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Mortality in mild cognitive impairment varies by subtype, sex and lifestyle factors. The Mayo Clinic Study of Aging

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Abstract

Background—Etiologic differences in mild cognitive impairment (MCI) subtypes may impact mortality.

Objective—To assess the rate of death in MCI overall, and by subtype, in the population-based Mayo Clinic Study of Aging.

Methods—Participants aged 70–89 years at enrollment were clinically evaluated at baseline and 15-month intervals to assess diagnoses of MCI and dementia. Mortality in MCI cases vs. cognitively normal (CN) individuals was estimated using Cox proportional hazards models.

Results—Over a median follow-up of 5.8 years, 331 of 862 (38.4%) MCI cases and 224 of 1292 (17.3%) cognitively normal participants died. Compared to CN individuals, mortality was elevated in persons with MCI (hazard ratio [HR] = 2.03; 95% CI: 1.61 to 2.55), and was higher for non-amnesic MCI (naMCI; HR = 2.47; 95% CI: 1.80 to 3.39) than for amnesic MCI (aMCI; HR = 1.89; 95% CI: 1.48 to 2.41) after adjusting for confounders. Mortality varied significantly by sex, education, history of heart disease, and engaging in moderate physical exercise (p for interaction <0.05 for all). Mortality rate estimates were highest in MCI cases who were men, did not exercise, had heart disease, and had higher education vs. CN without these factors, and for naMCI cases vs. aMCI cases without these factors.

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DISCLOSURES

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Conclusions—These findings suggest stronger impact of etiologic factors on naMCI mortality. Prevention of heart disease, exercise vigilance, may reduce MCI mortality. Delayed MCI diagnosis in persons with higher education impacts mortality, and higher mortality in men may explain similar dementia incidence by sex in our cohort.

Keywords

Mild cognitive impairment; mortality; cohort studies; incidence studies; prognosis; outcomes research

INTRODUCTION

Mild cognitive impairment (MCI) is considered an intermediate stage between normal cognitive function and dementia [1]. It is an important clinical entity for the study of aging as both the incidence and prevalence of MCI are high in the elderly population [2]. Previous studies have demonstrated an increased risk of mortality in MCI cases compared to cognitively normal (CN) individuals [2–6]. However, only one of these studies [6] differentiated between mortality rates in amnesic MCI [aMCI; single (SD) and multiple domain (MD)] and non-amnesic MCI (naMCI), but provided no information on impact of number of domains affected on mortality for the naMCI.

MCI phenotypes, assessed by the subtype (aMCI, naMCI) or by the number of domains affected, may impact MCI outcomes. The number of domains affected reflects the extent or severity of disease; for example, MD MCI is associated with a higher risk of progression to dementia [2]. Furthermore, etiologic differences in MCI subtypes [2] may have implications for mortality and may provide insights for reducing mortality in persons with MCI. We hypothesize that mortality in MCI may differ by subtype and number of domains affected. These associations have not been fully examined, but are clinically important since excess mortality in MCI should be considered in long-term care planning for patients with MCI, and is of public health importance. The objective of the current study, therefore, was to compare mortality in persons with MCI overall and by subtype and number (single vs. multiple) of affected domains, with mortality in cognitively normal (CN) individuals in the Mayo Clinic Study of Aging (MCSA).

MATERIALS AND METHODS

Study design and participants

Participants were an age- and sex-stratified random sample of non-demented Olmsted County, Minnesota, residents, 70–89 years old on October 1, 2004 (N = 1,969), and March 1, 2008 (N= 521). All individuals were identified using the Rochester Epidemiology Project (REP) [7] medical records linkage system. Details of the MCSA design and methodology have previously been published [8]. The present analysis includes 2,154 individuals who were without dementia at the baseline in-person evaluation.

Standard protocol approvals, registrations and patient consent

The study protocol was approved by the institutional review boards of the Mayo Clinic and the Olmsted Medical Center. All individuals provided written informed consent before participating.

