Risk and protective factors for cognitive impairment in persons aged 85 years and older

Rosebud O. Roberts, MB, ChB, MS
Ruth H. Cha, MS
Michelle M. Mielke, PhD
Yonas E. Geda, MD, MSc
Bradley F. Boeve, MD
Mary M. Machulda, PhD, LP
David S. Knopman, MD
Ronald C. Petersen, MD, PhD

Correspondence to Dr. Roberts: roberts.rosebud@mayo.edu

ABSTRACT

Objective: To determine risk and protective factors for mild cognitive impairment (MCI) among persons 85 years and older.

Methods: Participants in the population-based prospective Mayo Clinic Study of Aging were comprehensively evaluated at baseline and at 15 monthly intervals to determine incident MCI. At baseline, lifestyle factors in midlife and late life were assessed by self-reported questionnaire; vascular and comorbid conditions were abstracted from participants' medical records.

Results: Of 256 participants who were cognitively normal at enrollment (median age 87.3 years, 62% women), 121 developed MCI at a median 4.1 years of follow-up. Predictors of MCI were *APOE* ε4 allele (hazard ratio [HR] 1.89; $p = 0.008$), current depressive symptoms (HR 1.78; $p = 0.02$), midlife onset of hypertension (HR 2.43; $p = 0.005$), increasing number of vascular diseases (HR 1.13; $p = 0.02$), and chronic conditions from the Charlson Comorbidity Index (HR 1.08; $p = 0.006$). Models were adjusted for sex and education, with age as the time variable. The risk of MCI was reduced for participants who reported engagement in artistic (HR 0.27; $p = 0.03$), craft (HR 0.55; $p = 0.02$), and social (HR 0.45; $p = 0.005$) activities in both midlife and late life, and in the use of a computer in late life (HR 0.47; $p = 0.008$).

Conclusions: Chronic disease burden increases risk of MCI, whereas certain lifestyle factors reduce risk in persons 85 years and older. This implies that preventive strategies for MCI may need to begin in midlife and should persist throughout late life. ***Neurology*® 2015;84:1854–1861**

GLOSSARY

AD = Alzheimer disease; **aMCI** = amnestic mild cognitive impairment; **CCI** = Charlson Comorbidity Index; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; **FAQ** = Functional Activities Questionnaire; **HR** = hazard ratio; ***ICD-9*** = *International Classification of Diseases-9*; **MCI** = mild cognitive impairment; **MCSA** = Mayo Clinic Study of Aging; **naMCI** = nonamnestic mild cognitive impairment; **NPI-Q** = Neuropsychiatric Inventory Questionnaire.

Individuals aged 85 years and older are the most rapidly growing group in the United States and worldwide.[1] Studies of the oldest old are difficult to conduct and to interpret. Persons aged 90 years and older typically have sensory losses, difficulty providing valid and reliable information, high comorbidity, and a high prevalence of dementia[2]; most are typically women. Often, factors associated with risk of cognitive impairment at younger ages are no longer predictive, raising the possibility that multiple coexisting diseases might be more predictive than solitary diseases. Because many individuals aged 90 years and older already have early stages of mild cognitive impairment (MCI), studies are often cross-sectional and can only assess risk of dementia or Alzheimer disease (AD). Furthermore, potential interventions at these ages may have limited long-term benefit. The goal of this study was to identify risk and protective factors for incident MCI among cognitively normal persons aged 85–89 years at enrollment to the Mayo Clinic Study of Aging (MCSA).

METHODS

Study cohort at baseline. Participants were randomly selected from among Olmsted County, Minnesota, residents for participation in the MCSA. Details of the study design and methodology have been published.[3,4] Briefly, residents aged 70–89 years were identified using the medical records linkage system of the Rochester Epidemiology Project (REP).[5] Eligible participants were

Supplemental data at Neurology.org

From the Divisions of Epidemiology (R.O.R., M.M. Mielke, Y.E.G., R.C.P.) and Biomedical Statistics and Informatics (R.H.C.), Department of Health Sciences Research, the Department of Neurology (R.O.R., B.F.B., D.S.K., R.C.P.), and the Department of Psychiatry and Psychology (M.M. Machulda), Mayo Clinic, Rochester, MN; and the Departments of Psychiatry and Psychology and Neurology (Y.E.G.), Mayo Clinic, Scottsdale, AZ.

