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Coronary heart disease is associated with non-amnestic mild cognitive impairment

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Abstract

The progression of amnestic mild cognitive impairment (a-MCI) to Alzheimer's disease and hypothesized progression of non-amnestic mild cognitive impairment (na-MCI) to non-degenerative or vascular dementias suggest etiologic differences. We examined the association between coronary heart disease (CHD) and mild cognitive impairment (MCI) subtypes in a population-based cohort. Participants (n = 1969; aged 70-89 years) were evaluated using the Clinical Dementia Rating Scale, a neurological examination, and neuropsychological testing for diagnoses of normal cognition, MCI, or dementia. CHD was defined as a history of myocardial infarction, angina, angiographic coronary stenosis, or coronary revascularization and ascertained by participant interview and from medical records. CHD was significantly associated with Na-MCI (OR = 1.93; 95% CI = 1.22-3.06) but not with a-MCI (OR = 0.94; 95% CI = 0.69-1.28). In contrast, ApoE ε4 allele was significantly associated with a-MCI (OR = 1.75; 95% CI = 1.28-2.41), but not with na-MCI (OR = 1.17, 95% CI = 0.69-2.00). The association of CHD with prevalent na-MCI but not with a-MCI suggests that CHD and na-MCI may have similar underlying etiologies.

Keywords

Cognitive impairment; Coronary heart disease; Myocardial infarction; Angina; Coronary artery bypass grafting; Population-based

1. Introduction

Mild cognitive impairment (MCI) is a transitional stage between normal cognitive aging and dementia. Presumably, risk factors for dementia are also involved in the pathogenesis of MCI.

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MCI is subclassified into two forms - amnestic MCI (a-MCI) and non-amnestic MCI (na-MCI). It is hypothesized that a-MCI progresses to Alzheimer's type dementia, whereas na-MCI progresses to non-degenerative or vascular dementias (Petersen et al., 1995; Farlow et al., 2004). Consistent with this, several investigators have shown an association between a-MCI and ApoE ε4 allele (Farlow et al., 2004; Tervo et al., 2004; Devanand et al., 2005), and others have shown an association between na-MCI and hypertension (Reitz et al., 2007). Consequently, we hypothesize that the ApoE ε4 allele, an important risk factor for Alzheimer's disease (AD), is associated with a-MCI, whereas vascular risk factors and markers of generalized atherosclerosis are associated with na-MCI. The presumed mechanism for the role of generalized atherosclerosis in MCI and dementia may be associated with coronary heart disease (CHD) leading to decreased cardiac output, cerebral hypoperfusion, and neuronal damage. Alternatively, CHD may also be a marker for subclinical cerebrovascular disease and associated cognitive impairment.

Studies examining the association between CHD and cognitive impairment have yielded inconsistent results. A positive association has been reported in some (Aronson et al., 1990; Breteler et al., 1994; Singh-Manoux et al., 2003) but not all studies (Grubb et al., 2000; Bursi et al., 2006). This inconsistency in reported studies may be due to various reasons. This includes differences in criteria for cognitive impairment such as a global measure of cognition based on the Mini-Mental State Examination (Breteler et al., 1994) or as dementia (Bursi et al., 2006). Select subgroups have been studied (Aronson et al., 1990). The investigation of the associations of CHD with MCI has not distinguished between a-MCI and na-MCI. The spectrum of CHD examined has been limited to myocardial infarction (Aronson et al., 1990) or to myocardial infarction and coronary artery bypass grafting (CABG) (Breteler et al., 1994; Petrovitch et al., 1998). This latter problem may relate to the complexity of assessing the entire spectrum of CHD such that frequently only CHD severe enough to result in a cardiac event such as a myocardial infarction is investigated (Aronson et al., 1990; Breteler et al., 1994; Bursi et al., 2006). Consequently, subjects with severe CHD who are not surgical candidates, and those with less severe CHD (e.g., stable angina), may not be included in studies assessing the association of CHD with cognitive impairment.