Measurements of cognitive function

All study participants were interviewed by a nurse or study coordinator, had a neurological evaluation by a physician, and completed neuropsychological testing administered by a psychometrist [8]. The interview included questions on memory administered to the participant, and the Clinical Dementia Rating scale [9] and Functional Activities Questionnaire [10] were administered to an informant. The physician examination included a medical history review, a complete neurological examination, administration of the Short Test of Mental Status [11] and the Unified Parkinson's Disease Rating Scale [12].

The neuropsychological testing used nine tests to assess performance in four domains: (i) *memory* [Logical Memory–II (delayed recall) and Visual Reproduction–II (delayed recall) from the Wechsler Memory Scale–Revised and the Auditory Verbal Learning Test] [13, 14]; (ii) *executive function* (Trail Making Test Part B, and Digit Symbol Substitution from Wechsler Adult Intelligence Scale–Revised) [15, 16]; (iii) *language* (Boston Naming Test and Category Fluency Test) [17, 18]; and (iv) *visuospatial skills* (Picture Completion and Block Design from the Wechsler Adult Intelligence Scale–Revised) [16]. Raw scores were age-adjusted using normative data [19]. The age-adjusted scores for tests in each domain were scaled, summed and scaled again to obtain the domain-specific cognitive z-scores. For each domain, a score greater than one standard deviation (SD) below the age-specific mean was considered as possible cognitive impairment. However, the final decision for a diagnosis of MCI, dementia or normal cognition was made by a consensus decision of the 3 evaluators following a review of all the available information [8, 20].

MCI criteria

The criteria for MCI included: (i) cognitive concern raised by the participant, informant, study coordinator, or examining physician; (ii) impairment in one or more of the four cognitive domains from the cognitive battery of tests; (iii) essentially normal functional activities; and (iv) absence of dementia. Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [21]. Individuals with MCI were categorized as having amnesic MCI (aMCI) and non-amnesic MCI (naMCI), and as single (SD) or multiple domain (MD) aMCI and naMCI based on number of affected domains. Participants were categorized as cognitively normal (CN) if they did not meet criteria for MCI or dementia and performed in the normal cognitive range based on the normative data for this community [22].

Covariates and potential confounders

Participant information collected at the baseline evaluation included age, sex, educational attainment, and weight, height, and gait-speed (m/s). Medical co-morbidities including diabetes mellitus, hypertension, stroke, and heart disease (defined as history of atrial

fibrillation, coronary heart disease, or congestive heart failure) were ascertained using the REP medical records linkage system. Depressive symptoms and apathy were ascertained using the Neuropsychiatric Inventory Questionnaire (NPI-Q) [23], and moderate physical exercise (i.e., brisk walking, hiking, aerobics, strength training, golfing without a golf cart, swimming, tennis doubles, moderate use of exercise machines, yoga, martial arts, and weight lifting) in the year prior to enrollment was assessed by questionnaire [24]. Blood was drawn and Apolipoprotein E (APOE) genotype was determined.

Longitudinal follow-up and ascertainment of death

Participants were evaluated at 15-month intervals using the same protocol used at baseline to assess diagnoses of cognitively normal, MCI or dementia. Deaths during follow-up were determined from Mayo Clinic databases. In addition, the underlying cause of death was retrieved using the REP resources for 527 of the 555 participants (95%) who died during the follow-up period. The causes of death were assigned to five categories: the circulatory system, dementia, the respiratory system, neoplasms and 'other' [25].

