ORIGINAL CONTRIBUTION

Cardiac Disease Associated With Increased Risk of Nonamnestic Cognitive Impairment

Stronger Effect on Women

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Objective: To investigate the association of cardiac disease with amnestic and nonamnestic mild cognitive impairment (aMCI and naMCI, respectively). Nonamnestic mild cognitive impairment, a putative precursor of vascular and other non-Alzheimer dementias, is hypothesized to have a vascular etiology.

Design: A prospective, population-based, cohort study with a median 4.0 years of follow-up.

Setting: Olmsted County, Minnesota.

Participants: A total of 2719 participants were evaluated at baseline and every 15 months using the Clinical Dementia Rating scale, a neurological evaluation, and neuropsychological testing. A diagnosis of normal cognition, MCI, or dementia was made by consensus. Cardiac disease at baseline was assessed from the participant's medical records.

Main Outcome Measures: Incident MCI, aMCI, or naMCI.

Results: Of 1450 participants without MCI or dementia at baseline, 366 developed MCI. Cardiac disease was associated with an increased risk of naMCI (hazard ratio, 1.77 [95% CI, 1.16-2.72]). However, the association varied by sex (P=.02 for interaction). Cardiac disease was associated with an increased risk of naMCI (hazard ratio, 3.07 [95% CI, 1.58-5.99]) for women but not for men (hazard ratio, 1.16 [95% CI, 0.68-1.99]). Cardiac disease was not associated with any type of MCI or with aMCI.

Conclusions: Cardiac disease is an independent risk factor for naMCI; within-sex comparisons showed a stronger association for women. Prevention and management of cardiac disease and vascular risk factors may reduce the risk of naMCI.

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MILD COGNITIVE IMPAIRMENT (MCI) is an important stage for the early detection of and intervention for dementia.[1] Amnestic MCI (aMCI) is hypothesized to preferentially progress to dementia due to Alzheimer disease,[2-4] whereas nonamnestic MCI (naMCI) may preferentially progress to vascular and other non-Alzheimer dementias.[5] This suggests that vascular risk factors and vascular diseases may be associated with naMCI; however, the associations have not been systematically examined.

Our studies in Olmsted County, Minnesota, have shown a higher risk for men than for women for both incident aMCI and incident naMCI.[6] This suggests that risk factors for MCI and its subtypes, or that the timing and frequency of these risk factors, may vary for men and women. The cardiovascular literature has demonstrated differences between men and women with regard to the age at development of vascular risk factors (in particular, cardiac disease) and the severity of these conditions when they present.[7] We previously observed a cross-sectional association of coronary heart disease with MCI, but we did not examine sex differences.[8] In the present prospective cohort study, we investigated the association of cardiac disease with MCI, aMCI, and naMCI by sex.

METHODS

STUDY COHORT AT BASELINE

The Mayo Clinic Study of Aging is a population-based study designed to investigate risk factors for MCI in Olmsted County. Details of the study design and subject recruitment are published elsewhere.[6,9,10] In brief, we constructed a sampling frame of Olmsted County resi-

dents who were 70 to 89 years of age on October 1, 2004 (n=9953) using the medical records-linkage system of the Rochester Epidemiology Project.[11,12] We selected an age- and sex-stratified random sample (n=5233) and identified 4398 residents who were eligible for the study. Of these, 2719 (61.8%) agreed to participate in the baseline assessment either in person (n=2050; full participants) or by telephone only (n=669). The study protocol was approved by the institutional review boards of the Mayo Clinic and the Olmsted Medical Center.

IN-PERSON EVALUATION

Each participant was interviewed by a nurse or a coordinator, evaluated by a physician, and underwent extensive cognitive testing by a psychometrist. The participant interview included a self-assessment of memory and demographic information; the Clinical Dementia Rating scale[13] and the Functional Activities Questionnaire were administered to an informant.[14] The physician evaluation included the Short Test of Mental Status,[15] a review of the medical history, and a neurological examination. The cognitive testing battery included 9 tests that assess function in memory, executive function, language, and visuospatial skills domains. The raw scores on each test were transformed into age-adjusted scores using normative data from Mayo's Older Americans Normative Studies and were scaled to have a mean (SD) of 10 (3).[16] Domain scores were computed by summing the adjusted and scaled test scores within a domain and rescaling the scores.[6,9,10]

DIAGNOSTIC CRITERIA

Cognitive domain scores were compared with the means (standard deviations) of domain scores generated by normal participants from the Olmsted County population.[16] A cognitive domain score of 1.0 SD or more below the mean was considered as possible cognitive impairment, but the decision about impairment was based on a consensus agreement among the examining physician, nurse, and neuropsychologist, taking into account education level, prior occupation, visual or hearing deficits, and other information.[6,9,10]

