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The BIOCARD Index: A Summary Measure to Predict Onset of Mild Cognitive Impairment

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Abstract

Background—Changes in neuropsychological testing, neuroimaging, and cerebrospinal fluid may precede mild cognitive impairment (MCI). However, these markers are not routinely performed in outpatient clinical visits.

Objective—To evaluate whether a simple clinical index, consisting of questions given to patients and their informants, could predict the onset of symptoms of MCI among cognitively normal individuals.

Methods—222 participants in the BIOCARD study received a detailed history, physical examination, and neuropsychological testing annually. An index was calculated by including questions about memory problems, depression, age, education, history of cerebrovascular disease risk factors, and brain injury, family history of dementia, and the Mini-Mental State examination (MMSE) score. Cox regression analyses were used to determine if this index score was related to diagnosis of MCI.

Results—The BIOCARD Index score mean for individuals who progressed to MCI was 20.3 (SD=2.9), whereas the score for individuals who remained normal was 24.8(SD=2.3), ($p<0.001$), [Hazard Ratio (HR) (Standard error (SE) for subsequent diagnosis of MCI = 0.75 (0.67–0.84), ($p<0.001$)].

Conclusion—Lower BIOCARD Index score predicted symptoms of MCI several years before the MCI diagnosis. The BIOCARD Index can be easily used in clinics to identify cognitively normal older individuals who are at risk for deterioration.

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Keywords

mild cognitive impairment; index; predictor

Introduction

A proportion of older individuals with normal cognition have Alzheimer's disease (AD) pathology, based on autopsy findings ¹⁻³ and amyloid imaging studies ⁴⁻⁶. Recent studies have indicated that individuals with these biomarker changes, known as pre-clinical AD ⁷ are at increased risk for developing cognitive decline. If individuals at risk for progressive cognitive decline could be identified early, interventions such as disease risk factor management and participation in a clinical research trial to prevent progression to the stages of mild cognitive impairment (MCI) or dementia could be provided which may have a therapeutic benefit.

Previous studies following cognitively normal individuals over time have shown that changes in neuropsychological test performance ⁸, cerebrospinal fluid (CSF) biomarkers ⁹ and magnetic resonance imaging (MRI) biomarkers ¹⁰ may precede the onset of clinical symptoms indicative of MCI. However, these tests and markers are not routinely performed in a clinical visit, and they require additional training for administration and application of normative data for scoring or an interventional procedure (lumbar puncture) not routinely administered in a standard clinical evaluation for cognitive impairment.

The current study evaluates whether a simple clinical index consisting of questions related to symptoms, demographics, past medical history, and performance on a commonly used mental status exam given to patients, and questions about symptoms and functional performance given to a patient's informant, could predict the diagnosis of MCI. Unlike prior studies, which have developed clinical risk scores for assessing the risk for dementia ¹¹⁻¹⁴ the current study is the first to our knowledge to evaluate the risk of MCI.

Methods

Study design

The study was conducted within the BIOCARD study which has been described previously ⁸, and was designed to recruit and follow a cohort of individuals with normal cognition who were primarily in middle age. Approximately three quarters of the participants had a first degree relative with dementia by design. The overall goal of the study was to identify variables among individuals with normal cognition that could predict the subsequent development of MCI and dementia due to AD. Study assessments included a comprehensive neuropsychological test battery administered annually, and magnetic resonance imaging (MRI) scans, cerebrospinal fluid (CSF), and blood specimens obtained approximately every two years. ApoE genotype was established for each participant after enrollment. The original study was initiated at the National Institute of Health (NIH) in 1995, and was stopped in 2005 for administrative reasons. In 2009, the National Institute on Aging (NIA) and the National Institute of Mental Health (NIMH) funded a research team at

the Johns Hopkins University School of Medicine to re-establish the cohort, to continue the annual clinical and neuropsychological test assessments, to collect blood, and to evaluate the previously acquired MRI scans, CSF, and blood specimens. In 2015, the collection of both MRI and CSF biomarkers were reinitiated and amyloid imaging was begun.

Participant selection

A total of 349 individuals were initially enrolled in the study. Recruitment was performed by the staff of the Geriatric Psychiatry Branch of the intramural program of the NIMH beginning in 1995 and ending in 2005. Subjects were recruited via printed advertisements, articles in local or national informational lectures, or word-of-mouth.