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invited to participate in person or by telephone. This study is limited to participants who were aged 85–89 years at enrollment (October 1, 2004, or March 1, 2008) and were cognitively normal at the baseline evaluation.

In-person evaluation. The evaluation consisted of 3 components. A nurse or study coordinator interviewed the participant to assess memory and administered the Clinical Dementia Rating scale[6] and the Functional Activities Questionnaire (FAQ)[7] to an informant to assess participant functioning. A physician evaluation included the Short Test of Mental Status[8] and a neurologic examination. A psychometrist performed neuropsychological testing using 9 tests to assess performance in memory, executive function, language, and visuospatial skills. The raw test scores were transformed into age-adjusted scores using normative data.[9] Domain scores were computed by summing and scaling the age-adjusted test scores within domains to allow comparisons across domains.[9]

Diagnostic criteria. MCI was diagnosed per published criteria—cognitive concern, impairment in 1 or more of the 4 cognitive domains, essentially normal functional activities, and absence of dementia[3,4,10]—and classified as amnestic (aMCI) or nonamnestic MCI (naMCI). Dementia was diagnosed according to *DSM-IV* criteria.[11] Participants were considered cognitively normal if they performed within the normative range and did not meet MCI or dementia criteria.[3,4,10]

Exposures and covariates. Demographic information, weight, height, and timed gait speed (m/s) were determined at the interview. A stroke history was obtained by the physician and validated in the medical record. Depressive symptoms in the previous month were assessed using the Neuropsychiatric Inventory Questionnaire (NPI-Q).[12] Participants completed self-administered questionnaires on engagement in exercise and in cognitive activities in midlife (age 50 years) and late life (1 year prior to the evaluation). Medical comorbidities and date of onset of these conditions were abstracted from participant medical records using the REP medical records-linkage system.[5,13] *APOE* genotyping was performed. Chronic disease burden was assessed from a weighted Charlson Comorbidity Index (CCI) score[14] using *ICD-9* codes (table e-1 on the *Neurology*® Web site at Neurology.org). This score takes into account disease severity, and was developed to assess impact of disease burden on health outcomes. Vascular disease burden was assessed as the total number of vascular diseases and related conditions: type 2 diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, congestive heart failure, atrial fibrillation, peripheral vascular disease, stroke, and obesity.

Longitudinal follow-up. Follow-up was performed at 15-month intervals. To avoid potential bias in making a diagnosis, clinical and cognitive findings from previous evaluations were not considered. Participants who declined the in-person evaluation at follow-up were invited to participate by a telephone interview that included the Telephone Interview of Cognitive Status–Modified,[15] the Clinical Dementia Rating scale,[6] and the NPI-Q.[12]

Standard protocol approvals, registrations, and patient consent. This study was approved by the Institutional Review Boards of the Mayo Clinic and Olmsted Medical Center. Written informed consent was obtained from all participants.

Statistical analyses. The date of MCI onset was assigned at the midpoint between the last assessment as cognitively normal and the first-ever assessment as MCI; participants who developed dementia without an MCI diagnosis were included. Persons who were lost to follow-up or died were censored at their last evaluation. We estimated follow-up time from baseline to onset of MCI, date of censoring, or last follow-up. We investigated bivariate associations of risk and protective factors with MCI using Cox proportional hazards models adjusted for sex and education, with age as a time variable. Exposures and covariates were *APOE* ε4 allele (any ε4 vs no ε4), type 2 diabetes, hypertension, dyslipidemia, body mass index, engagement in exercise and cognitively stimulating activities, high-sensitivity C-reactive protein, and smoking (current and former vs never). When possible, we characterized variables as present in midlife (≤65 years) or late life (>65 years); or in midlife only, late life only, or both. We performed stratified analyses by MCI subtypes and by sex. In multivariable models, we included variables that were significantly associated with MCI.