Therefore, the purpose of this study was to investigate the cross-sectional associations of a comprehensive assessment of measures of CHD with MCI subtypes in a population-based sample of subjects in the Mayo Clinic Study of Aging. We have detailed information on measures of CHD from an interview conducted at baseline and from information obtained from the patient medical records (Melton, 1996). In addition, these participants have also been prospectively evaluated and characterized for a-MCI and na-MCI using previously published criteria.

2. Methods

2.1. Study subjects

Study subjects were participants in a longitudinal study to estimate the prevalence and incidence of MCI in Olmsted County, MN. Extensive details of the study design and methodology have been previously published (Roberts et al., 2008). Briefly, the study was approved by the Institutional Review Boards of the Mayo Clinic and Olmsted Medical Center. From an enumeration of Olmsted County residents aged 70-89 years on October 1, 2004 (n = 9953), we randomly selected 5233 subjects and invited them to participate in the study. We excluded subjects who died before their initial contact (n = 263), subjects who were terminally ill and in hospice (n = 56), subjects who could not be located (n = 114), and subjects who had previously been diagnosed with dementia (n = 402). The diagnoses of dementia were derived from the indices of the medical records-linkage system (Melton, 1996) and were confirmed by a neurologist (D.S.K.). From an eligible cohort of 4398 subjects invited to the study, 2719

(61.8%) agreed to participate in the study; 669 participated by telephone and 2050 participated through a face-to-face evaluation; 1679 declined participation. Of the 2050 subjects who participated in the face-to-face evaluation, 67 subjects were found to be demented through the face-to-face evaluation and 14 subjects did not complete the evaluation and therefore could not be assigned a diagnosis; these 81 subjects were excluded from the analyses. This cross-sectional study was based on 1969 subjects who completed the face-to-face evaluation and were found not to be demented.

2.2. Participant evaluation

Participants underwent a nurse evaluation and risk factor assessment that included the Clinical Dementia Rating Scale (Morris, 1993), a neurological evaluation, and neuropsychological testing using nine cognitive tests to assess performance in four cognitive domains: memory (Wechsler, 1987; Ivnik et al., 1992), executive function (Reitan, 1958; Wechsler, 1987), language (Kaplan et al., 1982; Lucas et al., 1998), and visuospatial skills (Wechsler, 1987). The data for each participant were reviewed by an expert panel including physicians, neuropsychologists, and the nurses who evaluated the participant. A diagnosis of normal cognition, MCI, or dementia was reached by consensus.

2.3. MCI cases

Participants were categorized as having prevalent MCI according to published criteria, and using all the information obtained from the face-to-face evaluation (Roberts et al., 2008). These criteria included cognitive concern by a physician, patient, or nurse; impairment in one or more of the four cognitive domains; essentially normal functional activities; and no dementia (Petersen, 2004). Participants with MCI were further classified as having a-MCI if the memory domain was impaired or na-MCI if there was no memory impairment.

2.4. Cognitively normal controls

Controls were all the subjects in the study who were found to be free of MCI or dementia. A diagnosis of normal cognition was assigned according to published criteria (Ivnik et al., 1992; Petersen, 2004). A diagnosis of dementia was made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV (American Psychiatric Association, 1994).

2.5. Assessment of coronary heart disease

CHD was defined as a history of myocardial infarction, angina, angiographic coronary stenosis, or coronary revascularization. Ascertainment and criteria are described below.

2.6. Myocardial infarction

A history of myocardial infarction was ascertained from three sources: 1) self-report of a physician diagnosis from the interview and risk factor assessment performed by a nurse; 2) International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 410-410.92 for acute myocardial infarction, 412 for old myocardial infarction (National Center for Health Statistics, 1980), or the equivalent codes from the ICD-8 Adapted Codes for Hospitals (H-ICDA) (Commission on Professional and Hospital Activities, 1973) based on information from the medical index of the Rochester Epidemiology Project (Melton, 1996); and 3) validated diagnoses of myocardial infarction determined from a separate surveillance study conducted in Olmsted County since 1979 (Targonski et al., 2001). Diagnoses in the surveillance study were based on standardized epidemiologic criteria that included cardiac pain, Minnesota coding of the electrocardiogram, and biomarker results (Gillum et al., 1984; White et al., 1996; Alpert et al., 2000; Apple et al., 2002; Roger et al., 2002; Luepker et al.,

2003). Probable or definite myocardial infarction was defined using information from any one of the three sources as described in Table 1.