A diagnosis of MCI was defined according to published criteria as cognitive concern by the participant, informant, nurse, or physician; impairment in 1 or more of the 4 cognitive domains (from cognitive battery); essentially normal functional activities; and absence of dementia.[9,10,17] Participants with MCI were classified as having aMCI if the memory domain was impaired and naMCI if only nonmemory domains were impaired, and as having single- or multiple-domain aMCI or naMCI according to the number of cognitive domains that were impaired. Dementia was based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).[18] Participants who performed within the normative range and did not meet criteria for MCI or dementia were considered cognitively normal.[6,9,10,17]

CRITERIA FOR CARDIAC DISEASE

A history of cardiac disease (defined by ≥1 diagnosis of atrial fibrillation, coronary heart disease, or congestive heart failure) was ascertained from the medical records at baseline using the Rochester Epidemiology Project medical records-linkage system.[8,11] Atrial fibrillation was defined as electrocardiographic evidence of atrial fibrillation and/or treatment for atrial fibrillation. Coronary artery disease was defined as a history of myocardial infarction (including validated diagnoses of myocardial infarction from a separate surveillance study since 1979 in Olmsted County using standard epidemiologic criteria), percutaneous coronary intervention, coronary artery bypass grafting, angiographic coronary stenosis of greater than 50% in 1 or more coronary arteries based on information from the cardiac catheterization laboratory of the Mayo Clinic, or angina specifically attributed to ischemic cardiac pain with or without treatment, as previously described.[8] Congestive heart failure was defined as a physician diagnosis and the presence of characteristic symptoms of heart failure.

ASSESSMENT OF COVARIATES

At baseline, we assessed depressive symptoms using the Neuropsychiatric Inventory Questionnaire administered to an informant,[19] smoking history by interview, body mass index from measurement of height and weight, and moderate exercise by questionnaire. The physician assessed a history of stroke, which was validated from the medical records whenever possible. A history of type 2 diabetes mellitus, dyslipidemia, and hypertension was ascertained from the medical records, and *APOE* genotyping was determined.

LONGITUDINAL FOLLOW-UP

Follow-up of participants was performed at 15-month intervals using the baseline protocol for evaluation and diagnosis. A diagnosis of normal cognition, MCI, or dementia was made at every follow-up visit without taking into account any cognitive and clinical findings from previous evaluations. Full participants who declined an in-person evaluation at follow-up were invited to participate by use of a telephone interview that included the Telephone Interview of Cognitive Status–modified,[20] the Clinical Dementia Rating,[13] and the Neuropsychiatric Inventory Questionnaire.[19]

STATISTICAL ANALYSES

Full participants who were cognitively normal at baseline were considered at risk for incident MCI. Participants who developed dementia without an interim diagnosis of MCI were considered to have passed through an undetected MCI stage. The onset of MCI or dementia was defined by the midpoint between the last assessment as cognitively normal and the first-ever assessment as having MCI or dementia. Participants who refused participation further, who could not be contacted, or who died during follow-up were censored at their last evaluation. We computed the person-years of follow-up as the time from baseline evaluation to onset of MCI or dementia, censoring, or date of last follow-up. We estimated incidence rates by cardiac disease and sex using incidence density methods. Rates were directly standardized to the Olmsted County population on October 1, 2004,[6,10] and adjusted for nonparticipation at baseline as previously described.[21,22] Our analyses were restricted to participants who were full participants at baseline. We only considered a first MCI event and did not take into account participants who were identified as cognitively normal after an MCI diagnosis (n=69; 41 were men and 28 were women; $P=.17$).

We investigated the association of cardiac disease with incident MCI and MCI subtypes (aMCI and naMCI) using multivariable proportional hazards models with age as the timescale, and we estimated hazard ratios (HRs) and 95% CIs. All models were adjusted for education level (≤12 years vs >12 years), sex (when applicable), and nonparticipation at baseline using reciprocal probability weighting.[21,22] In a second model, we excluded participants with a history of stroke given that stroke is a strong risk factor for cognitive impairment. In a third model, we included participants with stroke and, additionally, adjusted for potential confounding by *APOE* ε4 geno-