At baseline, all participants completed a comprehensive evaluation including a clinical history, detailed physical and neurological examination, neuropsychological testing, neuropsychiatric assessments, blood and CSF collection, an electrocardiogram, and MRI scan as described previously⁸. Individuals were excluded from participating if they were cognitively impaired or had significant medical, neurological, or psychiatric disease. The analyses presented here are based on 222 participants of the 286 participants who were alive and enrolled in the BIOCARD study in 2009. 56 subjects were excluded from analyses because they developed symptoms of MCI or dementia at or prior to their visit in 2009.

Neuropsychological test assessment

The neuropsychological test battery performed annually covered all major cognitive domains⁸. The complete neuropsychological test battery is described elsewhere⁸.

Consensus diagnoses

Each participant in these analyses received an annual consensus diagnosis by the research team of the BIOCARD Clinical Core at Johns Hopkins including neurologists, neuropsychologists, research nurses, and research assistants. The diagnosis was established through (1) review of clinical data pertaining to the medical, neurologic, and psychiatric status of each subject, (2), reports of changes in cognition by both subject and informant sources, based on the Clinical Dementia Rating Scale (CDR)^{15, 16} and (3) review of longitudinal cognitive performance across multiple domains. These three sources of data were used to determine whether a participant is impaired. If impaired, the likely etiology of the impairment was identified. The estimated age at which the clinical symptoms began was based primarily on the reports of the subject and informant based on the CDR. We followed the clinical diagnostic criteria in the NIA/AA working group reports for the diagnosis of MCI¹⁷ and dementia due to AD¹⁸.

BIOCARD Index calculation

The BIOCARD Index presented here was based on information acquired as part of the annual assessment described above (see Figure 1). The index included the subject's age and education, and questions to the subject about the presence of memory problems or depression as assessed via the semi-structured CDR interview. A history of cerebrovascular disease risk factors including hypertension, diabetes, hypercholesterolemia, smoking, heart disease, or stroke/transient ischemic attack (TIA), as well as traumatic brain injury were

included based on an evaluation of subject history. Family history of dementia was established. In addition, the Mini-Mental State Examination (MMSE) score of the subject was included¹⁹. Using the CDR, an informant was also interviewed for the presence of memory problems in the subject (such as remembering appointments, or medication use) as well as functional problems for the subject in the performance of finances, shopping, and handling emergencies. The BIOCARD Index score was calculated as the sum of each of the above elements (see Figure 1) with a range of 0–29, and with points obtained for the absence of the above factors.

A modified BIOCARD Index score was also constituted which added points based on the presence of an Apolipoprotein E4 (APOE4) allele to the score. This modified BIOCARD Index score with APO E4 ranged from a score of 0–33 (with the addition of 0 points if a homozygous E4 was present, 2 points if a heterozygous E4 allele was present, and 4 points if a homozygous E4 was not present). The BIOCARD Index score was calculated based on information obtained during the first visit at Johns Hopkins in 2009 or later.

Statistical Analyses

A set of Cox regression analyses (*i.e.*, proportional hazards models) were used to determine if the BIOCARD Index score at the first visit at Johns Hopkins was related to the time to diagnosis of MCI²⁰. Only data from subjects who were cognitively normal at their first visit to Johns Hopkins were included in these analyses. Data from two groups were included, based on their most recent visit at Johns Hopkins: (1) subjects who remained cognitively normal (n=210) and (2) subjects who received a diagnosis of MCI on follow-up (n=12). For individuals with two or more consecutive diagnoses of MCI (including the last visit) the date of diagnosis was defined as the time from their first visit to Johns Hopkins to the first date of the consecutive diagnoses of MCI; otherwise, the date of the last diagnosis was used for the diagnosis of MCI. Individuals with a diagnosis of Impaired not MCI (n=12) were included in the group of cognitively normal subjects; however, the results were the same when these individuals were excluded from analyses. The data were adjusted for left truncation because individuals were required to be symptom free at baseline. We calculated the hazard ratio (HR; *i.e.*, relative hazard) for the BIOCARD Index scores, which indicates the change in relative risk of progression for each one unit change in the predictor. Group differences in descriptive statistics were compared with t-tests for continuous variables or chi-square tests for dichotomous variables, uncorrected for multiple comparisons. All data analyses presented here used R, version 2.14.1.