2.7. Angina pectoris

A history of angina was ascertained from 1) self-report of a physician diagnosis with or without self-report of treatment with nitrates, beta-blockers, or calcium channel blockers specifically stated as treatment for angina; and 2) ICD-9-CM codes 413-413.9 (or equivalent H-ICDA codes) for angina from the medical records-linkage system. Subjects were characterized as having probable angina if they reported a physician diagnosis of angina with or without treatment for angina and had an ICD-9-CM code for angina (Table 1).

2.8. Angiographic coronary stenosis

Angiographic coronary stenosis was ascertained from the cardiac catheterization laboratory of the Mayo Clinic, and was defined as a stenosis of ≥50% in one or more coronary arteries.

2.9. Coronary revascularization

Coronary revascularization was ascertained from the medical and surgical indices of the medical records-linkage system, and was defined as a history of coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI; e.g., balloon dilatation, angioplasty).

2.10. Assessment of potential confounders

Potential confounders were determined from the interview and risk factors assessment performed by a nurse. Date of birth, years of education, cigarette smoking, and history of diabetes, hypertension, and stroke were assessed by interview. Subjects were requested to bring the bottles containing their current medications to the appointment and the name and dose of all current medications were noted. Subjects were characterized as having diabetes based on self-report of a physician diagnosis of diabetes, complications attributed to diabetes, and pharmacologic treatment for diabetes, and they were characterized as having hypertension based on self-report of hypertension or treatment for hypertension assessed from the current medications. Current symptoms of depression were ascertained from the Neuropsychiatric Inventory Questionnaire (Kaufer et al., 2000). Blood pressure was measured twice using a standard sphygmomanometer, height was measured using a stadiometer, and weight was measured using an electronic balance. Serum triglycerides, total cholesterol, and high density lipoprotein were measured from the blood draw. ApoE genotyping was performed for each subject using standard methods (Hixson and Vernier, 1990).

2.11. Statistical analyses

The characteristics of study subjects are presented using descriptive statistics. Comparisons between MCI cases and controls were made using chi-squared tests for categorical variables or Wilcoxon rank sum tests for continuous variables. Associations between CHD and MCI were investigated using multivariable logistic regression models and reported as odds ratios (OR) and 95% confidence intervals (95% CI). All models were controlled for age (as a continuous variable), sex, and years of education (as a continuous variable) to reduce possible confounding. Analyses were repeated for any MCI, a-MCI, and na-MCI. CHD was defined as a history of definite (validated) myocardial infarction, coronary revascularization procedures, or angiographic coronary stenosis. In addition, the associations of the individual components of CHD with MCI were examined.

In additional multivariable analyses, the association of CHD with MCI was examined after adjusting for potential confounders that were either significantly associated with MCI or have been associated with both CHD and cognition in the literature (fully-adjusted model). First,

we included adjustment for ApoE genotype (ApoE ε3/4, ApoE ε4/4 vs. ApoE ε2/2, ApoE ε2/3, ApoE ε3/3) in the multivariable models. Subjects with ApoE ε2/4 (2.3%) were excluded because the ε2 allele is considered protective and the ε4 allele is considered a risk factor for cognitive impairment. Then we examined effects of additionally including diabetes, hypertension, BMI, stroke, depression, dyslipidemia in the models for a fully-adjusted model. Since some of these confounders (e.g., stroke) may be in the causal pathway between CHD and MCI, adjusting for these variables may result in over-controlling and a bias in the estimates of the ORs towards the null. We investigated potential effect modification (interaction) by assessing associations of CHD with MCI subtypes across strata of age (<80 vs. ≥80 years), sex, years of education (≤12 vs. >12 years), and ApoE ε4 allele carrier status (ε4 positive vs. ε4 negative) in separate analyses and by including an interaction term in the multivariable models.

