and it is therefore unclear why they include smoking in this paper rather than any other exposure that has been studied in PD.
- Sentences such as "Many or all of these limitations also exist in epidemiologic studies of PD conducted by other researchers in subsequent years", "The results are inconsistent for rural living (Figure 3)", "Rural living, well-water consumption and farming lack specificity", "The results lacked specificity or biological plausibility and neither the biological gradient nor the latency period until PD diagnosis following pesticide use was adequately assessed", "Although the overall meta-analysis RRs were positive, however, estimates from individual studies were considerably less consistent than those for cigarette smoking", are vague, debatable, and not contributive.
- I am not convinced by the approach used by the authors to classify studies into high and poor quality studies. They have developed their own method of quality assessment, but I am not convinced that some of the items included (especially the incident/prevalent type of cases) is particularly relevant for PD given the long disease course and the fact that pesticides have not been shown to be associated with a worse or better prognosis. As other approaches are available, the reader is left with the question of why developing quality criteria specific for this study.

- "We did not combine the attributes into a single scale as others have done because we could not be certain that any specific study feature would necessarily result in a "better-quality study." : again, it is unclear why the authors do not follow standard approaches. Based on the criteria listed, it seems fairly simple to assess study quality.
- The figures present only fixed effects estimates. Why not present random effects estimates?
- My understanding is that random effects estimates should be preferred in presence of heterogeneity. The authors present both fixed and random effects estimates which considerably complicates the reading and does not provide a clear message because they do not seem to decide which one is more appropriate. I suggest using random effect estimates when there is evidence of heterogeneity and fixed effects when there is not; this will allow the authors and the readers to reach a conclusion in a clearer way. As there seems to be considerable heterogeneity for most exposures, the authors should probably favour random effects estimates over fixed effects ones.
- "Although the hypothesis that paraquat might cause PD is highly specific, there is disagreement concerning biological plausibility (67)": I have read carefully this reference and I have failed to find any sentence that supports this statement. On the contrary, this paper points that there is considerable evidence, both epidemiologic and toxicologic, pointing towards a role of paraquat.
- table 3: tier 2 studies are not presented
- Table 3 : I have trouble understanding why the random RR for pesticides goes from 1.56 before adjustment for publication bias to 1.11 after adjustment even though there is no evidence of significant publication bias. This seems like a very strong impact. Do the authors know why adjustment for publication bias sometimes increases the strength of the RRs and sometimes decreases it? Are there other approaches to address this issue?