Response to Reviewer #4’s Report

1. “There needs to be clear pathways from referral to the centres through to recruitment as cases/controls in the study. Specifically, were all referral that met diagnostic and age criteria included in the study as cases/controls? If not, what were the numbers of cases/controls not included?”

Response On page 7 of the revised text, we state: “All subjects aged 65 or older at their initial ADDTC examination were eligible for this study.”

2. “The authors mention in the results section that 72% of the controls had occupational data compared with 85% of the cases. Is this difference statistically significant. It could be an area of bias.”

Response Our statement was misleading, because many of the subjects seen at the ADDTCs were missing both age-at-initial examination and occupational information. Others were below age 65 and missing occupational information. We have now detailed the situation with missing values (page 10). Among the AD patients, 8.5% were missing age-at-initial examination information and 4.8% were below age 65 at their initial examination. Among the AD patients eligible for study inclusion based on age, only 1.4% were missing occupational information. Among the patients who did not receive an AD diagnosis, 9.2% were missing age-at-initial examination and 16.4% were below age 65. Among the non-AD patients eligible for study inclusion, 1.5% were missing occupational information. Only the percentages of subjects below age 65 are significantly different between the AD and non-AD subjects.

3. “To exclude the potential confounds of women/age/occupation, perhaps the authors could conduct logistic regression analysis for men only in order to determine whether the relationship persists with potential confounding factors in the model.”

Response We note that we made an error when we added separate male and female univariate odds ratio estimates. Dr. Sobel used incorrect data. This error has been corrected in the current version of the paper. The male/female results are essentially flipped, with the females having higher odds ratios. Among females, the OR estimates for medium MF exposure (2.5) and medium/high MF exposure (2.8) are statistically significant. The OR estimate for high MF exposure is 4.6, but is not statistically significant.

We have conducted and included multivariate analyses by gender. The ORs for MF exposure do not deviate materially from the corresponding univariate ORs. That is, there was no change in the OR from “high” to near 1.0. We note, however, that the ORs for high MF, when age-at-onset was used in the multivariate analyses, did change somewhat. For females, the OR dropped from 4.6 to 3.2, while for males the OR increased from 2.3 to 3.5.
For females, the univariate ORs for high and medium/high MF exposure were 4.6 and 2.8. The corresponding multivariate ORs, using age-at-exam were 4.0 and 3.3. Using age-at-onset the corresponding multivariate ORs were 3.2 and 2.9.

For males, the univariate ORs for high and medium/high MF exposure were 2.3 and 1.4. The corresponding multivariate ORs, using age-at-exam were 2.1 and 1.4. Using age-at-onset the corresponding multivariate ORs were 3.5 and 1.3.

OTHER ITEMS NOT SPECIFIC TO REVIEWER #4’S COMMENTS

1. We found a typo – there were 543, not 553, controls.

2. We have re-analyzed the entire study. We found a small error in the determination of age-at-initial examination among subjects over age 100. This led to an increase of one female case (non-exposed), and a minor change in the age-at-initial examination distribution. None of the results were materially changed.

3. Finally, the editors asked that we remove the detailed discussion of previous studies. We have done so by presenting a “traditional” summary of earlier research.

4. We have also added to our discussion of the strengths and weaknesses of the present study.

4. For consistency, we changed ‘women’ to ‘females’ and ‘men’ to ‘males’.