Statistical analysis

Baseline differences between MCI cases and controls were examined using Chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables. As the aim of the study was to assess the association of MCI with mortality, individuals who progressed from CN to dementia without a diagnosis of MCI ($n=23$) during follow-up were excluded. We considered MCI/CN status as a time-dependent covariate; thus, we categorized subjects according to their diagnosis at each cycle (CN, CN with previous MCI, MCI) and computed the follow-up time in that category. Kaplan-Meier survival curves - taking into account age at baseline visit and age at death or last contact alive - were constructed for persons with MCI (any and by subtypes) vs. individuals who remained CN during follow-up (reference group); differences in survival were estimated using the log-rank test. Hazard ratios (HR) and 95% confidence intervals (95% CI) for mortality for MCI vs CN were initially estimated using Cox proportional hazards models using age as the time variable [26], and adjusting for sex, education and APOE $\epsilon 4$ carrier status (any $\epsilon 4$ vs. none). In addition, variables with an established or potential association with MCI and mortality (i.e., history of stroke, heart disease, diabetes mellitus, hypertension, depression, apathy, baseline gait-speed, body mass index, marital status and participation in moderate physical exercise), were considered as potential confounders. Variables that were significantly associated with MCI and death in the bivariate associations ($P<0.05$) were included in the final multivariable models. Consequently, the final multivariable Cox proportional hazards models were adjusted for sex, years of education, APOE $\epsilon 4$ carrier status, baseline gait-speed, history of stroke, heart disease, diabetes mellitus, hypertension, physical activity, depression and apathy. As the sample size decreased with each sub-categorization (especially for the naMCI group), analysis was employed only by type of MCI (aMCI and naMCI) and single vs. multiple (i.e. >1) domains affected in each subtype (aMCI, naMCI). Potential effect modification by the potential confounders was examined; interaction terms with APOE $\epsilon 4$ carrier status, hypertension and history of stroke were not statistically significant and data are not presented.

All hypothesis testing was conducted assuming an $\alpha < 0.05$ significance level and a two-sided alternative hypothesis. All statistical analyses were performed using SAS (SAS Institute, Cary, NC).

RESULTS

Participant characteristics

Among 2,154 participants at enrollment, 1,292 were cognitively normal and 862 had MCI. Of the 862 MCI cases, 406 (47.1%) had prevalent MCI (298 with aMCI and 108 with naMCI) and 456 (52.9%) developed incident MCI during the follow-up (334 with aMCI and 122 with naMCI). One-hundred-eighty-one MCI cases developed dementia at a later follow-up visit.

Characteristics of the MCI cases by subtype, and CN individuals, are presented in Table 1. Compared to CN or aMCI, participants with naMCI had lower education, slower gait speed, higher body mass index, and higher frequency of diabetes, stroke, heart disease, depressive symptoms, and death, but a lower frequency of moderate exercise. Compared to CN participants, MCI cases combined were older, had fewer years of education, a slower gait speed, a lower frequency of engagement in moderate exercise at baseline and of being married, and had a higher frequency of an APOE $\epsilon 4$ allele, diabetes mellitus, a history of stroke or heart disease, and depressive symptoms or apathy.

At baseline, individuals with naMCI were more likely to have myocardial infarction ($p = 0.046$), hemiplegia ($p = 0.005$) and cerebrovascular disease ($p = 0.051$) compared to aMCI individuals. Similarly, at the last study visit, individuals with naMCI had a significantly higher frequency of cerebrovascular disease ($p = 0.011$) and hemiplegia ($p = 0.011$) compared to individuals with aMCI (results not shown in tables).

The characteristics of participants by MCI subtype and number of domains affected are presented in Supplementary Table 1. Of the 862 individuals with MCI, 632 (73%) were diagnosed with aMCI (392 [62%] had single domain (SD) aMCI] and 230 with naMCI (182 [79%] had SD naMCI). Multiple domain (MD) naMCI had the smallest sample size ($n = 23$) but the highest frequency of deaths (47.9%) compared to 37% of SD aMCI, 35.4% of MD aMCI and 41.8% of SD naMCI.

Survival and mortality associated with MCI

Over a median (IQR) follow-up of 5.8 years (3.9, 7.4), there were 331 (38.4%) deaths in individuals with MCI compared to 224 (17.3%) deaths in CN individuals. Participants with MCI were more likely to have dementia and less likely to have neoplasms as their underlying cause of death compared to CN individuals, but there were no significant differences in the underlying cause of death between individuals with aMCI and naMCI, including dementia as cause of death (Supplementary Table 2). Based on participants who were cognitively normal or had prevalent MCI diagnosis at baseline. The median survival age was highest for CN individuals (92.6 years) lower for individuals with aMCI (aMCI: 88.4, SD aMCI: 87.8 and MD aMCI: 89.4 years, respectively). Individuals with naMCI had

the shorter median survival (naMCI: 85.1, SD naMCI: 87.7 and MD naMCI: 75.7 years, respectively; Fig. 1; log rank test $p < 0.001$ for all comparisons).