2.12. Additional analyses

To capture the association of a broader spectrum of CHD with MCI, we defined definite or probable CHD by including probable myocardial infarction and probable angina in the criteria for CHD. We then investigated the associations between definite or probable CHD and MCI subtypes using multivariable logistic regression analyses as described above.

2.13. Association of CHD with cognitive test scores

We calculated a z-score for each of the nine cognitive tests by scaling the raw scores on each test using the mean and standard deviation for the entire sample. The scaled scores in each domain were summed and scaled to obtain a domain score. The domain scores were then summed and scaled to obtain a global score for cognitive function with a mean = 0, standard deviation = 1. We investigated the associations between CHD and the scaled tests scores, the domain scores, and the global scores in using multivariable linear and logistic regression models adjusted for age, sex, and education. All analyses were performed using SAS® version 8.0 software (SAS® Institute, Cary, NC).

3. Results

Of the 1969 non-demented subjects who participated in the face-to-face evaluations, 329 subjects (16.7%) had MCI: 241 subjects (12.2%) had a-MCI and 88 subjects (4.5%) had na-MCI (Table 2). Subjects with MCI were slightly older at the time of evaluation, were more likely to be men, to have a lower number of years of education, a history of stroke, and depression compared to controls. There were no significant differences in the prevalence of dyslipidemia (76.9% in MCI cases vs. 74.1% in controls; $p = 0.3$) or in the use of lipid lowering agents (47.4 % in MCI cases vs. 49.0% in controls; $p = 0.6$).

CHD was significantly associated with na-MCI in the age-, sex-, and years of education-adjusted model (Table 3), but not with a-MCI. The association of CHD with na-MCI remained significant with additional adjustment for ApoE ε4 genotype (OR = 1.75; 95% CI = 1.09-2.82; $p = 0.02$) and after adjusting for variables in the fully-adjusted model (Table 3). Angiographic coronary stenosis was significantly associated with na-MCI (Table 3); the OR for the association remained elevated two-fold after adjusting for ApoE ε4 allele (OR = 2.62; 95% CI = 0.83-8.26; $p = 0.10$) and after adjustment for variables in the fully-adjusted model (Table 3), but the association was no longer statistically significant. A history of CABG or PCI was not significantly associated with na-MCI or with a-MCI (Table 3).

There was a significant association of ApoE ε4 carrier status with a-MCI (OR = 1.75; 95% CI = 1.28-2.41; $p < 0.001$) but not with na-MCI (OR = 1.17; 95% CI = 0.69-2.00; $p = 0.55$) in models adjusted for age, sex, and years of education.

There was no effect modification observed when the association between CHD and na-MCI was examined across strata of age (OR =1.72, 95% CI = 0.75-3.95 in subjects aged <80 years vs. OR =1.90, 95% CI = 1.09-3.31 in subjects aged ≥80 years; *p* for interaction = 0.86); sex (OR =1.67, 95% CI = 0.88-3.15 in men vs. OR =2.06, 95% CI = 1.07-3.99 in women; *p* for interaction = 0.71); ApoE allele status (OR =1.03, 95% CI = 0.37-2.85 in subjects with the ApoE ε4 allele vs. OR =1.95, 95% CI = 1.14-3.35 in subjects without the ApoE ε4 allele; *p* for interaction = 0.25), or years of education (OR =1.83, 95% CI = 1.04-3.22 in subjects with ≤12 years of education vs. OR =1.86, 95% CI = 0.84-4.12 in subjects with >12 years of education; *p* for interaction = 0.76). When a cutpoint of 9 years of education was used, we still observed no effect modification (OR =2.76, 95% CI = 0.89-8.52 in subjects with ≤9 years of education vs. OR =1.87, 95% CI = 1.13-3.11 in subjects with >9 years of education; *p* for interaction = 0.42).