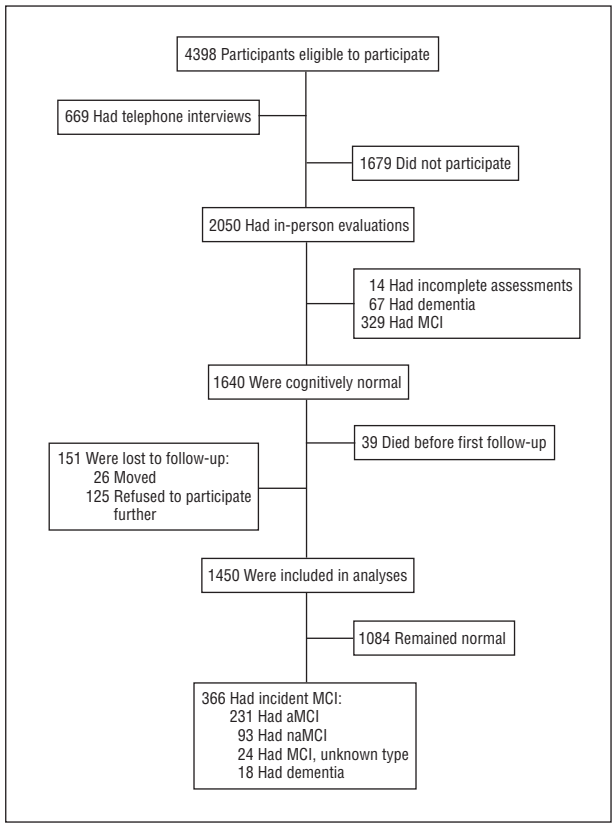

Figure 1. Study flowchart. There were 669 persons who participated only by telephone at baseline, and they were not included in the present study; 24 persons with mild cognitive impairment (MCI) participated by telephone at follow-up, and their MCI subtype is unknown; 18 developed dementia without an interim diagnosis of MCI. aMCI indicates amnestic MCI; and naMCI, nonamnestic MCI.

type, diabetes, hypertension, body mass index, depressive symptoms, use of statins, dyslipidemia, moderate exercise, and a history of stroke. We also examined potential effect modification by age at baseline, sex, education level, and *APOE* ε4 genotype.

RESULTS

STUDY SAMPLE

Figure 1 shows the flowchart of our study. Of the 1640 cognitively normal participants, 39 died before the first follow-up, and 151 were lost to follow-up. Participants lost to follow-up had a lower education level (55.0% had ≤12 years of education vs 43.2% of participants with follow-up; $P = .006$), but both participants lost to follow-up and those with follow-up were similar with regard to sex, age, frequency of stroke, and cardiac disease. Of 1450 participants with follow-up, 348 developed incident MCI and 18 developed incident dementia over a median of 4.0 years of follow-up (interquartile range, 2.5-5.1 years; 5351.4 person-years). Of the 348 participants with incident MCI, 231 (66.4%) had aMCI (154 with single-domain impairment and 77 with multiple-domain impairment), 93 (26.7%) had naMCI (73 with single-domain impairment and 20 with multiple-domain impairment), and 24 (6.9%) had MCI of unknown subtype (follow-up by telephone interview only). Of the 93 participants with naMCI, 87 (93.5%) had impairment in executive function, 20 (21.5%) in visuospatial skills, and 6 (6.5%) in language (these frequencies are not mutually exclusive).

Table 1 shows the characteristics of study participants at baseline by sex. Men were younger, more frequently married, and had a higher frequency of type 2 diabetes mellitus, atrial fibrillation, coronary heart disease, and any type of cardiac disease compared with women.

The frequency of cardiac disease was greater for younger and older men than for younger and older women (**Figure 2**A and B). Men 70 to 79 years of age at baseline had a higher frequency of atrial fibrillation (14.3% vs 5.4%; $P < .001$), coronary artery disease (48.1% vs 24.4%; $P < .001$), and any type of cardiac disease (52.2% vs 28.1%; $P < .001$) than women 70 to 79 years of age at baseline (Figure 2A); this pattern was similar for participants 80 to 89 years of age (Figure 2B). Both men and women showed higher frequencies of cardiac disease at 80 to 89 years of age at baseline than at 70 to 79 years age at baseline; however, older women differed more from younger women (14%; Figure 2C) than did older men differ from younger men (11%; $P = .52$; Figure 2D).

The incidence of MCI was higher for participants with cardiac disease than without (73.2 vs 62.1 per 1000 person-years): 75.7 vs 66.9 per 1000 person-years for men and 71.4 vs 58.7 per 1000 person-years for women. Differences for aMCI were minimal (data not shown). The incidence of naMCI was nearly 2-fold higher for participants with cardiac disease than without (23.4 vs 12.2 per 1000 person-years). In particular, the incidence was higher for women with cardiac disease than without (24.3 vs 7.4 per 1000 person-years) but was similar for men with cardiac disease and those without (22.3 vs 18.9 per 1000 person-years). **Figure 3** shows the cumulative incidence of naMCI by cardiac disease and sex.