Compared to CN individuals, mortality was increased in persons with MCI (hazard ratio [HR] = 2.03; 95% CI: 1.61 to 2.55), with higher estimates for prevalent than for incident MCI cases (Table 2). In multivariable analyses by MCI subtype, mortality rate estimates were higher for naMCI (HR = 2.47; 95% CI: 1.80 to 3.39) than for aMCI (HR = 1.89; 95% CI: 1.48 to 2.41) compared to CN. When examined by number of domains affected, the HRs were significantly elevated for both SD and MD aMCI and naMCI; estimates for both SD and MD naMCI individuals were higher than for SD and MD aMCI. Lastly, estimates for SD aMCI were higher than for MD aMCI, but HRs for MD naMCI were higher than those for SD naMCI.

There were significant interactions (both additive and multiplicative) between MCI and sex ($p=0.047$), education ($p=0.019$), history of heart disease ($p=0.006$) and participation in moderate physical exercise ($p=0.004$). Specifically, HRs were highest for MCI cases who were men, had a higher education (>12 years), history of heart disease, and who did not exercise (Figure 2; Table 3). A similar pattern of interactions was observed when examined by MCI subtype. The mortality rate estimates were highest for participants with naMCI who were men, had heart disease, did not exercise or had high education when compared to CN without the opposite characteristics (Supplementary Table 3).

DISCUSSION

The present population-based prospective study indicated an increased mortality in individuals with MCI compared to CN individuals over a median follow-up of almost 6 years. The hazard ratio was elevated for both MCI subtypes, but was higher for naMCI than aMCI, for single than for multiple domain aMCI, and for multiple than for single domain naMCI. The study findings also suggest that the association of MCI with mortality is modified by sex, years of education, history of heart disease and participation in moderate physical exercise.

Previous studies have also indicated an increased risk for mortality in persons with MCI compared to cognitively normal individuals [2–6]. A recent study reported an increased HR of death in naMCI (SD and MD combined) and for both SD aMCI and MD aMCI at 13 years of follow-up, with MD aMCI having the highest mortality rate compared to cognitively normal individuals [6]; only the MD aMCI had an increased HR for death compared to CN individuals at 5 years. [6] By contrast, the present findings suggested higher mortality rates in general for naMCI than for aMCI (versus. the CN group). It is not always easy to explain differences in results between studies. However, differences in study methodology (e.g., criteria used, follow-up time, or covariates employed in analyses) [6] and study populations (e.g. age range, distributions of risk factors and comorbidities in the population, etc.) could partly explain differences in findings across studies. Our finding that MD naMCI had a higher mortality rate than SD naMCI (vs. CN individuals) is consistent with our hypothesis that multi-domain MCI might have a greater extent of disease than single domain MCI which therefore could contribute to a higher mortality risk. Despite this,

HRs were similar for any SD MCI compared to any MD MCI, and for SD aMCI compared to MD aMCI; however these estimates were all significantly elevated compared to CN. Continued follow-up of the MCSA cohort over a longer follow-up period and with a greater number of accrued deaths will determine whether estimates of risk are indeed higher for MD than SD MCI.