When we examined the broader spectrum of CHD, definite or probable CHD was significantly associated with na-MCI (OR = 1.68, 95% CI = 1.07-2.65; *p* = 0.02) after adjusting for age, sex, and years of education. The OR for na-MCI remained elevated but the association was no longer statistically significant after adjusting for ApoE ε4 allele (OR = 1.54; 95% CI = 0.96-2.46; *p* = 0.07) and for variables in the fully-adjusted model (OR = 1.59; 95% CI = 0.97-2.61; *p* = 0.07). Definite or probable CHD was not associated with a-MCI (OR = 0.98; 95% CI = 0.73-1.33; *p* = 0.91). The lack of a significant association in these latter analyses may in part be due to the lower certainty of the diagnoses of probable myocardial infarction and probable angina. Probable angina was also not significantly associated with na-MCI (OR = 1.37; 95% CI = 0.81-2.30; *p* = 0.24) or with a-MCI (OR = 0.80; 95% CI = 0.55-1.15; *p* = 0.23).

In linear regression models, definitive CHD was significantly associated with impairment in measures of psychomotor speed and attention (Digit Symbol Substitution and Trail Making Test B), and the overall domain score for executive function (Table 4). In logistic regression models, subjects with definitive CHD were 32% more likely to have an impaired Digit Symbol Substitution z-score in the lowest quartile; the ORs for Trail Making Test B and for the executive function domain z-scores were also elevated 20% and 25%, but the confidence intervals included 1.

4. Discussion

In our population-based sample of 70-89 year olds, subjects with a history of CHD had a 93% higher likelihood of na-MCI. The association remained significant after adjusting for ApoE ε4 allele and for variables in the fully adjusted model. There was also a positive association between a history of angiographic coronary stenosis and na-MCI (OR = 3.21). In addition, CHD was significantly associated with measures of psychomotor speed and executive function. In contrast, we observed no significant associations between CHD and a-MCI, but ApoE ε4 allele was significantly associated with a-MCI, but not with na-MCI. Our findings suggest that CHD and na-MCI may share similar underlying etiologies.

The positive association of CHD with na-MCI, but not with a-MCI has not been reported previously, to our knowledge. This association of CHD with na-MCI is another piece of evidence in favor of a vascular contribution to the pathogenesis of na-MCI (Petersen, 2004; Panza et al., 2008). It is possible that small vessel disease or less severe cerebrovascular disease have only a minimal impact on the risk of a-MCI but, on the other hand, may elicit the distinct pattern of cognitive impairment characterized by na-MCI. More severe vascular disease such a stroke may impact both na-MCI and a-MCI (Skoog, 2000), but with greater effects on pathogenesis of na-MCI than on a-MCI. This is supported by cross-sectional findings from the present study; ApoE ε4 allele, the strongest genetic predictor of late onset AD, was significantly

associated with a-MCI (OR = 1.75; p <0.001) but not with na-MCI (OR = 1.17; p = 0.55). In contrast, a history of stroke (suggestive of severe cerebrovascular disease) was associated with both a-MCI and na-MCI, but the association was much stronger with na-MCI (OR = 3.52; p <0.0001) than with a-MCI (OR = 1.69; p = 0.01) (Knopman et al., 2008). Overall, our findings suggest that na-MCI may be prodromal for dementias with a substantial cerebrovascular component, whereas a-MCI may be prodromal for AD and dementias with a degenerative etiology.

In keeping with the observed association of CHD with na-MCI, we observed significant associations between CHD and non-memory measures of cognition. Specifically, CHD was associated with measures of psychomotor speed and processing (Digit Symbol Substitution and Trail Making Test B), and with the domain score for executive function, but not with measures of memory. These findings are consistent with reports of an association of vascular disease with impairment in Digit Symbol Substitution, executive function, and with na-MCI in other studies (Lopez et al., 2003; Mariani et al., 2007). Given the potential vascular etiology for na-MCI, it is possible that other markers of systemic atherosclerosis, such as carotid artery stenosis with concomitant cerebral hypoperfusion, would have a similar or even stronger association with na-MCI. However, we are unable to assess the association of carotid stenosis or occlusion with na-MCI since we did not perform a carotid ultrasound as part of this study.