COHORT ANALYSES FOR ANY TYPE OF MCI, aMCI, AND naMCI

Table 2 shows the associations of cardiac disease at baseline with risk of MCI and MCI subtypes. Cardiac disease was associated with naMCI for both men and women combined. However, the association varied by sex ($P = .02$ for interaction). For women, cardiac disease was associated with an increased risk of naMCI. The HR remained elevated even after the exclusion of participants with a history of stroke, and the association persisted in the fully adjusted model, including stroke. For men, the risk of naMCI did not differ by history of cardiac disease. There were no interactions of cardiac disease with age, education, or *APOE* ε4 carrier status. For women, the risk of naMCI was an HR of 2.25 (95% CI, 1.05-4.81) for atrial fibrillation, an HR of 2.05 (95% CI, 1.08-3.87) for coronary artery disease, and an HR of 2.82 (95% CI, 1.34-5.94) for congestive heart failure. For men, the estimates were an HR of 1.23 (95% CI, 0.65-2.34) for atrial fibrillation, an HR of 1.20 (95% CI, 0.70-2.04) for coronary artery disease, and an HR of 0.87 (95% CI, 0.34-2.19) for congestive heart failure.

Table 1. Distribution of Risk Factors at Baseline for Men and Women Separately and Combined

Characteristic	Participants, No. (%)			*P* Value[a]
	Both Sexes (n = 1450)	Men (n = 722)	Women (n = 728)	
Age at baseline, y				
70-79	766 (52.8)	414 (57.3)	352 (48.4)	.001
80-89	684 (47.2)	308 (42.7)	376 (51.6)	
Education, y				
>12	829 (57.2)	422 (58.4)	407 (55.9)	.33
≤12	621 (42.8)	300 (41.6)	321 (44.1)	
Marital status				
Married	903 (62.3)	600 (83.1)	303 (41.6)	<.001
Never or previously	547 (37.7)	122 (16.9)	425 (58.4)	
APOE genotype[b]				
ε3ε3, ε2ε2, and ε2ε3	1089 (75.5)	541 (75.0)	548 (75.9)	.85
ε3ε4 and ε4ε4	317 (22.0)	160 (22.2)	157 (21.7)	
ε2ε4	37 (2.6)	20 (2.8)	17 (2.4)	
BMI ≥ 30[c]				
No	1031 (72.4)	526 (73.8)	505 (71.0)	.25
Yes	393 (27.6)	187 (26.2)	206 (29.0)	
Dyslipidemia				
No	328 (22.6)	165 (22.9)	163 (22.4)	.83
Yes	1122 (77.4)	557 (77.1)	565 (77.6)	
Current smoker				
No	1399 (96.5)	695 (96.3)	704 (96.7)	.65
Yes	51 (3.5)	27 (3.7)	24 (3.3)	
Type 2 diabetes mellitus				
No	1202 (82.9)	583 (80.7)	619 (85.0)	.03
Yes	248 (17.1)	139 (19.3)	109 (15.0)	
Hypertension				
No	350 (24.1)	171 (23.7)	179 (24.6)	.69
Yes	1100 (75.9)	551 (76.3)	549 (75.4)	
Any cardiac disease[d]				
No	781 (53.9)	310 (42.9)	471 (64.7)	<.001
Yes	669 (46.1)	412 (57.1)	257 (35.3)	
Atrial fibrillation				
No	1238 (85.4)	592 (82.0)	646 (88.7)	<.001
Yes	212 (14.6)	130 (18.0)	82 (11.3)	
Coronary artery disease				
No	861 (59.4)	340 (47.1)	521 (71.6)	<.001
Yes	589 (40.6)	382 (52.9)	207 (28.4)	
Congestive heart failure				
No	1300 (89.7)	643 (89.1)	657 (90.2)	.46
Yes	150 (10.3)	79 (10.9)	71 (9.8)	
Stroke				
No	1312 (90.5)	649 (89.9)	663 (91.1)	.44
Yes	138 (9.5)	73 (10.1)	65 (8.9)	

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] *P* values refer to men vs women.

[b] Because 7 participants had missing data (1 man and 6 women), the percentages were computed among the remaining informative sample. The *P* value for ε4 carrier vs noncarrier was .80 (with ε2ε4 excluded).

[c] Because 26 participants had missing data (9 men and 17 women), the percentages were computed among the remaining informative sample.

[d] Any cardiac disease was defined as 1 or more diagnoses of atrial fibrillation, coronary artery disease, or congestive heart failure.

COMMENT

In our population-based elderly cohort, a history of cardiac disease was significantly associated with an increased risk of naMCI. The association varied by sex; men with cardiac disease had the highest risk of naMCI. However, the HR for the association of cardiac disease with naMCI within the same-sex group was greater among women than men. These findings suggest that cardiac disease is an independent, modifiable risk factor for naMCI in older persons, particularly in women.