Differences in MCI progression to dementia, etiologic differences, and co-morbidities in the elderly could account for the observed differences in mortality in the MCI subtypes. Individuals with aMCI and naMCI with and without later dementia had an elevated mortality compared to CN individuals. However, the HR was higher for aMCI and naMCI cases who progressed to dementia compared to those who did not, with higher estimates for naMCI than aMCI. This could suggest that differences in MCI etiology or a greater burden of comorbidities among those who developed dementia, in addition to the effects of dementia, contributed to the higher mortality rate. Indeed, at baseline and also at last follow-up we observed significant differences between individuals with aMCI and naMCI in regard to myocardial infarction and cerebrovascular disease. Furthermore, this is consistent with the interaction of heart disease with MCI observed in the present study. Together, these findings suggest that cardiovascular and/or cerebrovascular diseases contribute to mortality among individuals with MCI and especially with naMCI, which is etiologically related to heart disease, stroke, and possibly to age-related vascular brain injury [27–31]. The higher frequency of myocardial infarction and hemiplegia in participants with naMCI vs. aMCI at baseline suggest that vascular conditions could have played a role in mortality in naMCI. Lastly, shared risk factors for cardiovascular disease and naMCI such as sleep apnea [32], may increase both etiology and mortality in naMCI. Together, our findings suggest that prevention and optimal management of risk factors for MCI may not only prevent MCI risk, but may also reduce MCI mortality rates.

The higher mortality rate in men with MCI is consistent with other studies [6, 33]. Men have a lower life expectancy and a higher mortality rate in 6 out of the 10 major causes of death in the US [34]. Previous findings in the MCSA cohort showed a higher frequency of heart disease in men than in women [27]. However, adjustment for history of heart disease in models stratified by sex did not appreciably decrease the mortality rates (data not presented), suggesting that other factors may also be involved.

Physical activity is beneficial for multiple chronic conditions (e.g., coronary heart disease, hypertension, stroke, diabetes type 2, metabolic syndrome, colon and breast cancer, or depression), and all-cause mortality [35]. In addition, a growing body of literature suggests that exercise attenuates cognitive impairment and dementia risk [36]. Physical activity may attenuate neurodegeneration and age-related loss of synapses, facilitate neuroprotective neurotrophic factors and neuroplasticity, and reduce the occurrence of vascular risk factors that are detrimental to cognitive function and dementia risk [36]. These beneficial effects of exercise are consistent with the higher rates of mortality in persons with aMCI and naMCI who did not exercise.

In the present study, MCI cases with higher education had the highest mortality rate. Our findings are consistent with some [37, 38, 39], but not all previous studies [37, 38]. However,

our results are consistent with the hypothesis that education may be a proxy for cognitive reserve. With increasing brain pathology, persons with higher education activate compensatory processes that delay the clinical manifestations of cognitive impairment [39]. Thus, the later diagnosis of MCI may be accompanied by more severe underlying brain pathology, faster cognitive and functional decline, and increased mortality [37].

The higher mortality rate in participants with MCI has important public health implications given the role of dementia as an important cause of death [6]. Since clinical MCI is considered a prodromal stage of dementia, the American Academy of Neurology recommends that clinicians monitor MCI patients for adverse outcomes [40]. Greater attention to management of co-morbidities (such as sleep apnea, depression, certain medications, heart disease, diabetes, atrial fibrillation) [41] could reduce MCI risk and progression to dementia. In the absence of approved medication for MCI, non-pharmacologic interventions such as engagement in intellectually stimulating activities, social activities, regular physical exercise, and appropriate nutrition could reduce, prevent, or delay MCI risk, progression to dementia, and mortality [42, 43].

The current study has several strengths. This is a large, prospective, population-based study that avoids temporal ambiguity between MCI and mortality and strengthens causal inference. Participants undergo a comprehensive evaluation to assess cognitive function, and the diagnosis is made by a consensus decision of three independent evaluators who are blinded to previous MCI diagnosis, thus reducing misclassification bias and enhancing the validity of MCI diagnosis.

The study has certain potential limitations. Despite the adjustment for several potential confounders in the statistical models, there may be residual confounding. We included gait-speed in the models since it was associated with mild cognitive impairment and mortality in our data and may be a marker for overall health and physical functioning [44]. However, we recognize that this could constitute over-adjustment and may have biased our findings toward the null. This is particularly relevant to models that compared mortality in MCI individuals who later developed dementia to CN individuals since gait speed could be in the causal pathway from brain pathology to dementia. A longer period of follow-up and a greater number of accrued deaths (e.g. for MD naMCI) should enhance the precision of these estimates. Finally, MCSA participants were mostly of Northern European descent, thus generalizing findings to other ethnicities should be done with caution.

