Reviewer's report

Title: A Case-Control Study of Occupational Magnetic Field Exposure and Alzheimer's Disease: Results from the California ADDTC

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Reviewer: Curtis Noonan

Reviewer's report:

General

This paper presents the findings from a case-control study that was conducted from among Alzheimer's disease (AD) cases and non-AD control identified through multi-site collaborative treatment centers. The authors describe elevated odds ratios (ORs) for magnetic field (MF) exposure and AD. Overall this paper presents a study which is well described and rather straightforward with regard to methodological approaches and data analysis. The authors have adopted a strategy which matches their previous studies from a similar case population base.

The large majority of the paper is devoted to a lengthy discussion of past studies and proposed biological hypotheses to support the present findings. However, some of the literature review approaches and comments raise concerns that the heterogeneity of findings from previous studies was not objectively presented. Also, at several points this discussion runs the risk of over-interpreting the findings of the present study by using this data to reflect on the validity of other studies. Below are some minor comments on the methodological and data presentation portions of the paper and several comments on the discussions and interpretations offered by the authors.

In summary, this study's findings are of sufficient value to warrant presentation with minor changes to Methods/Results, but the concerns described below with regard to the Discussion should be addressed.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Comments on Methods/Results:

1. There appears to be some different findings when the multivariate models include age at onset versus age at exam (page 9 and Table 5). The failure to resolve these differences and the presentation of several models suggests that the model building strategy may be flawed or the authors are not confident with the interpretation of these two variables. The authors could explore other model building approaches and evaluation of goodness of fit or other criteria. In either case, there could be some discussion of why it was necessary to include both options as the "final" models and what the differences between the models suggests.

2. Why evaluate "high" MF and "high/med" MF? Separating by High Med and Low (as in Table 3) would be more appropriate for describing dose-effect trend.

3. Occupational information was reported on the ADDTC data form. It is unclear who would have provided this information, presumably next-of-kin for AD patients. Was it different for non-dementia patients? Also, the form apparently requested "primary" occupation and a short description of the tasks carried out. It would be informative to know what proportion of the patient records included this additional description of job tasks. Was this information differential with respect to who was reporting this information or with respect to case/control status?

Comments on Discussion:

4. The above concerns regarding occupational data are raised in light of the author's decision to disregard several studies in the discussion because they were based upon death certificate reporting of occupation. It is unclear from the data presented whether or not reporting of "primary" occupation offered more precision or accuracy than that reported on death certificates. It appears that detailed occupational histories were not taken by ADDTC, thus reporting of primary occupation by next-of-kin at
ADDTC may have resulted in exposure data quality and precision similar to reporting of such data by next-of-kin on death certificates. For example, the predominant occupation for High MF exposure in this study (75% of High MF cases and 100% of High MF controls) is “seamstress/clothing cutter/dressmaker.” Similar resolution for these occupations can be found in occupational codes used on death certificates. The studies by Savitz et al. and Noonan et al. did not report on these occupations because they were focused on male cases/controls and did not have adequate numbers of such occupations in their data set.

5. There are also inconsistencies between the studies that were excluded from the discussion; then some, but not all, of the studies were discussed in subsequent paragraphs and presented in Tables 6 and 7.

6. The authors’ state that 4 previous studies had higher proportions of M/H exposures than the present study and the previous two studies by the same authors. It does not necessarily follow that these 4 previous studies suffered from misclassification bias resulting in bias toward the null. It is expected that there will be variation in exposure distributions between studies which consider different study populations and different exposure assessment methods, but these observations cannot be used to infer validity for the present study, or by contrast to argue against validity for selected other studies.

7. While the authors make the claim that the proportion of M/H exposures between the two ADDTC studies is different, it is not clear from the data presented if these proportions are significantly different, nor is it readily apparent whether or not this is important or relevant in interpreting the present study (see also comment above).

8. The meaning of the following statement is not clear: “In the two studies, the 95% CIs greatly overlap.” This is not the appropriate way to interpret CIs from two independent studies. If the authors are interested in providing a summary measure of the two studies, they should consider a pooled analysis.

9. Page 16: discussion on Feychting et al. the reviewer has the same concern (expressed above) about inferring exposure misclassification by looking at differences in exposure differences between Feychting et al. and the ADDTC studies.

10. Page 16: discussion on Graves et al. there is a confusing contradiction in the discussion of this study. First, overall exposure could be quite low. Second, An unknown number of subject, classified as having experienced MF exposure, would not have been so classified in other studies. This contradiction should be resolved. More importantly, the reviewer does not understand what point is being made here.

11. In the same discussion of the Graves et al. study, the authors indicate that for the Sobel et al. studies and the current study, occupational information most likely related to the last occupation. This is the first mention of this assumption, and it is somewhat questionable. ADDTC data was collected on primary occupation (page 7) which is, not necessarily, the same as last occupation.

12. Page 19: review of Qiu et al. similar comments as above regarding proportion of exposed subjects.

13. For discussion of Noonan et al. (22), the numbers appear to be inverted for AB(1-42) and the AB ratio by high and low quartile of MF exposure.

14. Presentation of both CIs and p-values in the text, as well as Tables 4, 5, and 7 is redundant. Of the two, CIs are far more informative. For Table 3, p-values would be more informative that “NS.”

15. Section on Seamstresses (page 20-21) Given the apparent heterogeneity of findings with regard to MF studies and the apparent consistency with regard to seamstress occupation as a risk factor for AD, is it possible that another seamstress-associated exposure is more etiologically relevant than MF (e.g., vibrations, repetitive motion, limited mental exercise/problem solving, clothing dyes).

16. The Discussion ends somewhat awkwardly with a brief discussion of MF Exposure and Vascular
Dementia and a brief discussion of Smoking. Although these topics are tangentially related, in this reviewer’s opinion they are speculative and distract from the main focus of the present study. Indeed, the speculation that the effect of smoking on AD is different depending upon MF exposure (acting through melatonin), suggests that the authors should have evaluated MF as an effect modifier when evaluating smoking in the present study.

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No

**Declaration of competing interests:**

I declare that I have no competing interests.