Our findings support the hypothesis that naMCI has a vascular etiology.[23] For women, the association of cardiac disease with naMCI persisted after the exclusion of participants with a history of stroke and after adjustment for several confounders. The similar incidences of naMCI for men with and without cardiac disease (both of which are higher than for women without cardiac disease) suggests that factors besides cardiac disease (eg, stroke) may account for this higher incidence in men without cardiac disease. Consistent with this, the HR for naMCI for women was nonsignificantly elevated after the

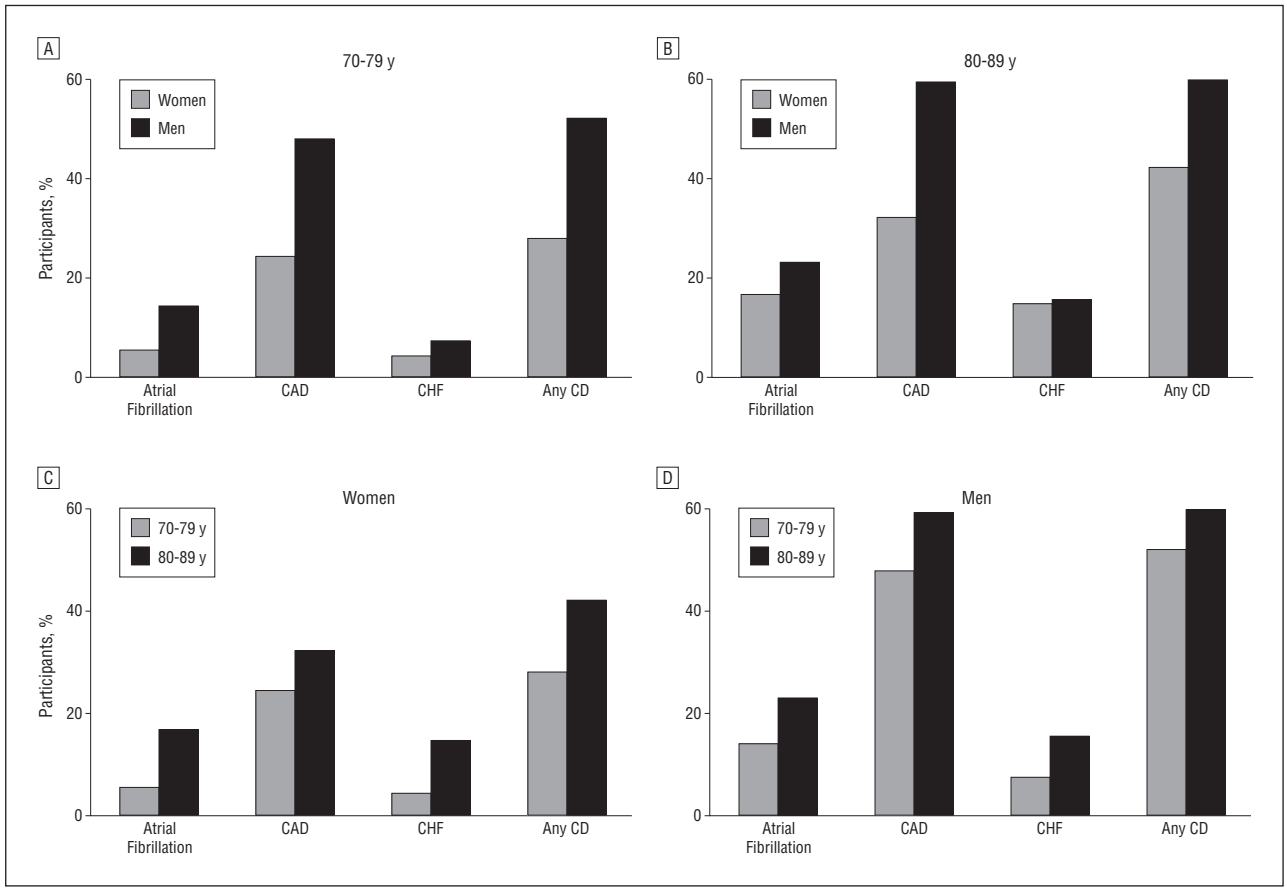

Figure 2. Frequency of cardiac disease by age (A and B) and sex (C and D). CAD indicates coronary artery disease; CD, cardiac disease; and CHF, congestive heart failure.