The absence of an association between myocardial infarction and MCI observed in our study is consistent with findings observed between cognitive performance or dementia in a longitudinal study (Petrovitch et al., 1998) and in a case-control study (Bursi et al., 2006). However, other investigators have reported an association between electrocardiographic evidence of myocardial infarction and evidence of vascular disease, including angina, and cognitive impairment (Breteler et al., 1994; Singh-Manoux et al., 2003). The lack of an association with a prior myocardial infarction could be due to survival bias wherein subjects with myocardial infarction who were at greatest risk of cognitive impairment may not have survived. This hypothesis is supported by the strong positive association between angina, myocardial infarction, and all coronary heart disease observed in a middle-aged cohort (Singh-Manoux et al., 2003); presumably, because these subjects were younger than the age group typically studied, the likelihood of death from myocardial infarction was lower, and the potential for survival bias was minimal. On the other hand, potential drastic changes in lifestyle, cardiac rehabilitation measures, and intensive therapeutic interventions among survivors of a myocardial infarction may decrease systemic and cerebral atherosclerosis, or may improve cardiac function, cardiac output, and cerebral perfusion, and improve or prevent further cognitive damage (Petrovitch et al., 1998; Phillips, 2008). Similarly, surgical therapies for CHD may improve cardiac function, which in turn may improve cerebral perfusion, with beneficial effects on cognitive function (Petrovitch et al., 1998). This may also explain the lack of a significant association between CABG or PCI and cognitive impairment in the present study, and is consistent with the lack of an association between CABG and dementia reported by other investigators (Petrovitch et al., 1998; Selnes et al., 2003; Knopman et al., 2005). Nonetheless, the positive association of angiographic coronary stenosis with na-MCI in the present study suggests that the severity of the CHD or irreversible cognitive damage prior to the surgery, or alternately, possible residual effects of bypass surgery may have lasting adverse effects on cognitive function (Roach et al., 1996). Other studies have reported an association between CHD and cognitive impairment in men but not in women (Ahto et al., 1999); however, we observed no sex differences in the associations.

We observed a significant association between CHD and stroke (OR = 1.91; 95% CI = 1.37-2.64) in the present study, suggesting that the association of CHD with na-MCI may be confounded by the association of CHD with stroke. However, even after adjustment for stroke, the significant association of CHD with na-MCI persisted. Although CHD may not directly

cause directly cause na-MCI, CHD may be a marker for cerebral atherosclerosis and cerebral small vessel disease that may lead to cerebral micro-infarctions and cognitive impairment (Skoog, 2000).

Potential limitations of our study include misclassification of CHD. When we restricted the criteria of CHD to definite criteria only, and the association of CHD with na-MCI remained the same in the fully adjusted models. However, the lack of statistical significance of probable or definite CHD with na-MCI in the fully-adjusted model suggests either potential misclassification of CHD or angina or lack of power. Similarly, the lack of statistical significance in the association of angiographic coronary stenosis with na-MCI in the fully-adjusted model may be due to lack of power. Our cross-sectional design precludes our ability to attribute causality. Longitudinal follow-up of this cohort will enable us to determine whether CHD predicts incident na-MCI, non-degenerative or vascular dementias. The sample is 98.6% Caucasian; thus, our findings are generalizable to persons with similar characteristics.

Despite these limitations, our study has several important strengths. The population-based design increases the generalizeability of study findings to the population and minimizes the potential for referral bias. The medical records-linkage system serving the population of Olmsted County provided physician diagnoses of the study exposures to confirm information from self-report. We prospectively characterized participants as having MCI using a specified protocol at the time of evaluation in contrast to retrofitting MCI criteria to previously collected data. Our ability to characterize subjects using definite criteria for CHD minimized misclassification bias.

