Author's response to reviews

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

Authors:

Zoreh Davanipour (zdavani@aol.com)
Pey-Jiuan Lee (peylee@usc.edu)
Eugene Sobel (sobel55@earthlink.net)

Version: 2 Date: 18 August 2006

Author's response to reviews: see over
The page numbers specified in the review have been altered to reflect the current page numbers. Changes have been highlighted in green. Highlights in yellow are text changes we made when re-reading the manuscript, but not in response to specific reviewer comments.

Review by Dr. Joseph Bowman

There were no “major compulsory revisions”.

Minor Essential Revisions

1. We have changed the title to include the full meaning of ADDTC.

2. We have changed “extremely low frequency” to “power frequency” on p. 4, 2\textsuperscript{nd} para, line 2.

3. We have added “and Système International d'Unités” to p. 8, line 6.

4. We have changed “M/F” to “MF” on p. 12, para 1, line 1.

5. The section on pp 26-27 on smoking and Alzheimer's disease has been rewritten. Two references have been added.

6. The sentences with the two uses of “result” have be altered (page 27).

Discretionary Revisions

1. We have not changed lines 6-7 on p. 21.

2. We have deleted “certainly” in Item #3, p. 25.

3. We have added “(perhaps not always in the pilot seat)” to “aviator/pilot” in Table 2 to explain our reasoning that perhaps the 6 subjects some less exposed to “pilots”.
Review by Hans Kromhout

Combination of the specific case-control study with a somewhat detailed literature view

Professor Kromhout states that we should separate the case-control study from the literature review. We obviously did not think so. Most papers review previous work in a rather cursory manner, treating studies essentially equally. We feel strongly that the studies which used non-expert diagnoses (e.g., death certificates) for cause of death are significantly biased towards the null hypothesis (no association) for the study of Alzheimer’s disease (AD) and magnetic field (MF) exposure due to a high rate of false “positive” diagnoses. The use of death certificates and other governmental databases for the determination of occupation for purposes of classification of magnetic field exposure is also a source of bias, but probably not as important. We think that we stated this rather clearly in our manuscript.

The occupational data for our study were collected as part of the “usual” information on occupation collected: job title and a short description of tasks. In fact, we needed to photocopy the original information because the occupation listed on the public use tapes were already classified according to a common government (U.S. Census Bureau) classification scheme. Use of this classification scheme for determination of occupational MF exposure would have been completely inappropriate. We certainly acknowledge that the information related to occupation is not the data we would have collected had we been able to design a study *de novo*.

We also thought that because BMC Neurology in an online journal, a longer paper would be acceptable. If the editor(s) request that we separate the case-control study from the literature review for separate publication in BMC Neurology we will certainly do so. Professor Kromhout does not mention the discussion of our hypotheses. We do think, however, that including these three components in one paper is best.

It appears that Professor Kromhout thought that we had designed the study components related to case-control sample size determination and subject ascertainment. We have reviewed our write up and attempted to make it clear that we used all the subjects that had been diagnosed by the neurologists at the California Alzheimer’s Disease Diagnosis and Treatment Centers from which data were available to us. We have added to the descriptions of the exposure assessment and the analysis methodologies.
We suggest that it may be appropriate for BMC Neurology to allow Professor Kormbrou the opportunity to concurrently publish a critique of the paper, with a response from us.

Major Compulsory Revisions

In addition to Professor Kromhout’s misreading of the study design (Item 1, below), we have a fundamental disagreement with his methodologic comments (Items 2 and 3, below). Furthermore, we do think that this manuscript is an appropriate place for an “entire review of the literature”. Such a review is badly needed. However, as we stated above, if the editors believe we should have separate manuscripts (in BMC Neurology), we will certainly comply.

1. Professor Kromhout writes that we selected cases and controls from various hospitals. This is incorrect. As we wrote – and have hopefully made clearer (pp. 5-6) – we used the data available from the data coordinating center for 8 ADDTC centers through 1998. Thus, we did not recruit any subjects to participate in our study and therefore there is no question about a response rate. We a priori determined that ADDTC subjects with a diagnosis of multi-infarct dementia or mixed AD and multi-infarct dementia were not eligible for inclusion in the study for reasons explained in the manuscript.

There were 1763 subjects with a diagnosis of definite or probable AD and 553 subjects with a diagnosis other than AD, mixed AD or multi-infarct dementia, thereby making them eligible for inclusion in the study as controls. Table 1 clearly specifies all the diagnoses of these 553 subjects. Of these subjects, 1501 cases and 396 controls had occupational information. The reasons for the missing occupational information are not known with certainty, but surely have nothing to do with whether or not a subject’s occupation had low, medium or high magnetic field exposure. Most likely the reasons include not considering “housewife” as an occupation, and lack of knowledge of the informant, if the subject was considered too demented to respond properly. Thus, the missing occupational information would not bias the results.