Results

The demographic characteristics of the individuals in this analysis and the BIOCARD cohort as a whole are shown in Table 1. The mean time of follow-up for all subjects in the analysis was 3.6 years. The mean time from baseline to a diagnosis of MCI for individuals who progressed was 2.2 years (SD=1.0). The demographics of the 12 individuals who progressed to MCI and the 210 individuals who remained with normal cognition are described in Table 2. The 12 individuals who progressed to MCI were older ($p<0.001$) and more likely to have

diabetes ($p=0.008$) and heart disease ($p=0.004$) than the 210 individuals who remained normal.

The BIOCARD Index score mean for individuals who progressed to MCI was 20.3 ($SD=2.9$), whereas the BIOCARD Index score for individuals who remained normal was 24.8 ($SD=2.3$), ($p<0.001$). For both the BIOCARD Index score and the modified BIOCARD Index score (which includes APOE4 status), Cox regression models showed a significant relationship between lower scores and time to onset of MCI, [BIOCARD Index $HR=0.75$, 95% confidence interval, $CI=0.67-0.84$; modified BIOCARD Index with ApoE4 $HR=0.76$, 95% $CI=0.67-0.86$, (both $p<0.001$)] see Table 3. The survival curve for individuals with a BIOCARD Index score above the median compared to individuals with a BIOCARD Index score below the median is shown in Figure 2.

Because age and years of education are known to be risk factors for MCI and dementia, we conducted a sensitivity analysis to test if the BIOCARD Index scores are associated with risk of progression to MCI after removing age and years of education from the scores. For each subject, we recalculated the index score without including points for age and education. A Cox regression model with the re-calculated BIOCARD Index score, baseline age, and years of education as predictors showed that the relationship between lower BIOCARD Index scores and risk of progression to MCI remained significant ($HR=0.81$, $p=0.02$, see Table 3). The modified BIOCARD Index score with ApoE (excluding age and education) had only a trend for an association with a diagnosis of MCI ($HR=0.82$, $p=0.053$). In these Cox models, baseline age and years of education were coded categorically using the same coding scheme as for the BIOCARD Index (*i.e.*, education = 0, 1, or 2; age = 0, 1, 2, 3 or 4), which allows for a direct comparison between the regression results using the Index score with and without points for age and education.

Specific elements within the BIOCARD Index score were examined for their risk of progression to MCI using separate Cox models for each variable. Increasing age ($HR=1.19$, 95% $CI=1.09-1.31$ ($p<0.001$)) and fewer years of education [$HR=0.71$, 95% $CI=0.55-0.93$] were both associated with risk of progression to MCI, even after accounting for index score values. Adjusting for baseline age and education, a history of diabetes [$HR=3.84$, 95% $CI=1.05-14.01$ ($p=0.037$)] and history of heart disease [$HR=3.26$, 95% $CI=1.01-10.57$ ($p=0.044$)] and the presence of memory complaints by the subject [$HR=5.52$, 95% $CI=1.13-26.87$ ($p=0.031$)] were associated with risk of progression to MCI. The presence of an Apolipoprotein E4 allele taken alone was not associated with risk of progression.

Discussion

In this study, a clinical index score, the BIOCARD Index, was developed. Longitudinal clinical and cognitive evaluations were performed in a large cohort of individuals with normal cognition at baseline to determine whether the index score predicted time to diagnosis of MCI. Our data showed that a lower score on the BIOCARD Index at baseline was associated with this outcome several years before the diagnosis of MCI. Specific factors within the index which were associated with progression were advanced age, lower education, memory complaints by the subject, and a history of either diabetes or heart

disease. The addition of ApoE4 status into the index score did not improve the score's ability to predict a diagnosis of MCI.

The BIOCARD study has previously published data showing that lower performance on several tests of episodic memory [*e.g.*, Paired associates recall and Logical Memory ²¹] and a test of naming [Boston Naming Test ²²] were associated with onset of clinical symptoms indicative of a diagnosis of MCI ⁸. In addition, changes in the volume of temporal lobe structures based on MRI ²³ and CSF A β 1–42 and phosphorylated tau levels ⁹ were predictive of clinical symptoms indicative of a diagnosis of MCI years before symptoms onset.