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Table 1

Diagnostic criteria for definite or probable coronary heart disease

Level of certainty	Myocardial infarction (*n* = 246)	Coronary revascularization	Angiographic coronary stenosis[a]	Angina
Definite	Validated MI (*n* = 157; 63.8%)	Surgical or medical index code for CABG or PCI (*n* = 472)	Confirmed by cardiac catheterization lab (*n* = 419)	--
Probable	Self-report and medical index code (*n* = 89; 36.2%)			Self-report + medication + medical index code (*n* = 118)
				Medication + medical index(*n* = 32)
				Self-report and medical index code (*n* = 167)

MI = myocardial infarction; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

[a] Stenosis of ≥50% in at least one coronary artery.

Table 2

Characteristics of participants with MCI (cases) and without MCI (controls). Mayo Clinic Study of Aging 2004-2006

Variable	All subjects (*n* = 1969)	MCI[a] cases			Normal cognition (*n* = 1640)	*p* value[b]
		Amnestic (*n* = 241)	Non-amnestic (*n* = 88)	All MCI (*n* = 329)		
Age, median (Q_1, Q_3)	80.4 (75.4, 84.0)	82.7 (79.0, 86.0)	82.5 (78.4, 85.4)	82.7 (79.0, 85.8)	79.6 (75.1, 83.6)	<0.0001
Sex, *n* (% male)	1002 (50.9)	150 (62.2)	42 (47.7)	192 (58.4)	810 (49.4)	0.003
Education (years)	13 (12, 16)	12 (12, 16)	12 (12, 14)	12 (12, 15)	13 (12, 16)	<0.0001
Stroke or TIA, (*n*, %)	346 (17.6)	61 (25.3)	30 (34.1)	91 (27.7)	255 (15.5)	<0.0001
Hypertension, (*n*, %)	1388 (70.5)	166 (68.9)	68 (77.3)	234 (71.1)	1154 (70.4)	0.795
Diabetes, (*n*, %)	356 (18.1)	44 (18.3)	22 (25.0)	66 (20.1)	290 (17.7)	0.309
Cigarette smoking, (*n*, %)	970 (49.3)	122 (50.6)	43 (48.9)	165 (50.2)	805 (49.1)	0.731
Depression, (*n*, %)	268 (13.6)	60 (24.9)	26 (29.5)	86 (26.1)	182 (11.1)	<0.0001
BMI, median (Q_1, Q_3)	27.2 (24.3, 30.3)	26.8 (24.0, 29.7)	27.4 (24.3, 30.1)	26.9 (24.1, 29.8)	27.3 (24.4, 30.5)	0.089
ApoE ε3/4 ApoE ε4/4[c]	423 (23.1)	70 (30.8)	19 (22.6)	89 (29.2)	334 (21.9)	0.006

MCI = mild cognitive impairment; TIA = transient ischemic attack; BMI = body mass index.

[a] A consensus diagnosis of mild cognitive impairment.

[b] *p* value for comparison of subjects with and without MCI; these comparisons were not adjusted for potential confounders.

[c] Fourteen cases with a-MCI, 4 cases with na-MCI, and 75 cognitively normal subjects had missing ApoE ε4 data. Five cases with a-MCI, 1 case with na-MCI, and 37 cognitively normal subjects with ApoE ε2/4 are not included.

Table 3

Association of coronary heart disease with MCI and MCI subtypes. Mayo Clinic Study of Aging 2004-2006