In sensitivity analyses, we estimated the annualized percent change (slope) in FAQ score, memory, and executive function *z* scores for each participant, and computed and compared the average slope for participants grouped by performance of activities in midlife or late life. Associations were considered significant at p values <0.05, using SAS version 9.3 (SAS Institute, Cary, NC).

Table 1 Characteristics of study participants at baseline, overall and by sex

Characteristics	Total (n = 256)	Men (n = 97)	Women (n = 159)
Age, y[a]	87.3 (86.1, 88.9)	87.0 (85.9, 88.3)	87.7 (86.1, 89.2)
Education, y	13.0 (12.0, 16.0)	12.0 (12.0, 16.0)	13.0 (12.0, 15.0)
APOE ε4 allele[a,b]	48 (18.8)	27 (27.8)	21 (13.3)
BMI ≥ 30 kg/m^2[c]	57 (23.1)	21 (22.3)	36 (23.5)
Type 2 diabetes mellitus	48 (18.8)	20 (20.6)	28 (17.6)
Hypertension	207 (80.9)	77 (79.4)	130 (81.8)
Stroke	36 (14.1)	13 (13.4)	23 (14.5)
Depressive symptoms[d]	30 (12.1)	12 (12.8)	18 (11.7)
hs-CRP, mg/dL[e]	0.13 (0.07, 0.28)	0.13 (0.06, 0.27)	0.15 (0.08, 0.28)
Gait speed, m/s	0.85 (0.76, 1.09)	0.95 (0.76, 1.09)	0.85 (0.69, 1.09)
Charlson comorbidity score[a]	4 (3, 6)	5 (3, 7)	4 (3, 6)
Vascular disease burden[a]	3 (2, 4)	4 (3, 5)	3 (2, 4)
Duration of follow-up	4.1 (2.6, 6.1)	4.0 (2.5, 5.9)	4.1 (2.6, 6.1)

Abbreviations: BMI = body mass index (kg/m^2); hs-CRP = high-sensitivity C-reactive protein. Data are n (%), based on nonmissing data, or median (25th, 75th percentiles).
[a] $p < 0.05$ represents a significant difference between men and women.
[b] One woman with missing data; the frequency of *APOE* genotype in the total cohort was ε2ε2, 0.78%; ε2ε3, 11.4%; ε2ε4, 1.2%; ε3ε3, 69.0%; ε3ε4, 16.9%; ε4ε4, 0.78%.
[c] Nine persons had missing data (3 men, 6 women).
[d] Eight persons had missing data (3 men, 5 women).
[e] Thirty-nine persons had missing data (10 men, 29 women).

RESULTS Of the 301 participants who were cognitively normal at enrollment, 256 (85.0%; median age, 87.3 years, 62.1% [n = 159] women) had ≥1 follow-up evaluation (table 1). Women had a lower frequency of an *APOE* ε4 allele, were older, had a lower median CCI score, and had a lower vascular disease burden than men. Participants with no follow-up were younger (median age, 86.6 years; $p = 0.03$) but did not differ from those with follow-up regarding sex, education, *APOE* ε4 allele,