It may be unusual for there to be “so few controls relative to the number of cases” in hospital-based case-control studies, as stated by Professor Kromhout. But this is primarily because the number of available cases is usually limited and controls are more plentiful. The rule of thumb is to ascertain as many cases as feasible and use, if financially possible, up to twice as many controls. Because we used an existing data set for the study, we did not have the ability to recruit additional controls.

In any case, there is no methodological or theoretical problem with having more cases than controls. With our total sample and the prevalence of medium to high occupation MF exposure among the controls, the power to identify a true odds ratio of 1.5 or greater is over 90%, using a significance level of 0.05.
Therefore, there is no adverse consequence of having 3 times as many cases as controls. We will include such a statement, if the editors desire. However, we are confident that nearly all epidemiologists and clinicians will realize this.

2. Conducting subgroup analyses is problematic, particularly because of the small percentage (3.8%) of MF exposed female subjects. However, we have added univariate analyses of MF for men and women separately. See the section on univariate analyses (pages 10-11) and Table 4.

The multivariate logistic regression procedure, with forward stepwise variable inclusion, is the standard and accepted analytic methodology for odds ratio model building. It would therefore be up to Professor Krombout to demonstrate that in this situation such a methodology is inappropriate.

It should also be noted that the univariate and multivariate OR estimates for MF exposures are nearly identical. This provides strong evidence that the effect of MF exposure is independent from the other variables.

In short, we believe that Professor Krombout’s argument is incorrect.

3. The assignment methodology we used has been used in numerous studies. It is, in fact, based on exposure assessments. The JEMs (Job Exposure Matrix) are based on measurement of only a very few subjects in specific occupations and are clearly subject to great error. As we stated in the manuscript, hopefully now with increased clarity, we chose occupations as exposed when most of the workers have exposure above 2 mG or intermittently above 10 mG. We did not classify occupations as exposed when the estimated average exposure (geometric mean) was above 2 mG because this procedure classifies a substantial proportion of workers as exposed when, in fact, their mean exposure is below 2 mG.

In addition, we have used the exact same exposure methodology in two (2) earlier studies. It seems to us that the use of the same exposure methodology is a good idea. At worst, we can argue that work in the occupations we have chosen for M/H MF exposure is a risk factor for Alzheimer’s disease. Furthermore, the only known commonality of these occupations is MF exposure. For example, there are no known chemical exposures common to the occupations. The use of differing JEMs in studies is akin to a Tower of Babel.

4. We did use the occupational tasks to insure that the occupation as listed on the ADDTC form was appropriate for use of the exposure assessment data collected by Bowman et al. [7] and Hansen et al. [8]. We have added material (p. 8, lines 6-12) to make this clearer.
The page numbers specified in the review have been altered to reflect the current page numbers. Changes have been highlighted in green. Highlights in yellow are text changes we made when re-reading the manuscript, but not in response to specific reviewer comments.

Review by Curtis Noonan

Major Compulsory Revisions

Comments on Methods/Results

1. Age-at-exam is a variable presumably with very little error. On the other hand, onset is a concept which is very difficult to define. There is no agreed upon definition of onset and it is certainly mostly in the eyes of the beholder. Age-at-onset is clearly a retrospective determination. Thus, age-at-onset is a variable which has significant variation in meaning and error in determination. One the other hand, age-at-onset has more relevance than age-at-exam. The timing of the exam with respect to the stage of dementia is certainly variable, depending upon several family parameters, including finances, insurance, availability of care.

   It is our opinion that there are no important differences in the odds ratio estimates of MF exposure or the significance levels when the age-at-exam or age-at-onset variables are included. We simply modeled both age variables for completeness.

   We have added a few sentences to explain the use of each age variable. The addition is the 2nd paragraph of the Statistical Analysis subsection (p. 9).

   The multivariate model point estimates of the MF exposure odds ratio are very close to the univariate point estimate. We see no reason to think that the model building strategy may be flawed. We also have little interest in interpretation the results for age-at-onset and age-at-exam. Their inclusion in the model did not materially affect the variable of interest, namely MF exposure.

2. We evaluated high and medium/high MF exposure separately because those are the two exposures of primary interest to us. We have added trend information for each sex separately and for men and women combined. These additions can be found in the first full paragraph on page 11 and in Table 4. There were significant trends for the men and for the men and women combined.

3. The occupational information was reported by the person who accompanied the subject to the ADDTC or, when the dementia was mild or non-existent, presumably the subject. Only 3 of the controls were non-demented (Table 1). The person reporting the occupation and tasks is not identified on the ADDTC form. Tasks were always provided when occupational title was provided. As stated on pp. 9-10
paragraph of Background section), 85.1% of the cases and 71.6% of the controls had occupational information. Because we do not know who reported the information, we cannot answer the last question: was the information differential based on who reported the occupational information.