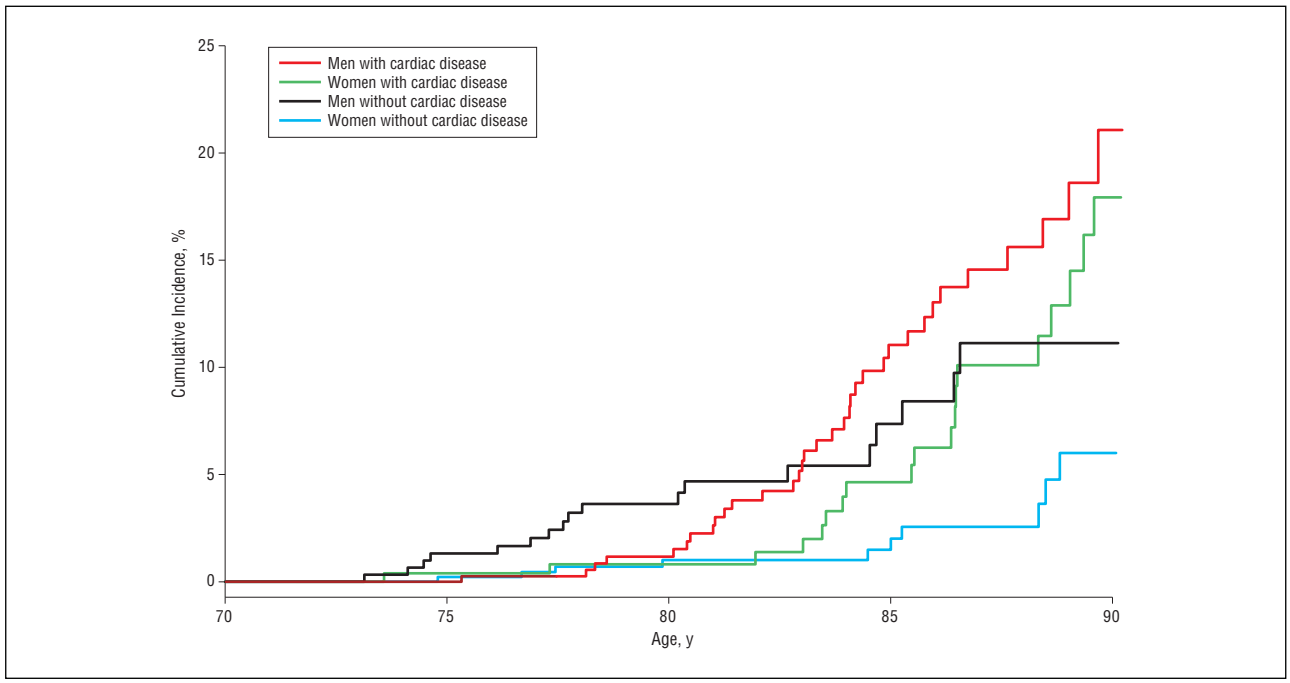

Figure 3. Cumulative incidence of nonamnestic mild cognitive impairment by disease and sex. The cumulative incidence at 90 years of age was 21% for men (red) and 18% for women (green) with cardiac disease and was 11% for men (black) and 6% for women (blue) without cardiac disease.

Table 2. Association of Cardiac Disease With Incident MCI and MCI Subtypes by Sex[a]

Variable	Persons at Risk, No.	Persons With Incident MCI, No. (%)	Model 1[b] HR (95% CI)	Model 1[b] *P* Value	Model 2[c] HR (95% CI)	Model 2[c] *P* Value	Model 3[d] HR (95% CI)	Model 3[d] *P* Value
Any MCI								
Men								
No	310	75 (24.2)	1.0 [Reference]		1.0 [Reference]		1.0 [Reference]	
Yes	412	113 (27.4)	1.13 (0.84-1.51)	.41	1.15 (0.84-1.57)	.38	1.00 (0.70-1.43)	.99
Women								
No	471	102 (21.7)	1.0 [Reference]		1.0 [Reference]		1.0 [Reference]	
Yes	257	76 (29.6)	1.17 (0.87-1.58)	.30	1.16 (0.84-1.60)	.37	1.22 (0.86-1.74)	.26
Both sexes								
No	781	177 (22.7)	1.0 [Reference]		1.0 [Reference]		1.0 [Reference]	
Yes	669	189 (28.3)	1.16 (0.94-1.43)	.16	1.16 (0.93-1.45)	.18	1.10 (0.86-1.41)	.45
Amnestic MCI[e]								
Men								
No	310	52 (16.8)	1.0 [Reference]		1.0 [Reference]		1.0 [Reference]	
Yes	412	69 (16.7)	1.01 (0.70-1.45)	.96	1.08 (0.74-1.59)	.69	0.87 (0.57-1.33)	.51
Women								
No	471	69 (14.6)	1.0 [Reference]		1.0 [Reference]		1.0 [Reference]	
Yes	257	41 (16.0)	0.97 (0.65-1.43)	.87	1.00 (0.66-1.52)	1.0	0.91 (0.58-1.43)	.69
Both sexes								
No	781	121 (15.5)	1.0 [Reference]		1.0 [Reference]		1.0 [Reference]	
Yes	669	110 (16.4)	1.00 (0.76-1.30)	.97	1.04 (0.79-1.39)	.76	0.89 (0.65-1.20)	.44
Nonamnestic MCI[e]								
Men								
No	310	20 (6.5)	1.0 [Reference]		1.0 [Reference]		1.0 [Reference]	
Yes	412	34 (8.3)	1.16 (0.68-1.99)	.59	1.09 (0.61-1.93)	.78	1.45 (0.73-2.89)	.29
Women								
No	471	14 (3.0)	1.0 [Reference]		1.0 [Reference]		1.0 [Reference]	
Yes	257	25 (9.7)	3.07 (1.58-5.99)	.001	2.48 (1.23-5.01)	.01	2.47 (1.17-5.21)	.02
Both sexes								
No	781	34 (4.4)	1.0 [Reference]		1.0 [Reference]		1.0 [Reference]	
Yes	669	59 (8.8)	1.77 (1.16-2.72)	.009	1.53 (0.98-2.41)	.06	1.84 (1.12-3.03)	.02