The results from this study are an important extension of previous results because they are focused on the elements that can be easily obtained inexpensively in an outpatient clinical setting by a general practitioner. Neuropsychological testing, MRI, or CSF analyses with their associated costs, and in the case of CSF tests patient discomfort, are more difficult to obtain in a routine outpatient clinical visit. The results from the neuropsychological tests, MRI and CSF tests noted above though may be more sensitive to the earliest changes of pre-clinical AD than the BIOCARD Index score, as the changes in cognition, MRI, and CSF were evident more than 5–6 years prior to the onset of clinical symptoms, whereas the mean time from baseline BIOCARD Index score to onset of clinical symptoms, was just over 2 years.

Indices of risk of cognitive decline and dementia have been developed in other studies. A Mid-Life Dementia Risk Score was developed in Finland combining age, education, gender, physical inactivity, hypertension, hypercholesterolemia, obesity, and ApoE4 status to predict dementia in middle-age adults' age 40–64 years ¹¹. Disadvantages of this index include the assessment of physical inactivity which can be imprecise, and the requirement for ApoE4 genotype testing which can be expensive in routine clinical practice. A Late-Life Dementia Risk Index was also developed to predict dementia in older adults age 65 years or older ¹². However, the Late-Life Dementia Risk Index includes results from MRI, carotid ultrasound, and ApoE4 genotype results, so it is more costly and time-consuming than the BIOCARD Index and may be impractical to administer in many clinical settings ¹³. Another dementia risk score was based on vascular risk factors in a community-based study and predicted incident cases of late onset Alzheimer's disease among individuals age 65 or older ¹⁴. This risk score included vascular risk factors such as history of hypertension, diabetes, smoking as well as high-density lipoprotein levels, waist to hip ratio, and apoE4 genotype. Each of these risk scores evaluated for risk of dementia rather than onset of MCI and required the use of costly ApoE4 testing.

The BIOCARD Index score was specifically designed to include elements that were inexpensive and could be easily obtained from a patient and their informant in a busy clinical practice. Several components of the score relate to vascular disease risk factors which could increase the risk for both vascular associated cognitive impairment and Alzheimer's disease, as vascular risk factors may directly affect amyloid- β protein in the brain ^{24, 25}. In particular, diabetes is associated with increased insulin which can affect extracellular amyloid- β level and regulation of tau protein phosphorylation in the

brain^{26, 27}. Heart disease can also lead to cognitive impairment through both cerebral hypoperfusion or cerebral embolism²⁸.

There are several limitations to this study which should be noted. Subjects in the BIOCARD cohort are well educated, predominantly Caucasian, and the majority have a family history of dementia, so results may not be generalizable to other populations. In addition participants with cognitive impairment at baseline were excluded from the analyses, so the BIOCARD Index score was not associated with cognitive impairment at the time of the evaluation, but was predictive of incident cognitive symptoms occurring subsequent to baseline. In addition, the number of subjects who progressed to MCI was small, so our results for the BIOCARD Index should be confirmed in a larger study.

Our results are consistent with the hypothesis in the working group report on “preclinical AD”⁷ suggesting that a systematic multimodal data collection such as demographics, subjective symptoms, functional complaints, prior medical history family history, and MMSE performance, as measured by the BIOCARD Index, can be used to predict decline in cognitive performance which is detectable during the phase of AD when pathology is developing. The BIOCARD Index may be a simple summary score that can be used in clinical practice which could have significant therapeutic implications. Treatments are available for vascular risk factors included in the index such as hypertension, diabetes, hypercholesterolemia, heart disease, stroke, and smoking, which could diminish the likelihood for subsequent cognitive decline. Patients with low performance on the index could be referred for additional evaluations such as neuropsychological testing, laboratory testing for confounding conditions, neuroimaging and potentially CSF studies, and they could be followed more closely by clinicians or referred to clinical research studies to monitor and prevent cognitive deterioration. The BIOCARD Index may be a valuable instrument which can be easily used in the clinic setting to identify individuals in mid-life and late-life who are at risk for cognitive deterioration and may benefit from therapeutic and lifestyle interventions, but additional studies are needed in other populations to confirm these results.