Table 2 Risk and protective factors for mild cognitive impairment

		Model (n = 121 events)[a]	
Characteristics	No. at risk/events	HR (95% CI)	*p* Value
Sex			
Women	159/82	1.00 (reference)	
Men	97/39	0.82 (0.56, 1.21)	0.33
Education (continuous), y		0.96 (0.91, 1.02)	0.22
APOE ε4 allele			
No	207/96	1.00 (reference)	
Yes	48/24	1.89 (1.18, 3.02)	0.008
Hypertension			
No	49/14	1.00 (reference)	
Late life only	148/71	1.69 (0.95, 3.01)	0.07
Midlife and late life	59/36	2.43 (1.30, 4.54)	0.005
Depressive symptoms			
No	218/94	1.00 (reference)	
Yes	30/20	1.78 (1.09, 2.89)	0.02
Charlson Comorbidity Index		1.08 (1.02, 1.15)	0.006
Vascular disease burden		1.13 (1.02, 1.26)	0.02
Cognitive activities[b]			
Artistic activities			
No	181/89	1.00 (reference)	
Midlife only	23/10	0.79 (0.41, 1.53)	0.48
Late life only	4/2	0.74 (0.17, 2.96)	0.63
Midlife and late life	18/3	0.27 (0.09, 0.87)	0.03
Craft activities			
No	84/42	1.00 (reference)	
Midlife only	57/30	0.85 (0.52, 1.41)	0.54
Late life only	7/2	0.35 (0.08, 1.45)	0.15
Midlife and late life	78/30	0.55 (0.33, 0.90)	0.02
Social activities			
No	33/20	1.00 (reference)	
Midlife only	42/17	0.46 (0.23, 0.91)	0.03
Late life only	8/4	1.09 (0.37, 3.23)	0.88
Midlife and late life	143/63	0.45 (0.26, 0.78)	0.005
Computer use			
No	141/71	1.00 (reference)	
Midlife only	7/3	1.02 (0.32, 3.28)	0.98
Late life only	49/16	0.47 (0.27, 0.83)	0.008
Midlife and late life	29/14	0.92 (0.50, 1.68)	0.77

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a] Estimates for variables that were significantly associated with mild cognitive impairment in models adjusted for age (as the time variable), sex, and education. The association with exercise was not significant; however, risk estimates for exercising ≥3 times week vs <3 times a week were HR 0.89 (95% CI 0.54, 1.46), $p = 0.64$ for midlife only; HR 0.55 (95% CI 0.26, 1.17), $p = 0.12$ for late life only; and HR 1.01 (95% CI 0.61, 1.67), $p = 0.96$ for midlife and late life.
[b] Thirty participants (12 men, 18 women) had missing data on cognitively stimulating activities.

diabetes, hypertension, gait speed, engagement in exercise, or cognitive activities.

Predictors of incident MCI. There were 121 incident MCI events over a median 4.1 (interquartile range 2.6, 6.1) years of follow-up. MCI risk was associated with an *APOE* ε4 allele, hypertension (midlife and late life), depressive symptoms, and increased with increasing CCI score and vascular disease burden (table 2). The risk was reduced in participants engaging in artistic, craft, and social activities in both midlife and late life, and computer use in late life. Estimates from the multivariable models were essentially unchanged (data are not presented). When stratified by midlife or late life, the risk of MCI was reduced in participants engaging in artistic, social, and group activities, and reading newspapers in midlife; and with artistic and craft activities, and computer use in late life (table e-2).

Predictors of MCI subtypes. In bivariate models, depressive symptoms were associated with an increased risk of aMCI; social activity in both midlife and late life was associated with reduced risk (table 3). The point estimates from the multivariable model were essentially unchanged, but the associations were marginally significant (data not presented). Significant predictors of naMCI were an *APOE* ε4 allele, diabetes (midlife and late life), hypertension (midlife and late life), increasing CCI score, and increasing vascular disease burden. The risk of naMCI was reduced with computer use in late life and with increasing gait speed. Estimates from the multivariable were similar; the association with education was significant (hazard ratio [HR] 0.74, $p = 0.004$). The associations of *APOE* genotype with naMCI persisted even with the ε3ε3 genotype as the reference category (table e-3).

Predictors of MCI by sex. In men, MCI was associated with depressive symptoms and higher CCI scores in bivariate models (table 4); estimates changed little in multivariate models (data not shown). In women, MCI risk factors were hypertension and diabetes in midlife and late life, and increasing vascular disease burden. The risk was reduced with engaging in crafts and artistic activities in midlife and late life, and computer use in late life in bivariate models, and changed little in multivariate models (data not shown).