The present findings suggest that MCI, regardless of type and number of domains affected, is associated with increased mortality compared to CN individuals. The findings also underscore the importance of MCI prevention by preventing or managing modifiable risk factors, effectively managing co-morbidities, vigilance in monitoring the clinical course of MCI, and developing non-pharmacologic interventions to prevent and reduce MCI progression to dementia and death.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Survival of individuals with MCI and cognitive normal individuals. Kaplan-Meier survival curves for single domain (SD aMCI), multiple domain (MD aMCI), single domain (SD naMCI), multiple domain (MD naMCI), vs. cognitively normal participants (No MCI) (median survival, 87.8, 89.4, 87.7, 75.7 versus 92.6 years respectively; $p < 0.001$).

Figure 2.

Interaction of mild cognitive impairment (MCI) with sex, heart disease (ht), participation in moderate physical exercise and education, and hazard of death. Hazard ratio estimates by MCI or cognitively normal (CN) individuals and categories of the effect modifiers, i.e., sex (A), heart disease (B), physical exercise (C) and education (D), retained from Cox proportional hazards models using age as time variable; sex stratified models (A) were adjusted for education and APOE $\epsilon 4$ carrier status, the remaining models (B, C, D) were also adjusted for sex.

Table 1

Characteristics of participants at baseline by cognitive status. The Mayo Clinic Study of Aging.

Baseline Characteristics	aMCI (n=632)	naMCI (n=230)	Cognitively Normal (n=1292)
Age, mean (SD), years	83.19 (5.31)	82.98 (5.30)	78.50 (4.99)
Education, mean (SD), years	13.46 (3.09)	12.88 (3.01)	14.18 (2.86)
Gait-Speed, [*] mean (SD), m/sec	0.93 (0.26)	0.91 (0.26)	1.09 (0.26)
BMI, [†] mean (SD), kg/m ²	26.83 (4.50)	28.12 (5.42)	27.90 (5.00)
Male, N (%)	343 (54.3)	115 (50.0)	644 (49.8)
Not married, [‡] N (%)	278 (44.1)	110 (47.8)	437 (33.8)
Smoking Status, Never, N (%)	326 (51.6)	119 (51.7)	662 (51.2)
Former, N (%)	284 (44.9)	101 (43.9)	583 (45.1)
Current, N (%)	22 (3.5)	10 (4.3%)	47 (3.6)
Moderate Exercise, [§] N (%)	289 (51.9)	97 (48.7)	773 (63.2)
APOE ε4 allele, // N (%)	203 (32.4)	72 (31.3)	294 (22.8)
Diabetes mellitus, N (%)	148 (23.4)	60 (26.1)	212 (16.4)
History of stroke, N (%)	90 (14.2)	42 (18.3)	91 (7.0)
Any heart disease, N (%)	234 (37.0)	96 (41.7)	356 (27.6)
NPI-Q [¶] Depression, N (%)	137 (22.6)	63 (28.5)	119 (9.5)
NPI-Q [¶] Apathy, N (%)	101 (16.7)	33 (14.9)	41 (3.3)
Deceased, N (%)	232 (36.7)	99 (43.0)	224 (17.3)

aMCI, amnesic mild cognitive impairment; naMCI, non-amnesic mild cognitive impairment; BMI, body mass index; NPI-Q, Neuropsychiatric Inventory Questionnaire. Percentages are based on non-missing data.

^{*} 131 aMCI, 64 naMCI, and 87 cognitively normal subjects with missing data.

[†] 27 aMCI, 12 naMCI, and 18 cognitively normal subjects had missing data.

[‡] 1 aMCI subject with missing data, percentage was based on non-missing.

[§] 75 aMCI, 31 naMCI, and 68 cognitively normal subjects with missing data, percentage was based on non-missing.

