**Supplementary Materials**

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**Figure 1- Schematic Representation of Study Design**

 Study at NIH Study at Johns Hopkins

 1995 2005 2009 2015

MRI

CSF

Clinical /Cognitive

Pib PET

Shown are types of data collected each year for BIOCARD between 1995 and 2016. MRI = magnetic resonance imaging, CSF = cerebrospinal fluid, NIH = National Institutes of Health, PiB PET = Positron emission tomography using Pittsburgh Compound B.

**Section 1 – Reasons for Exclusion of Subjects from Analyses**

Of the 342 subjects with baseline Hamilton Depression Scale scores, subjects were excluded from analyses for the following reasons: 1) subjects had not yet re-enrolled in the study or had withdrawn (n=29); 2) the estimated age of onset of clinical symptoms was determined to be at or prior to baseline, based on the report of the subject and an informant (n=11); 3) subjects were missing follow-up diagnosis (n=2); 4) subjects were missing the baseline cognitive variables included in the analyses (n=21).

**Section 2 – Details of Diagnostic Procedures**

Each subject included in these analyses received a consensus diagnosis by the staff of the BIOCARD Clinical Core at Johns Hopkins. This research team included: neurologists, neuropsychologists, research nurses and research assistants. During each study visit, each subject had received a comprehensive cognitive assessment and a Clinical Dementia Rating (CDR), as well as a comprehensive medical evaluation (including a medical, neurologic and psychiatric assessment). For the cases with evidence of clinical or cognitive dysfunction, a clinical summary was prepared that included information about demographics, family history of dementia, work history, past history of medical, psychiatric and neurologic disease, current medication use and results from the neurologic and psychiatric evaluation at the visit. The reports of clinical symptoms from the CDR interview with the subject and collateral source (e.g., spouse, child, friend) were summarized, and the results of the neuropsychological testing were reviewed (see Albert et al., 2014 for the complete battery).

The diagnostic process for each case was handled in a similar manner. Two sources of information were used to determine if the subject met clinical criteria for the syndromes of MCI or dementia: 1) the CDR interview conducted with the subject and the collateral source was used to determine if there was evidence that the subject was demonstrating changes in cognition in daily life, 2) cognitive tests scores (and their comparison to established norms) were used to determine if there was evidence of significant decline in cognitive performance over time. If a subject was deemed to be impaired, the decision about the likely etiology of the syndrome was based on the medical, neurologic, and psychiatric information collected at each visit, as well as medical records obtained from the subject, where necessary. More than one etiology could be endorsed for each subject (e.g., Alzheimer’s disease and vascular disease). One of four possible diagnostic categories was selected at each visit for each subject: 1) Normal, 2) Mild Cognitive Impairment, 3) Impaired Not MCI or 4) Dementia. The decision about the estimated age of onset of clinical symptoms was determined separately, and was based on responses from the subject and collateral source during the CDR interview regarding approximately when the relevant clinical symptoms began to develop. These diagnostic procedures are comparable to those implemented by the Alzheimer’s Disease Centers program supported by the National Institute on Aging.

Within the context of this study, the diagnosis of Impaired Not MCI typically reflected contrasting information from the CDR interview and the cognitive test scores (i.e., the subject or collateral source expressed concerns about cognitive changes in daily life but the cognitive testing did not show changes, or vice versa, the test scores provided evidence for declines in cognition but neither the subject nor the collateral source reported changes in daily life).

Reference:

Albert M, Soldan A, Gottesman R, McKhann G, Sacktor N, Farrington L, et al: Cognitive changes preceding clinical symptom onset of mild cognitive impairment and relationship to ApoE genotype. Current Alzheimer Research 2014; 11(8):773-784.

**Section 3 – Cox proportional hazard assumption**

The Schoenfeld residual method was used to check the proportional hazard assumptions. None of the models violated this assumption. The p-values from the global tests for the proportional hazard assumption were: 0.89 for the model examining whether HAM-D continuous was significantly associated with time to onset of clinical symptoms of MCI independent of baseline cognition (Table 3, HAM-D continuous), 0.79 for the model examining whether HAM-D >1 vs 0-1 was significantly associated with time to onset of clinical symptoms of MCI independent of baseline cognition (Table 3, HAM-D >1 vs 0-1), 0.94 for the model examining whether HAM-D continuous was significantly associated with time to onset of clinical symptoms of MCI, controlled for baseline cognition (Table 4, HAM-D continuous), and 0.92 for the model examining whether HAM-D ≥1 vs 0 was significantly associated with time to onset of clinical symptoms of MCI, controlled for baseline cognition (Table 4, HAM-D >1 vs 0-1).

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Kaplan-Meier survival curve plot showing development of incident MCI in those with Hamilton Depression Scale (HAM-D) >1 vs 0-1.

**Section 4 – Results of Sensitivity Analysis That Excluded Subjects with a Diagnosis of Impaired not MCI**

|  |  |
| --- | --- |
| Characteristic | Impaired not MCI (N=39) |
|  | N | % |
| Gender, female | 18 | 46.2 |
| Ethnicity, Caucasian | 38 | 97.4 |
|  | Mean | SD |
| Age | 57.9 | 7.7 |
| Years of Education | 17.6 | 2.3 |
| MMSE score | 29.5 | 0.88 |
| Cognitive composite score | -0.22 | 0.64 |
| HAM-D score  | 3.3 | 3.8 |
|  | N | % |
| HAM-D >1  | 22 | 56.4 |

Supplementary Table 1. Baseline participant characteristics of participants in the “Impaired not MCI” group, who had impaired cognition below the threshold for MCI diagnosis.

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | HR | 95% CI | P-value |
| HAM-D continuous |  |  |  |
|  Progression ≤ 7 years | 1.23 | 1.08, 1.39 | 0.001 |
|  Progression > 7 years | 0.96 | 0.81, 1.13 | 0.631 |
|  Cognitive composite score | 0.22 | 0.13, 0.35 | <.001 |
| HAM-D >1 vs 0-1 |  |  |  |
|  Progression ≤ 7 years | 2.36 | 1.03, 5.42 | 0.043 |
|  Progression > 7 years | 0.99 | 0.49, 2.00 | 0.981 |
|  Cognitive composite score | 0.23 | 0.14, 0.37 | <.001 |

Supplementary Table 2. Hazard ratios, 95% confidence intervals and p-values for baseline Hamilton depression scale scores in relation to clinical symptom onset, stratified by progression to MCI or dementia within vs after 7 years from baseline excluding “Impaired not MCI” from “normal” group. Hazard ratios were calculated by Cox regression analysis, and separate models were run for the continuous HAM-D scores and dichotomous HAM-D scores. Models were adjusted for gender, baseline age, education and the baseline cognitive composite score. HAM-D = Hamilton Depression Scale, CI = Confidence Interval, MCI = mild cognitive impairment.