Sensitivity analyses. Participants who never engaged in cognitively stimulating activities had greater average declines in FAQ score, memory, and executive function *z* scores compared to those who did; these differences did not reach statistical significance due to small sample sizes. For example, for computer use, decline in FAQ score was −0.790 for never vs −0.105 for computer use in late life only; decline in memory was

Table 3 Risk and protective factors for MCI stratified by MCI subtype

	Amnestic MCI (n = 71 events)		Nonamnestic MCI (n = 29 events)	
Characteristics	Model[a], HR (95% CI)	*p* Value	Model[a], HR (95% CI)	*p* Value
Sex				
Women	1.00 (reference)		1.00 (reference)	
Men	0.91 (0.56, 1.49)	0.71	0.64 (0.28, 1.46)	0.29
Education (continuous), y	1.00 (0.93, 1.09)	0.92	0.89 (0.78, 1.01)	0.07
***APOE* ε4 allele**				
No	1.00 (reference)		1.00 (reference)	
Yes	1.81 (0.99, 3.30)	0.05	3.29 (1.40, 7.74)	0.006
Hypertension				
No			1.00 (reference)	
Late life only			5.90 (0.78, 44.41)	0.08
Midlife and late life			9.84 (1.26, 76.63)	0.03
Diabetes mellitus				
No			1.00 (reference)	
Late life only			1.68 (0.67, 4.21)	0.27
Midlife and late life			4.73 (1.34, 16.62)	0.02
Depressive symptoms				
No	1.00 (reference)			
Yes	2.28 (1.26, 4.13)	0.007		
Charlson Comorbidity Index			1.18 (1.06, 1.32)	0.003
Vascular disease burden			1.39 (1.14, 1.71)	0.001
Social activities				
No	1.00 (reference)			
Midlife only	0.51 (0.21, 1.24)	0.14		
Late life only	1.32 (0.36, 4.81)	0.68		
Midlife and late life	0.48 (0.23, 0.98)	0.04		
Computer use				
No			1.00 (reference)	
Midlife only			1.20 (0.16, 9.03)	0.86
Late life only			0.10 (0.01, 0.75)	0.03
Midlife and late life			0.22 (0.03, 1.68)	0.15
Gait speed, m/s			0.13 (0.02, 0.95)	0.04

Abbreviations: CI = confidence interval; HR = hazard ratio; MCI = mild cognitive impairment.
[a] Estimates for variables that were significantly associated with amnestic MCI or nonamnestic MCI. Models were adjusted for age (as the time variable), sex, and education (as a continuous variable).

−0.074 for never and −0.044 for late life only; decline in executive function was −0.170 for never and −0.108 for late life only. For craft activities, the decline in FAQ score was −0.782 for never, −0.691 for midlife only, and −0.439 for both midlife and late life; decline in memory was −0.071 for never, −0.063 for midlife only, and −0.055 for both midlife and late life; decline in attention was −0.159 for never, −0.192 for midlife only, and −0.125 for both midlife and late life. For engagement in social activities, the average decline in FAQ was −0.954 for never, −0.782 for midlife only, and −0.418 for midlife and late life; decline in memory was −0.120 for never, 0.041 for midlife only, and −0.082 for both midlife and late life; decline in attention was −0.176 for never, −0.177 for midlife only, and −0.138 for both midlife and late life.

DISCUSSION In our cohort of 85- to 89-year-olds, the risk of MCI was elevated in participants with an *APOE* ε4 allele, hypertension onset in midlife, greater comorbidity and vascular disease burden, and depressive symptoms. By contrast, the risk was reduced with engagement in artistic, craft, and social activities in both midlife and late life, and with use of a computer in late life. Depressive symptoms and *APOE* ε4 were associated with aMCI, and vascular factors were associated with naMCI. Our findings suggest that strategies to reduce risk of MCI in the oldest old should include prevention and efficient management of vascular and other chronic diseases earlier in life. These nonpharmacologic interventions may have greatest benefit when initiated early and maintained. Furthermore, these efforts should begin in young adulthood or midlife, and should persist throughout late life.