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References

1. Hulette CM, Welsh-Bohmer KA, Murray MG, Saunders AM, Mash DC, McIntyre LM. Neuropathological and neuropsychological changes in “normal” aging: evidence for preclinical Alzheimer disease in cognitively normal individuals. *Journal of neuropathology and experimental neurology*. 1998; 57:1168–1174. [PubMed: 9862640]
2. Knopman DS, Parisi JE, Salviati A, et al. Neuropathology of cognitively normal elderly. *Journal of neuropathology and experimental neurology*. 2003; 62:1087–1095. [PubMed: 14656067]
3. Bennett DA, Schneider JA, Arvanitakis Z, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology*. 2006; 66:1837–1844. [PubMed: 16801647]
4. Morris JC, Roe CM, Xiong C, et al. APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Annals of neurology*. 2010; 67:122–131. [PubMed: 20186853]

5. Rowe CC, Ellis KA, Rimajova M, et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiology of aging*. 2010; 31:1275–1283. [PubMed: 20472326]
6. Reiman EM, Chen K, Liu X, et al. Fibrillar amyloid- β burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America*. 2009; 106:6820–6825. [PubMed: 19346482]
7. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2011; 7:280–292.
8. Albert MSA, Gottesman R, McKhann G, Sacktor N, Farrington L, Grega M, Turner RS, Lu Y, Li S, Wang M-C, Selnes O. and the BIOCARD Research Team. Cognitive changes preceding clinical symptoms onset of mild cognitive impairment and relationship to ApoE genotype. *Current Alzheimer Res*. 2014; 11:773–784.
9. Moghekar A, Li S, Lu Y, et al. CSF biomarker changes precede symptom onset of mild cognitive impairment. *Neurology*. 2013; 81:1753–1758. [PubMed: 24132375]
10. Miller MI, Younes L, Ratnanather JT, et al. The diffeomorphometry of temporal lobe structures in preclinical Alzheimer's disease. *NeuroImage Clinical*. 2013; 3:352–360. [PubMed: 24363990]
11. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *The Lancet Neurology*. 2006; 5:735–741. [PubMed: 16914401]
12. Barnes DE, Covinsky KE, Whitmer RA, Kuller LH, Lopez OL, Yaffe K. Predicting risk of dementia in older adults: The late-life dementia risk index. *Neurology*. 2009; 73:173–179. [PubMed: 19439724]
13. Barnes DE, Yaffe K. Predicting dementia: role of dementia risk indices. *Future neurology*. 2009; 4:555–560. [PubMed: 20161571]
14. Reitz C, Tang MX, Schupf N, Manly JJ, Mayeux R, Luchsinger JA. A summary risk score for the prediction of Alzheimer disease in elderly persons. *Archives of neurology*. 2010; 67:835–841. [PubMed: 20625090]
15. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *The British journal of psychiatry : The Journal of mental science*. 1982; 140:566–572. [PubMed: 7104545]
16. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993; 43:2412–2414.
17. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2011; 7:270–279.
18. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2011; 7:263–269.
19. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician *Journal of psychiatric research*. 1975; 12:189–198. [PubMed: 1202204]
20. Cox DR. Regression models and life-tables (with discussion). *JR Statist, Soc B*. 1972:187–220.
21. Wechsler, D. Wechsler Memory Scale: Revised Manual. San Antonio, TX: Psychological Corporation; 1987.
22. Kaplan, EGH., Weintraub, S. Boston Naming Test. Philadelphia: 1983.
23. Soldan A, Pettigrew C, Lu Y, et al. Relationship of medial temporal lobe atrophy, APOE genotype, and cognitive reserve in preclinical Alzheimer's disease. *Human brain mapping*. 2015; 36:2826–2841. [PubMed: 25879865]

24. Petrovitch H, White LR, Izmirlian G, et al. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu-Asia aging Study Neurobiology of aging. 2000; 21:57–62. [PubMed: 10794849]
25. Sparks DL, Martin TA, Gross DR, Hunsaker JC 3rd. Link between heart disease, cholesterol, and Alzheimer's disease: a review. Microscopy research and technique. 2000; 50:287–290. [PubMed: 10936882]
26. Vekrellis K, Ye Z, Qiu WQ, et al. Neurons regulate extracellular levels of amyloid beta-protein via proteolysis by insulin-degrading enzyme. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2000; 20:1657–1665. [PubMed: 10684867]
27. Park CR. Cognitive effects of insulin in the central nervous system. Neuroscience and biobehavioral reviews. 2001; 25:311–323. [PubMed: 11445137]
28. Breteler MM, Claus JJ, Grobbee DE, Hofman A. Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam Study. Bmj. 1994; 308:1604–1608. [PubMed: 8025427]