Abbreviations: HR, hazard ratio; MCI, mild cognitive impairment.
[a] Defined as the presence of atrial fibrillation, coronary artery disease, or congestive heart failure.
[b] Model 1 is adjusted for education at baseline, for potential nonparticipation at baseline, for sex where applicable, and with age as the time variable.
[c] Model 2 includes model 1 variables but excludes participants with a history of stroke.
[d] Model 3 includes model 1 variables, with additional adjustment for *APOE* ε4 genotype (ε3ε4 and ε4ε4 vs no ε4; participants with ε2ε4 were excluded), type 2 diabetes, hypertension, obesity, depressive symptoms, statin use, and moderate exercise, and includes participants with a history of stroke.
[e] For 24 participants, the MCI subtype was unknown because MCI was only determined by a telephone interview at follow-up.

exclusion of participants with a history of stroke, suggesting potential confounding of the association by stroke. Other mechanisms may contribute to the association of cardiac disease with naMCI. Cardiac sympathetic nerve dysfunction, detected by myocardial scintigraphy, has been associated with Lewy body diseases such as dementia with Lewy bodies, Parkinson disease, and Parkinson dementia.[24-26] This suggests that cardiac sympathetic nerve dysfunction may be an early marker of these non-Alzheimer dementias or that there is a shared etiology involving α-synuclein protein misfolding.[25] Obstructive sleep apnea, a risk factor for cardiovascular disease and stroke, may also play a role through hypoxia.[27,28] Finally, cardiac disease may contribute to cerebrovascular disease through microemboli to the brain from atrial fibrillation or hypoperfusion of the brain from impaired cardiac function. These adverse effects may lead to neuronal injury and to an increased risk of MCI, particularly of the naMCI subtype. This is consistent with our observation of possible confounding by stroke in the association of cardiac disease with naMCI for both men and women separately, including the suggestion that stroke is in the causal pathway for the association in women.

We previously reported a higher incidence of both aMCI and naMCI in men compared with women.[6,9,10] This may relate to the higher frequency of cardiac disease for men compared with women in our cohort. Some studies[29,30] have shown an earlier occurrence of death due to cardiovascular disease and coronary artery disease among men compared with women. This raises the possibility that men with severe cardiac disease may be underrepresented in our cohort owing to survival bias or nonparticipation and that our estimates may be biased toward the null association. The tendency to an earlier onset and higher frequency of vascular risk factors, and the earlier development of cardiac disease for men compared with women, may lead to an earlier and higher incidence of MCI in men.[7] This tendency in men has been attributed to the earlier occurrence of central obesity,[31-34] a harbinger of insulin resistance, dyslipidemia, and coronary artery disease.[35-37] Indeed, the men in our cohort had a higher frequency of cardiac disease at baseline than did the

women, particularly at younger ages (Figure 2A and B). The increased risk of naMCI for men without cardiac disease compared with women without cardiac disease may be due in part to a higher frequency of vascular risk factors or subclinical cardiac disease.

