Author's response to reviews

Title: Pesticide exposure and risk of Parkinson's disease: a family-based case-control study

Authors:

Dana B Hancock (dana.hancock@duke.edu)
Eden R Martin (EMartin1@med.miami.edu)
Gregory M Mayhew (GMayhew@med.miami.edu)
Jeffrey M Stajich (stajich@chg.duhs.duke.edu)
Rita Jewett (r.jewett@miami.edu)
Mark A Stacy (mark.stacy@duke.edu)
Burton L Scott (scott007@mc.duke.edu)
Jeffery M Vance (jvance@med.miami.edu)
William K Scott (bscott@med.miami.edu)

Version: 2 Date: 4 December 2007

Author's response to reviews: see over
Reviewer 1 (Harvey Checkoway)

Major Compulsory Revisions

1. “The authors do mention these [limitations], but should be more forthright in explaining how a sample of self- or physician-referred prevalent PD cases and patient-referred relative controls may not yield generalizable findings vis-à-vis a more standard sample of newly diagnosed PD cases from a well-defined population source and controls sampled from the same source.”

We have revised the discussion section detailing our advantages and limitations (page 20, lines 1-3) to explicitly state that our cases may not be representative of the general population of PD cases and that our findings may not be generalizable.

2. “Also, the definition of pesticide exposure seems to blur distinctions between occupational and residential exposures…An analysis of separate effects of occupational and residential exposure should be presented…”

In our environmental risk factor questionnaire, we asked participants “Have you ever applied pesticides to kill weeds, insects, or fungus at work, in your home, in your garden, or on your lawn?” However, the source (residential or occupational) of the pesticide application was not recorded as part of this question. We did collect (separately) occupational histories and examined whether sufficient numbers of individuals reported job categories with pesticide exposures (pesticide applicators, farmers, etc), but there were too few individuals with these job histories to be considered separately in the analysis. Thus, we were unable to examine residential exposures and occupational exposures separately. We have inserted a statement to clarify this point on (page 6, lines 23 to page 7, line 2).

Minor Compulsory Revisions

3. “The definitions of exposure variables are not standard and should be altered. Dosage (days/year) should be labeled ‘frequency’; and intensity should be labeled as either ‘cumulative exposure’ preferably, or ‘dose’.”

The recommended changes (‘dosage’ to ‘frequency’ and ‘intensity’ to ‘cumulative exposure’) have been incorporated in the revised manuscript.

Discretionary Revisions

4. “The control group was an admixture of relatives, but perhaps spouse controls could be eliminated (or analyses done without them) since they are not really ‘familial’.”

We are concerned that removal of the spouse controls will reduce our statistical power. Given the composition of our data set, we chose GEE because this method allowed for incorporation of all family members, related and unrelated. GEE requires specification of a correlation matrix to characterize the degree of relatedness between clustered individuals (i.e., individuals from the same family), but GEE is robust to misspecification of the correlation matrix. Even though spouse controls do not have the same degree of relatedness as familial controls, inclusion of spouses is not likely to introduce bias and change the results due to the robustness of GEE.
Reviewer 2 (Giancarlo Logroscino)

5. “The authors should better explain the need to subtract from AAE the mean duration of the disease among cases to calculate the reference age. Is there any problem in this procedure considering the broad range of possible age onset among cases?”

This calculation of the reference age for controls was necessary to give cases and controls comparable exposure periods. We have included a statement to explain the need for this adjustment on page 7 (lines 12-13). Given the population-averaged modeling by GEE, we believe that averaging the age-at-onset among cases for the reference age adjustment among controls is the most compatible adjustment for this method.

6. “Do the authors have any reliability assessment in their study for qualitative and quantitative data of pesticide exposure?”

As requested by the editors, a paragraph has been added to the methods section to give further details of the questionnaire (paragraph beginning on page 5, line 20). There is no reliability assessment of our questionnaire over time, and this is stated in the added paragraph.

7. “The gender distribution appears quite different among controls and cases. Is this important?”

