
From: Breckenridge Charles USGR <charles.breckenridge@syngenta.com>
Sent: Tuesday, December 02, 2014 8:00 PM
To: jack mandel
Subject: RE: Major Revisions requested EJEP-D-14-00578

Great. I will think about this overnight and call you tomorrow.

CBB

From: jack mandel [mailto:jckmandel@yahoo.com]
Sent: Tuesday, December 02, 2014 1:25 PM
To: Breckenridge Charles USGR
Subject: Fw: Major Revisions requested EJEP-D-14-00578

On Tuesday, December 2, 2014 7:59 AM, European Journal of Epidemiology (EJEP) <em@editorialmanager.com> wrote:

Dear Dr Mandel,

We have received the reports from our advisors on your 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, the reviewers have substantial reservations about your manuscript. In fact, one of them suggested to reject the manuscript as it stands. I will offer you the opportunity to make a revision, but we will send it again for review and you should not view this a pre-acceptance of the manuscript.

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.

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

<http://ejep.edmgr.com/>

Your username is: Jmandel
Your password is: mandel7327

We look forward to receiving your revised manuscript before 03 Feb 2015

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

COMMENTS FOR THE AUTHOR:

Reviewer #1: The manuscript "Association between Parkinson's disease and cigarette smoking, rural living, well water consumption, farming and pesticide use" by authors Breckenridge et al reports meta-analyses based on a systematic literature search regarding the mentioned risk factors in related to PD.

The study is comprehensive and the methods are sound. However, I have some concerns:

1. Significant heterogeneity is found for almost all risk factors examined (see table 2), but the authors make no effort to explain this heterogeneity. As the authors themselves mention, examining sources of heterogeneity among studies is much more informative than just computing a pooled estimate. I suggest that the analyses are complemented by analyses exploring different sources of heterogeneity. This would require systematic review of specific studies (preferably by at least two independent investigators) with regard to aspects of study design and quality, but would increase the scientific value of the manuscript substantially.

2. In the results and table 2, I find the focus on "Proportion of ORs that were not statistically significant/significantly decreased/significantly increased" quite irrelevant. This way of looking at the data put equal weights on the different studies and entirely ignores specific aspects, including statistical precision, a very important aspect.

3. In table 3, pooled estimates (I assume that is what is tabulated, but a bit unclear) differ considerably between previous meta-analyses and the present study for some exposures, notably Paraquat ever versus never, but estimates are lower in the present study for rural living, well-water, farming, herbicides, fungicides and insecticides exposure. What is the reason for this? A more thorough discussion of these results is needed.

4. The value of Table 4 is questionable. It just presents citations from different reviews and meta-analyses on the topic, selected by the authors. I suggest omitting this table.

5. Last, the authors all have a clear conflict of interest, and I think a more balanced discussion is needed in several places. For example, in the abstract: "The weight of evidence indicates that there is no causal relationship for any variable reviewed other than cigarette smoking. There may be risk factors for PD associated with a rural life style, farming, pesticide use or well water consumption that are related to PD, but the studies to date have not identified such factors." The authors need to acknowledge that the association between pesticides and PD might indeed be causal.

Reviewer #2: In this paper, the authors report the results of meta-analysis of the relation between Parkinson's disease (PD) and several exposures related to agriculture. For comparison, they also report the results of a meta-analysis of the relation between PD and cigarette smoking. They conclude that "There is a consistent negative association between current cigarette smoking, the duration and the number of cigarettes smoked and the risk of PD. In contrast, there are inconsistent associations between PD and rural living, well water consumption, farming, and pesticide use, when assessed quantitatively or qualitatively. The weight of evidence indicates that there is no causal relationship for any variable reviewed other than cigarette smoking."

These conclusions are mainly drawn based on a strict application of the Bradford-Hill criteria. There are several interesting papers on Bradford-Hill criteria that should be of interest to the authors of this paper (see for instance <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC524370/>). The main point is that Bradford-Hill criteria have often been applied as a checklist, although they were by no means intended to be used in this way by Hill himself, and that there are other issues that should be considered, in particular those that are specific to the exposure under investigation.

There have been several meta-analyses on the relation between PD and pesticides in the recent years, and in my view, the present paper does not add anything new to the previous studies whose main conclusions were that additional studies with improved methods of exposure assessment are necessary. Previous meta-analyses included all relevant exposures, examined potential sources of heterogeneity, identified areas for which additional data are needed, and made recommendations for future studies. In order to add to the evidence and to better understand this relation.

In reviewing the evidence and selecting the exposure variables for the analyses, the authors make key choices that are not discussed and that have important implications. In particular, they do not select pesticides overall as an exposure variable, whereas this is the exposure that has been most consistently studied; instead, they focus on the categories of herbicides, insecticides, and fungicides that were not assessed in many of the studies and that are more difficult to evaluate. Please note that in their conclusion, cited above, they only refer to pesticides overall, while they did not include this in their assessment. **It is probably not meaningless that all the authors of the present paper are either consultants or employees of the industry.**

Their strategy of comparing their findings for pesticides to findings for cigarette smoking is clearly not reasonable; these are two very different types of exposures and it is obvious that one is considerably simpler to assess than the other.

Statements such as "The weight of evidence indicates that there is no causal relationship for any variable reviewed other than cigarette smoking" show that the authors are not familiar with the current literature about the relation between smoking and PD: reverse causation and confounding are not dismissed as potential explanations for the inverse association between smoking and PD. This also points to the limits of using the Bradford-Hill criteria in assessing causality. One exposure may well fulfill these criteria, and still whether it is truly causal remains unclear.