A strength of our study was that it distinguished the impact of factors in midlife, late life, or both on MCI risk. For factors associated with reduced risk, this allowed us to disentangle the potential effects of reverse causation, where the outcome precedes and causes the exposure. Engaging in beneficial lifestyle activities in midlife only, or initiating them in late life, did not consistently confer benefit. Persons who performed certain activities only in midlife may have ceased to perform them in late life due to incipient cognitive impairment. Alternatively, those who performed activities in late life may have done so because they still could. Others may have discerned cognitive decline and initiated activities in late life as an effort to curb progression, suggesting reverse causation.

Our findings suggest that the burden of chronic conditions or vascular diseases may predict MCI in persons aged 85 years and older. Multiple chronic conditions may contribute to longstanding pathologic insults to the brain through cerebrovascular disease and related mechanisms, including endothelial dysfunction, inflammation, and oxidative damage, which lead to neuronal death, synaptic dysfunction, and cognitive impairment.[16] Certain established risk factors for cognitive impairment (e.g., hyperlipidemia, smoking, C-reactive protein, obesity) may not have predicted MCI because of survival bias, or because the

Table 4 Risk and protective factors for MCI stratified by sex

Characteristics	Men[a], HR (95% CI)	*p* Value	Women[a], HR (95% CI)	*p* Value
Education, y	0.96 (0.87, 1.05)	0.38	0.98 (0.90, 1.06)	0.54
APOE ε4 allele	2.07 (0.99, 4.33)	0.05	1.80 (0.94, 3.44)	0.08
Hypertension				
Late life only	1.74 (0.60, 5.07)	0.31	1.70 (0.85, 3.38)	0.13
Midlife and late life	2.95 (0.93, 9.33)	0.07	2.33 (1.10, 4.95)	0.03
Diabetes				
Late life only	0.92 (0.35, 2.40)	0.86	1.31 (0.73, 2.35)	0.36
Midlife and late life	0.46 (0.06, 3.46)	0.45	3.80 (1.18, 12.26)	0.03
Depressive symptoms	2.34 (1.04, 5.26)	0.04	1.43 (0.77, 2.66)	0.26
Charlson Comorbidity Index	1.14 (1.04, 1.26)	0.008	1.04 (0.97, 1.12)	0.25
Vascular disease burden	1.11 (0.93, 1.33)	0.26	1.14 (1.00, 1.30)	0.04
Artistic activities				
Midlife only	0.43 (0.06, 3.25)	0.42	0.84 (0.42, 1.71)	0.63
Late life only	1.07 (0.14, 8.04)	0.95	0.48 (0.06, 3.83)	0.49
Midlife and late life	0.52 (0.07, 3.84)	0.52	0.21 (0.05, 0.85)	0.03
Craft activities				
Midlife only	0.98 (0.37, 2.65)	0.97	0.81 (0.45, 1.47)	0.49
Late life only	0.28 (0.04, 2.10)	0.22	0.46 (0.06, 3.49)	0.45
Midlife and late life	0.63 (0.25, 1.57)	0.32	0.52 (0.28, 0.94)	0.03
Social activities				
Midlife only	0.94 (0.23, 3.79)	0.93	0.38 (0.17, 0.84)	0.02
Late life only	2.54 (0.54, 11.96)	0.24	0.51 (0.07, 3.87)	0.51
Midlife and late life	0.76 (0.25, 2.32)	0.62	0.40 (0.21, 0.75)	0.005
Computer use				
Midlife only[b]	—		1.50 (0.46, 4.87)	0.50
Late life only	0.62 (0.24, 1.59)	0.32	0.41 (0.20, 0.83)	0.01
Midlife and late life	1.41 (0.64, 3.11)	0.40	0.49 (0.15, 1.59)	0.24

Abbreviations: CI = confidence interval; HR = hazard ratio; MCI = mild cognitive impairment.
[a] Association of risk and protective factors with MCI in men and in women; models were adjusted for age (as the time variable), sex, and education. The reference group for categorical variables was persons who never developed the condition or did not perform the activity in midlife or late life.
[b] Risk estimates could not be computed due to zero cells.

cumulative burden of disease may have greater impact on risk than a single disease at very old ages.