// 5 aMCI and 5 cognitively normal subjects with missing data

[¶] 27 aMCI, 9 naMCI, and 33 cognitively normal subjects with missing data, percentage was based on non-missing.

Table 2

Hazard of death associated with mild cognitive impairment. The Mayo Clinic Study of Aging.

Comparison groups	Any MCI HR (95% CI)*	Amnesic MCI HR (95% CI)	Non-Amnesic MCI HR (95% CI)
Cognitively normal	1.00 (reference)	1.00 (reference)	1.00 (reference)
Any MCI	2.03 (1.61, 2.55)	1.89 (1.48, 2.41)	2.47 (1.80, 3.39)
Prevalent MCI	2.10 (1.60, 2.75)	1.99 (1.48, 2.67)	2.61 (1.71, 3.99)
Incident MCI	1.96 (1.50, 2.56)	1.78 (1.32, 2.42)	2.39 (1.62, 3.54)
MCI, incident dementia	3.24 (2.31, 4.53)	3.10 (2.14, 4.48)	3.95 (2.20, 7.11)
MCI, no incident dementia	1.82 (1.43, 2.31)	1.65 (1.27, 2.16)	2.31 (1.64, 3.25)
Single Domain MCI	2.12 (1.66, 2.70)	2.01 (1.54, 2.63)	2.40 (1.70, 3.38)
Multiple Domain MCI	1.82 (1.31, 2.51)	1.65 (1.15, 2.35)	2.73 (1.55, 4.80)

MCI, mild cognitive impairment.

* Hazard Ratio (95% Confidence Interval) from Cox proportional hazards models using age as time variable; models were adjusted for sex, years of education, baseline history of stroke, heart disease, diabetes mellitus, depression, apathy, moderate exercise, gait-speed, and APOE ε4 carrier status; reference group for all comparisons were cognitively normal subjects.

Table 3

Interaction of mild cognitive impairment with sex, history of heart disease, moderate physical exercise and hazard of death.

Characteristic	HRs (95% CI)	p-value
Sex[*]		
Women without MCI (reference)	1.00 ---	--
Men without MCI	1.96 (1.49, 2.58)	<.0001
Women with MCI	2.80 (2.12, 3.71)	<.0001
Men with MCI	3.79 (2.91, 4.93)	<.0001
Education[†]		
CN and > 12 years education (ref.)	1.00 ---	--
CN and 12 years education	1.12 (0.86, 1.46)	0.3447
MCI and 12 years education	2.04 (1.60, 2.60)	<.0001
MCI and > 12 years education	2.65 (2.09, 3.37)	<.0001
Heart Disease[‡]		
CN without heart disease (ref.)	1.00 ---	---
CN with heart disease	2.29 (1.76, 3.00)	<.0001
MCI without heart disease	2.72 (2.11, 3.50)	<.0001
MCI with heart disease	4.05 (3.12, 5.24)	<.0001
Moderate exercise^{//} (ref.)		
CN with exercise	1.00 ---	---
CN without exercise	2.01 (1.50, 2.68)	<.0001
MCI with exercise	2.83 (2.12, 3.78)	<.0001
MCI without exercise	3.44 (2.59, 4.56)	<.0001

HRs (95% CI), hazard ratio (95% Confidence interval); MCI, mild cognitive impairment; CN, cognitively normal; ref, reference.

* Adjusted for education and APOE $\epsilon 4$ carrier status with age as the time scale; P value for additive interaction 0.0003; P value for multiplicative interaction 0.047.

[†] Adjusted for sex and APOE $\epsilon 4$ carrier status with age as the time scale; P value for additive interaction <0.0001; P value for multiplicative interaction 0.0191.

[‡] Adjusted for sex, education and APOE $\epsilon 4$ carrier status with age as the time scale; P value for additive interaction 0.0028; P value for multiplicative interaction 0.006.

^{//} Adjusted for sex, education and APOE $\epsilon 4$ carrier status with age as the time scale; P value for additive interaction <0.0001; P value for multiplicative interaction 0.004.