Variable	Normal cognition[a] (*n*, %)	Any MCI (*n* = 329)			Amnestic MCI (*n* = 241)			Non-Amnestic MCI (*n* = 88)		
		(*n*, %)	OR (95% CI)[b]	*p* value	(*n*, %)	OR (95% CI)[b]	*p* value	(*n*, %)	OR (95% CI)[b]	*p* value
Coronary heart disease[c]										
Model 1	445 (27.1)	110 (33.4)	1.14 (0.87-1.49)	0.33	73 (30.3)	0.94 (0.69-1.28)	0.68	37 (42.0)	1.93 (1.22-3.06)	0.005
Model 2	445 (27.1)	110 (33.4)	1.12 (0.83-1.52)	0.45	73 (30.3)	0.94 (0.65-1.34)	0.72	37 (42.0)	1.85 (1.12-3.05)	0.02
Myocardial infarction[d]										
Model 1	128 (7.8)	29 (8.8)	0.99 (0.64-1.53)	0.98	23 (9.5)	1.06 (0.66-1.72)	0.80	6 (6.8)	0.77 (0.33-1.83)	0.56
Model 2	128 (7.8)	29 (8.8)	0.91 (0.55-1.49)	0.70	23 (9.5)	0.93 (0.53-1.64)	0.81	6 (6.8)	0.81 (0.33-1.97)	0.64
CABG or PCI										
Model 1	385 (23.5)	87 (26.4)	0.98 (0.74-1.30)	0.88	61 (25.3)	0.88 (0.63-1.22)	0.45	26 (29.5)	1.32 (0.81-2.17)	0.27
Model 2	385 (23.5)	87 (26.4)	0.92 (0.67-1.27)	0.62	61 (25.3)	0.86 (0.59-1.25)	0.42	26 (29.5)	1.17 (0.68-2.00)	0.58
Angiographic coronary stenosis[e]										
Model 1	331 (75.4)	88 (80.0)	1.33 (0.77-2.29)	0.30	59 (76.6)	1.02 (0.56-1.85)	0.95	29 (87.9)	3.21 (1.02-10.04)	0.05
Model 2	331 (75.4)	88 (80.0)	1.21 (0.65-2.25)	0.55	59 (76.6)	0.96 (0.48-1.95)	0.92	29 (87.9)	2.14 (0.68-6.75)	0.20

MCI = mild cognitive impairment; OR = odds ratio; CI = confidence interval; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

[a] *n* = 1640 were cognitively normal.

[b] Odds ratio (95% confidence intervals). Model 1 estimates are adjusted for age, sex, and years of education (continuous variables). Model 2 estimates (fully-adjusted model) are adjusted for age, sex, and years of education (continuous variables); diabetes, hypertension, stroke, BMI, depression, dyslipidemia, and ApoE genotype.

[c] CHD defined as definite (validated) myocardial infarction, CABG, PCI, or angiographic coronary stenosis.

[d] Definite myocardial infarction.

[e] Stenosis of ≥50% in at least 1 coronary artery; information was available for 439 cognitively normal, 77 a-MCI, and 33 na-MCI subjects.

Table 4

Association of definitive coronary heart disease with impaired cognitive function[a]

Cognitive measure[b]	β (SE)	*p* value	OR (95% CI)	*p* value
Executive function				
Digit Symbol Substitution	-0.149 (0.046)	0.001	1.32 (1.03-1.70)	0.03
Trail Making Test B	-0.135 (0.048)	0.005	1.20 (0.93-1.54)	0.15
Domain score	-0.158 (0.046)	0.001	1.25 (0.97-1.61)	0.09
Memory				
Logical memory	0.064 (0.050)	0.20	0.89 (0.69-1.13)	0.34
Visual reproduction	0.023 (0.049)	0.64	0.98 (0.77-1.25)	0.88
Auditory Verbal Learning Test	-0.047 (0.048)	0.33	0.98 (0.77-1.25)	0.87
Domain score	0.016 (0.048)	0.75	0.88 (0.69-1.12)	0.30
Language				
Boston Naming Test	0.082 (0.049)	0.09	0.95 (0.73-1.23)	0.70
Category fluency	-0.019 (0.047)	0.69	1.01 (0.79-1.28)	0.95
Domain score	0.039 (0.048)	0.42	0.92 (0.71-1.18)	0.51
Visuospatial skills				
Picture completion	-0.057 (0.049)	0.24	1.14 (0.88-1.48)	0.33
Block design	-0.061 (0.049)	0.21	1.12 (0.87-1.44)	0.39
Domain score	-0.074 (0.048)	0.12	1.01 (0.78-1.31)	0.96

SE = standard error; OR = odds ratio; CI = confidence interval.

[a] Adjusted for age, sex and education.

[b] Impaired cognitive function was defined as having a z-score in the lowest quartile.