BIOCARD Index		
<u>Patient</u>		
Have you notice changes with your memory recently?	Yes	0
	No	1
Do you feel sad or depressed	Yes	0
	No	1
Age	≥ 90	0
	80-89	1
	70-79	2
	60-69	3
	≤ 59	4
Education	<High School	0
	High School	1
	>High School	2
History of Hypertension	Yes	0
	No	1
History of Diabetes	Yes	0
	No	1
History of Hypercholesterolemia	Yes	0
	No	1
History of Heart disease	Yes	0
	No	1
History of Stroke or Transient Ischemic Attack	Yes	0
	No	1
Have you smoked in the past 30 days?	Yes	0
	No	1
Any traumatic brain injury with a chronic deficit?	Yes	0
	No	1
Any family member with dementia?	Yes	0
	No	1
Mini-Mental State Exam (MMSE) score	≤ 22	0
	23	1
	24	2
	25	3
	26	4
	27	5
	28	6
	29	7
	30	8
<u>Informant</u>		
Have you noticed changes with memory in the patient?	Yes	0
	No	1
Any changes in the patient's ability to perform finances?	Yes	0
	No	1
Any changes in the patient's ability to perform shopping tasks?	Yes	0
	No	1
Any changes in the patient's ability to remember appointments, holidays, or medications?	Yes	0
	No	1
BIOCARD Index Total Score		= _____
		(Range 0-29)

Figure 1.
BIOCARD Index

FIGURE 2.

Survival curve for the Cox regression model for individuals with a BIOCARD Index score above the median compared to individuals with a BIOCARD Index score below the median

Table 1

Participant Characteristics at Baseline

	Cohort as a whole (n=349)	Subjects in analysis (n=222)
Age, Years [Mean (SD)]	65.6 (10.5)	64.2 (9.7)
Education, Years [Mean (SD)]	17.2 (2.3)	17.2 (2.3)
Gender, % Female	57.6	61.3
Ethnicity, % Caucasian	97.1	99.1
Hypertension, %	33.0	36.5
Diabetes, %	8.3	8.6
Hypercholesterolemia %	43.3	50.5
Heart disease, %	12.6	11.7
Stroke or TIA, %	5.7	6.3
Smoking, %	5.2	4.5
Traumatic Brain Injury %	15.5	21.2

Table 2

Participant Characteristics at Baseline Stratified by Trial Outcome

	Remained Normal (n=210)	Progressed to MCI (n=12)
Age, Years [Mean (SD)]	63.6 (9.5)	75.0 (5.9) **
Education, Years [Mean (SD)]	17.3 (2.2)	15.8 (3.1)
Gender, % female	62.9	33.3 *
Ethnicity, % Caucasian	99.0	100.0
Hypertension, %	35.2	58.3
Diabetes, %	7.1	33.3 **
Hypercholesterolemia, %	49.5	66.7
Heart Disease, %	10.0	41.7 **
Stroke or TIA, %	5.7	16.7
Smoking, %	4.8	0
Traumatic Brain Injury, %	22.4	0
Apo E4 Carriers, %	31.9	16.7
MMSE [Mean (SD)]	29.3 (1.0)	28.3 (1.7)
BIOCARD Index Score [Mean (SD)]	24.8 (2.3)	20.3 (2.9)

Note. Significant differences between the group who remained normal and the group who progressed are indicated by asterisks:

*
 $p < 0.05$,

**
 $p < 0.01$

Table 3

Cox Regression Analysis to Determine if the BIOCARD Index Score is Associated with Time to Onset of Mild Cognitive Impairment (MCI)

	Hazard Ratio (95% CI)	p value
BIOCARD Index	0.75 (0.67–0.84)	<0.001
BIOCARD Index excluding age and education	0.81 (0.68–0.97)	0.02
Modified BIOCARD Index with ApoE4	0.76 (0.67–0.86)	<0.001
Modified BIOCARD Index with ApoE4 excluding age and education	0.82 (0.62–1.02)	0.053