The association of *APOE* ε4 with aMCI is consistent with a neurodegenerative etiology. The association with naMCI, however, was unexpected, but may relate to the adverse vascular effects of *APOE* ε2 and ε4.[17–19] *APOE* ε2 and ε4 alleles have been reported to increase atherogenic lipoproteins and accelerate atherogenesis.[20] These effects are consistent with the hypothesized vascular etiology for naMCI, and consistent with our findings in table e-3. Thus, although the small numbers suggest a spurious association, the present findings may be real. However, they remain to be validated in a larger population-based cohort of oldest old.

The association of midlife hypertension with MCI underscores the need for aggressive prevention at younger ages. Targeted education of the general population regarding the association of vascular disease with MCI risk may promote lifestyle changes and treatment compliance. Effectively monitoring and managing persons with hypertension particularly in midlife may also prevent adverse cardiovascular outcomes that increase MCI risk.[21,22]

Interestingly, our findings suggest that nonpharmacologic preventive strategies may reduce naMCI risk in the oldest old. Higher education may reduce risk by increasing cognitive reserve, which in turn may delay clinical expression of symptoms or counteract vascular assaults on the brain.[23,24] The reduced risk with computer use and with artistic or crafts activities suggest that these activities should be promoted throughout life. These activities may also increase cognitive reserve, maintain neuronal function, stimulate neural growth, and recruit alternate neural pathways to maintain cognitive function.[25]

By contrast, failure to observe protective factors for aMCI suggests that oldest old participants at risk for aMCI possibly have greater pathology resulting from both neurodegenerative and vascular effects that may be less amenable to nonpharmacologic interventions. Although we did not observe significant associations with exercise, the reduced HR for persons who exercised in late life suggests a potential benefit for MCI (0.55 for MCI, 0.66 for aMCI; table 2 footnote).

In sex-stratified analyses, MCI risk increased with increasing burden of chronic disease in men and with increasing burden of vascular disease in women. This difference raises the hypothesis that oldest old men may be sicker than women, and this multifactorial morbidity may contribute to MCI. The higher vascular disease burden in women, as observed with diabetes and hypertension, may increase MCI risk. A lower vascular disease burden in men may be due to the earlier onset of these conditions in men, leading to earlier mortality (survival bias). Finally, the protective effects of artistic and craft activities and computer use in women suggest opportunities for exploring comparable interventions in men.

Some of our findings are consistent with previous studies among persons 90 years and older. In particular, the beneficial effects of cognitively stimulating activities on cognition are consistent with previous findings.[25,26] Absence of a protective effect of education on aMCI risk in the present study is consistent with the rapid cognitive decline observed in highly educated late-stage aMCI patients from a memory clinic.[27] The association of increasing gait speed with decreased risk of naMCI is in keeping with the documented increase in the odds ratio of dementia with decreasing gait speed in persons in the 90+ study[28]

and with MCI in the MCSA cohort.[29] In the MCSA, depressive symptoms were associated with an increased risk of aMCI.[30] This is consistent with the putative role of aMCI as being a prodromal AD stage. Similarly, another study reported an association of late-life depressive symptoms with increased risk of AD, and suggested that recurrent depression was more likely to be etiologically associated with vascular dementia.[31] Together, these findings suggest that depressive symptoms may be in the causal pathway or may be a marker for incipient aMCI or AD.