Comments on Discussion

4. We have revised the statement (p. 13, paragraph 1) concerning studies eliminated from the discussion. The wording was admittedly confusing at best. We eliminated from Table 7 and from the discussion of odds ratio estimates of the risk of AD associated with occupational MF exposure those studies which used death certificate or other non-expert databases for the identification of AD cases. Non-expert diagnosis of AD as the primary or secondary cause of death is notoriously bad – leading to a high rate of false positives. (There are also false negatives, but that does not greatly bias odds ratio estimators towards 1.) All the eliminated studies used coded death certificate occupational information or other large databases for the determination of occupation. We did not eliminate these studies from Table 6 and the discussion of occupational MF exposure because we thought their inclusion strengthened our point about variation in the definitions of MF “exposure” and subsequent variation in the percentages of “exposed” subjects.

5. See 4, above.

6. We did not intend to imply that there was necessarily significant misclassification in the studies with higher proportions of M/H exposures then in our studies presented in Table 6. Rather, we think that the primary reason is the definition of exposure used. We have now written (p. 13, para 1) the following:
   “There is a wide range of percentages, due primarily to variation in exposure definition, use of average or mean job-specific estimates, and secondarily to the use of varying job exposure matrices.”

   The use of job exposure matrices can introduce some misclassification. For example many of these studies use 2 mG as a cut-point. They classify a worker as exposed if the geometric mean job exposure is greater or equal to 2 mG. If the mean is close to 2 mG, then a rather high percentage of workers in fact will have had an exposure less than 2 mG.

   We have removed the discussion of occupational exposures in the text of the subsection, now titled “Death Certificates-Governmental Databases: Alzheimer’s Disease Diagnosis” at the bottom of page 13.

   The next subsection (MF Exposure Assessment Rates and Analytic Results, page 14) clearly states that we believe that the studies with much higher rates of occupational exposure used an exposure definition that resulted in subjects with somewhat lower MF exposure being classified as exposed (2\textsuperscript{nd} para of subsection, page 15).
Our argument is that our exposed group actually had higher exposure to magnetic fields (as a group) than did the studies with much higher rates of exposure. This statement, of course, does not pertain to studies which used only subjects in the electric power industry.

7. We simply provided the exposure rates for the Rancho Los Amigos (RLA) ADDTC (second study) and the other 8 ADDTCs (current study) for informational purposes. In fact the rates of medium/high MF occupational exposure for women are lower in the 8 ADDTCs than in the RLA ADDTC. We have added this to the text on page 16, para 1. The difference is only relevant in the sense that the current papers findings relevant to women are quite unstable because of the small relative frequency of exposure. For example, if one of the seamstresses in the control group had not gone to an ADDTC, the estimated OR for high MF exposure among women would change from 1.9 to 2.8. However, the 2.8 estimate has a p-value of 0.2 (Fisher’s exact test).

8. We were not interested in producing a summary measure (estimate) of the perhaps common OR for the two studies. Our interest was in showing that the ORs from the two studies may be essentially identical. We have conducted a test of equality and have added that to our presentation on p. 17, para 0.

9. We did not state that there was exposure misclassification in the Feychting et al. study. Rather we inferred that their MF exposure methodology classified some occupations as exposed which we did not. It may be a matter of definition or the jobs classified as having ≥ 2 mG exposure (on average) included several for which many of the workers did not have at least 2 mG exposure. We believe that we simply were more stringent.

10. Graves et al. classified a worker as exposed if he/she had “probable intermittent exposures (a few minutes)” above 3 mG. Thus, average exposure could be considerably below 2 mG, for example. We see no contradiction in the two statements provided by Dr. Noonan. This is the only study of which we are aware which has such a lenient definition of MF exposure.

11. We did mention this in the Feychting et al. subsection. However, it should have been mentioned in the initial description of the occupational MF classification. We have added this information on page 7, para 1.

12. On page 8, para 1, we have added a clarification of a likely difference between our exposure algorithm and a usual job exposure matrix (JEM) method. JEMs usually use the geometric mean exposure of a sample of workers over a work day. Thus, occupations with mean exposure a bit over 2 mG, will have a high percentage of workers whose personal exposure is below 2 mG on average. We require that it be likely that workers in medium MF occupation have a geometric mean exposure between 2 mG and 10 mG or regular intermittent exposure above 10mG. The “likely” determination was made nearly 20 years ago and was probably not exactly numerical. However, our classification process is consistent.
Thus, we think that we have lower proportions of exposed subjects because we have fewer occupations which we classify as exposed.

Minor Revisions

13. Thank you for your careful review of our review of your important paper. The inversions have been corrected.

Discretionary Revisions

14. Actually, we think that p-values are more informative than a 95% CI. But we know that many epidemiologists like 95% CIs, so we put in both. We note that the 95% CIs can be easily approximated by using ± SD, provided in Table 3.

15. We think that MF exposure is the most likely factor in the association between sewing and AD. We have considered the exposures you mention, but they do not seem to be very relevant. There is very little vibration and, while motion is certainly repetitive, seamstresses do several different activities at their machine besides sewing. Many jobs have limited mental exercise/problem solving, but that may only make the onset a bit sooner perhaps. Dyes and chemicals vary in different materials and there seems to be no consistency in the materials used by individual seamstresses.

16. We have chosen to leave the vascular dementia and smoking discussion as it is.