In contrast, the development of cardiac disease may be delayed in women, but the effects may be more pronounced when they occur. This is consistent with the 3-fold increased risk of naMCI for women with vs without cardiac disease in our cohort. The later onset of cardiac disease for women has been described as a "cardiovascular advantage" and has been attributed to endogenous estrogen[38,39] and the ability of women (but not men) to increase the level of high-density lipoprotein in response to a diet high in saturated fat.[40] After menopause, women lose this cardiovascular advantage,[7,41,42] resulting in a 2- to 3-fold increased risk of coronary heart disease, with more dire consequences.[7] Thus, women may have a later onset of MCI, but when cognitive impairment occurs, it may progress more rapidly from MCI to dementia; alternately, cognition may decline so quickly that an MCI syndrome preceding dementia is not recognized. These hypotheses about sex differences in MCI etiology will be examined in a longer follow-up of our cohort.

Our findings are consistent with those of several investigators who have shown associations of cardiovascular disease with cognitive impairment and dementia.[8,43-47] Other studies have reported associations of cardiac disease with cognitive impairment,[48-51] a greater likelihood of naMCI than aMCI in subjects with heart disease,[50,52] a higher frequency of ischemic heart disease among men than women as observed in our study,[53-56] and that the effects of cardiac disease on cognitive impairment and on risk factors for cognitive impairment are greater in women than in men.[57] In the Rotterdam Study,[58] atrial fibrillation was associated with cognitive impairment in women but not in men. In the Framingham Study,[59] women with coronary artery disease, cardiac failure, and atrial fibrillation had a 3-fold higher risk of stroke than did men with those conditions. In contrast, some studies[60,61] did not find associations of atrial fibrillation with incident MCI.

A potential limitation of our study was that nonparticipants at baseline were more likely to be older, to be men, and to have greater comorbidity.[9] Despite the adjustment for potential nonparticipation bias using residual probability weighting, there may be some residual bias and an underestimation of the magnitude of associations. We did not take into account incident cardiac disease during follow-up. Third, the Olmsted County population is predominantly of Northern European ancestry, and although our findings may not apply to other ethnic groups,[9] they may be representative of US whites.[12]

Our study has several strengths. It was designed specifically to study risk factors for MCI; thus, risk factors were assessed at baseline, and the diagnosis of MCI was made during follow-up using published criteria. The population-based design reduced the potential for selection and volunteer biases. The internal validity of our findings was enhanced by the use of the medical records-linkage system to ascertain the history of vascular risk factors and vascular diseases at baseline, and to adjust for nonparticipation using propensity scores. The comprehensive cognitive evaluation by 3 independent evaluators who were kept unaware of previous diagnoses enhanced the validity of the MCI diagnosis.

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Author Contributions: Dr Roberts had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Roberts, Geda, Pankratz, Ivnik, and Petersen. *Acquisition of data:* Roberts, Geda, Knopman, Boeve, Tangalos, Ivnik, and Petersen. *Analysis and interpretation of data:* Roberts, Knopman, Cha, Pankratz, Mielke, and Petersen. *Drafting of the manuscript:* Roberts, Cha, and Petersen. *Critical revision of the manuscript for important intellectual content:* Roberts, Geda, Knopman, Pankratz, Boeve, Tangalos, Ivnik, Mielke, and Petersen. *Statistical analysis:* Cha and Pankratz. *Obtained funding:* Roberts, Tangalos, and Petersen. *Administrative, technical, and material support:* Roberts, Boeve, Ivnik, and Petersen. *Study supervision:* Roberts, Ivnik, and Petersen.
Conflict of Interest Disclosures: Dr Knopman serves as deputy editor for *Neurology*, serves on a data safety monitoring board for Lilly Pharmaceuticals, is an investigator in a clinical trial sponsored by Elan Pharmaceuticals, and receives research support from the National Institutes of Health (grants R01 AG011378, P50 AG016574, U01 AG006786, AG029550, AG032306, and U01 096917). Dr Petersen reported that he serves on scientific advisory boards for Pfizer Inc, Janssen Alzheimer Immunotherapy, Elan Pharmaceuticals, and GE Healthcare; has given a CME lecture for Novartis Inc; receives royalties from the publication of a book entitled *Mild Cognitive Impairment* (Oxford University Press, 2003); and receives research support from the National Institute on Aging (grants P50 AG016574 [principal investigator] and U01 AG006786 [principal investigator]) and the National Institutes of Health (grants R01 AG011378 [coinvestigator] and U01 AG024904 [coinvestigator]). Dr Roberts currently receives research support from the National Institute on Aging (grant U01 AG006786 [coinvestigator]), Abbott Laboratories, and the Driskill Foundation and previously received support through grant K01 AG028573 (principal investigator). Dr Tangalos served on a data safety monitoring board for Lilly Pharmaceuticals, remains an advisor to Lilly Pharmaceuticals, and is an investigator with Baxter.
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