We stated in the methods section of the original manuscript that both sex and age-at-examination were included as confounders in the GEE models examining associations of pesticides and the correlated lifestyle factors with PD. In the results section of the revised manuscript, we have inserted a statement to reiterate the importance of including both sex and age as confounders in GEE models when presenting the sex and age distributions of our data (page 12, lines 9-10).

8. “What was the participation rate among cases and among controls?”

As explained in statements inserted on page 5 (lines 7-13), a sampling frame cannot be established given the referral-based nature of the sample, so participation rates cannot be calculated for the cases. Family-based controls were enrolled based on number of relatives available, their locations, willingness to participate, and enrollment cost. Therefore, there is no simple way to determine the denominator for calculating a participation rate in controls.

9. “It is not evident from the method section how the different strata of duration and intensity were obtained. (For example the stratum of duration of more than 26 years).”

In the previous manuscript, we simply stated that dosage (now called frequency), duration, and intensity (now called cumulative exposure) were divided into tertiles of exposure. We have revised the methods section to thoroughly explain the division of frequency, duration, and cumulative exposure values into the high, middle, and low exposure categories on page 7 (lines 16-21).
10. “Incident/Prevalent bias. Did the authors restrict the analysis to cases with shorter duration of disease?”

As stated in the results section of the revised manuscript (page 12, lines 11-12), only 12% of the cases in this sample reported having PD symptoms for two years or less. Given this, analyses could not be restricted to cases with shorter duration of disease while maintaining sufficient statistical power. We have included a statement in the discussion section (page 20, lines 5-7) stating that prevalent case bias could not be controlled in our analyses due to the predominance of prevalent cases with longer duration in our sample.

11. “Did the authors separate childhood exposure and adulthood exposure for the analysis of farming and well water exposure?”

Tables 4 and 5 show the lack of significant associations of PD with farming and well water exposure when considering both childhood and adulthood exposures. Analyses were also conducted considering only adulthood exposures, but the removal of childhood exposures did not alter the lack of significant patterns for farming and well water exposures as stated on (page 15, lines 20-21 and page 16, lines 9-10). Childhood exposures were not examined separately.

12. “The authors should expand more the discussion on the importance of negative results in the stratum of subjects with positive family history and positive results in the stratum of subjects with negative family history.”

In the original manuscript, the implications of the differing patterns of association by family history were outlined in both the discussion and conclusion sections. We have revised these two sections so that the implications of the differing association patterns are presented in greater detail in the discussion section (page 16, line 21 through page 17, line 8) and then reiterated in the conclusion section (page 21, lines 11-16).
Reviewer 3 (George Mellick)

Discretionary Revisions

13. “It might be useful to learn more about the geographical and ethnic background of the sample investigated…this sample may be highly representative of a more rural lifestyle and extensive use of pesticides. Is this a fair comment?..”

After comparing our exposure frequencies of rural living factors and pesticide application to those of other case-control studies conducted in the United States and internationally, our sample does appear to be highly representative of a more rural lifestyle and extensive use of pesticides. We have inserted a statement in the discussion section (page 18, line 22 to page 19, line 2) to acknowledge this feature of our study. However, cases and relative controls may be overmatched on exposure history thus reducing the power of a family-based sample.

“...In terms of ethnic background, is any information available on the distribution of the background of individuals in the sampled region?...”

Participants in our study provided their self-reported race/ethnicity. We have no further information on their specific ethnic backgrounds.

14. “Some additional information about the structured telephone questionnaire would be beneficial to readers. Is this instrument freely available to other researchers? Has the instrument been examined for repeatability and reliability in PD patients and is this different to that seen in the family controls?...”

As requested by the editors, a paragraph has been added to the methods section to give further details of the questionnaire (paragraph beginning on page 5, line 20). There is no reliability assessment of our questionnaire over time, and this is stated in the added paragraph. A copy of the questionnaire has also been provided as an additional file to the revised manuscript.