Certain of our findings, however, are inconsistent with prior studies among persons aged 90 years and older. Although the association of *APOE* ε4 with incident MCI has not been reported in the oldest old, the impact of the ε4 allele on dementia risk is thought to be minimal or absent in the oldest old.[32] In the 90+ study, *APOE* ε4 carrier status (vs ε3ε3) was associated with dementia in cross-sectional but not in prospective analyses.[33] The frequency of an *APOE* ε4 allele was only 8.1% in the incident cohort, compared to 18.8% in the present study. Thus, earlier mortality associated with *APOE* ε4 may preclude detection of significant associations with cognitive risk in studies among persons age 90 years and older. With the ε3ε3 genotype as the reference group, the association of the ε4 allele with MCI persisted (table e-3). Hypertension in midlife was associated with naMCI risk, but a similar association was not observed in a 90+ study cohort[2] perhaps because of survival bias, cross-sectional design, different study endpoints, or to failure to take the age at onset of hypertension into account.

One potential limitation of our study is that cognitive activities and exercise were assessed only at baseline. Thus, we were unable to determine the effects of discontinuation of these activities during follow-up. Second, there may be residual reverse causation; declining cognition could have promoted engagement in cognitive activities in some participants.[34] However, declining cognitive activities have been shown to predict cognitive impairment, but not the reverse.[26] Given the old age of participants, there is a potential for recall bias. We previously assessed the reliability of the physical activity questionnaire in 87 persons who completed the questionnaire at 2 time periods. The internal consistency was moderate to good, a Cronbach α of 0.71, and the test-retest Spearman rank correlation coefficient was 0.50 for moderate exercise.[35] Engagement in cognitive activities in midlife/late life may simply be a marker for healthy cognition, with a noncausal association with MCI. Finally, our findings are based on a cohort with a primarily Northern European ancestry.

Strengths of our study include the population-based, prospective design, the comprehensive evaluation of participants, and the assignment of cognitive status by consensus both at enrollment and follow-up. The ascertainment of chronic diseases and medical conditions from the medical records allowed us to reliably determine the presence and onset of risk factors in midlife and late life. The ascertainment of cognitively stimulating activities and exercise in a population-based cohort of cognitively normal 85- to 89-year-olds allowed us obviate the potential impact of reverse causation. Blinding the study evaluators to previous clinical assessments and cognitive diagnosis contributed to unbiased ascertainment of cognitive status during follow-up.

AUTHOR CONTRIBUTIONS

R.O. 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

Comment: Too much of a good thing may still be good for your brain

Approximately 5 million Americans live with mild cognitive impairment (MCI) and Alzheimer disease (AD). Age adds a layer of complexity to disease management not present with younger adults, as older adults have a greater likelihood of multiple chronic conditions that can diminish their capacity to function independently. Chronic disease burden increases risk of MCI, while certain lifestyle factors may reduce MCI risk.[1] This implies that preventive strategies for MCI may need to begin in midlife and persist throughout late life.

While we cannot cure MCI or AD, there is increasing evidence that disease risk may be modifiable. Besides age and family history (not modifiable), the strongest risk factors in the literature include hypertension, diabetes, cardiovascular disease, hypercholesterolemia, obesity, low levels of mental and physical activities, decreased social engagement, and poor dietary patterns.[1–3]

The present study[1] focused on 256 cognitively normal participants over a median of 4.1 years, of whom 121 (47%) developed MCI. Using medical records and patient-reported history, the investigators were able to tease out medical conditions that increased the risk of MCI (including hypertension, vascular disease, depression, and increasing numbers of chronic medical conditions). More importantly, they were able to discern protective effects from midlife and late-life activities, including arts and crafts, social engagement, and using a computer. While self-reports of how much artistic, social, or physical activities one does 30 years prior could be contaminated with reporting biases, these findings are consistent with other clinicopathologic studies[2,3] that clearly demonstrate the beneficial effects of cognitively and socially stimulating activities on the rate of cognitive decline and the level of Alzheimer pathology.

Long ago, "an apple a day keeps the doctor away" was a common expression, suggesting that eating well could improve health. Perhaps today the expression should expand to include painting an apple, going to the store with a friend to buy an apple, and using an Apple product.

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James E. Galvin, MD, MPH

From the Departments of Neurology, Psychiatry, and Population Health, Center for Cognitive Neurology, NYU Langone Medical Center, New York.

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