JAMA Neurology | Original Investigation

Association Between Mentally Stimulating Activities in Late Life and the Outcome of Incident Mild Cognitive Impairment, With an Analysis of the *APOE* ε4 Genotype

Janina Krell-Roesch, PhD; Prashanthi Vemuri, PhD; Anna Pink, MD; Rosebud O. Roberts, MBChB, MS; Gorazd B. Stokin, MD, PhD; Michelle M. Mielke, PhD; Teresa J. H. Christianson, BS; David S. Knopman, MD; Ronald C. Petersen, MD, PhD; Walter K. Kremers, PhD; Yonas E. Geda, MD, MSc

IMPORTANCE Cross-sectional associations between engagement in mentally stimulating activities and decreased odds of having mild cognitive impairment (MCI) or Alzheimer disease have been reported. However, little is known about the longitudinal outcome of incident MCI as predicted by late-life (aged ≥70 years) mentally stimulating activities.

OBJECTIVES To test the hypothesis of an association between mentally stimulating activities in late life and the risk of incident MCI and to evaluate the influence of the apolipoprotein E (*APOE*) ε4 genotype.

DESIGN, SETTING, AND PARTICIPANTS This investigation was a prospective, population-based cohort study of participants in the Mayo Clinic Study of Aging in Olmsted County, Minnesota. Participants 70 years or older who were cognitively normal at baseline were followed up to the outcome of incident MCI. The study dates were April 2006 to June 2016.

MAIN OUTCOMES AND MEASURES At baseline, participants provided information about mentally stimulating activities within 1 year before enrollment into the study. Neurocognitive assessment was conducted at baseline, with evaluations at 15-month intervals. Cognitive diagnosis was made by an expert consensus panel based on published criteria. Hazard ratios (HRs) and 95% CIs were calculated using Cox proportional hazards regression models after adjusting for sex, age, and educational level.

RESULTS The final cohort consisted of 1929 cognitively normal persons (median age at baseline, 77 years [interquartile range, 74-82 years]; 50.4% [n = 973] female) who were followed up to the outcome of incident MCI. During a median follow-up period of 4.0 years, it was observed that playing games (HR, 0.78; 95% CI, 0.65-0.95) and engaging in craft activities (HR, 0.72; 95% CI, 0.57-0.90), computer use (HR, 0.70; 95% CI, 0.57-0.85), and social activities (HR, 0.77; 95% CI, 0.63-0.94) were associated with a decreased risk of incident MCI. In a stratified analysis by *APOE* ε4 carrier status, the data point toward the lowest risk of incident MCI for *APOE* ε4 noncarriers who engage in mentally stimulating activities (eg, computer use: HR, 0.73; 95% CI, 0.58-0.92) and toward the highest risk of incident MCI for APOE ε4 carriers who do not engage in mentally stimulating activities (eg, no computer use: HR, 1.74; 95% CI, 1.33-2.27).

CONCLUSIONS AND RELEVANCE Cognitively normal elderly individuals who engage in specific mentally stimulating activities even in late life have a decreased risk of incident MCI. The associations may vary by *APOE* ε4 carrier status.

JAMA Neurol. doi:10.1001/jamaneurol.2016.3822
Published online January 30, 2017.

Author Video Interview and JAMA Report Video

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Yonas E. Geda, MD, MSc, Mayo Clinic Translational Neuroscience and Aging Program, Mayo Clinic, Collaborative Research Bldg, 13400 E Shea Blvd, Scottsdale, AZ 85259 (geda.yonas@mayo.edu).

Dementia has become a global epidemic, causing substantial burden not only for society but also for caregivers and patient families.[1] Therefore, it is critical to examine potential protective lifestyle-related factors against cognitive decline and dementia, preferably based on cohort studies involving large sample sizes.

Various terms have been used to describe activities that keep the mind active and may contribute to healthy aging. Indeed, cognitive, intellectual, or mentally stimulating activities are associated with a decreased risk of cognitive decline[2] and dementia.[3-10] To date, few studies have investigated whether cognitive activities are related to the outcome of mild cognitive impairment (MCI), which is the intermediate zone between normal cognitive aging and dementia.[11] Our group has reported a cross-sectional association between mentally stimulating activities and decreased odds of having MCI.[12] A cohort study involving a convenience sample of community-dwelling elderly found an association between cognitive activities and a decreased risk of amnestic MCI,[13] as well as vascular cognitive impairment.[14]

In the present population-based cohort study, we sought to determine whether engaging in mentally stimulating activities in late life could be of potential benefit in reducing the risk of incident MCI in persons 70 years or older. The study dates were April 2006 to June 2016. We have made rigorous efforts to ensure that our study participants were cognitively normal at baseline, and we had a well-established research infrastructure to follow up the cohort to the outcome of incident MCI. Such an undertaking minimizes potential for reverse causality, although theoretically it may not completely eliminate it. We hypothesized that elderly persons who report engaging in mentally stimulating activities at least 1 to 2 times per week have a significantly decreased risk of developing new-onset MCI compared with persons who report fewer mentally stimulating activities. Because apolipoprotein E (*APOE*) ε4 carrier status is a well-known risk factor for MCI and dementia,[15-18] we also conducted a stratified analysis by *APOE* ε4 genotype. We hypothesized that (1) *APOE* ε4 carriers have a higher risk of developing incident MCI compared with *APOE* ε4 noncarriers regardless of engaging in mentally stimulating activities and (2) *APOE* ε4 carriers who report engaging in mentally stimulating activities have a decreased risk of developing incident MCI compared with *APOE* ε4 carriers who do not report engaging in mentally stimulating activities.

Key Points

Question Does engaging in a mentally stimulating activity in old age associate with neurocognitive function?

Findings In this population-based cohort study, 1929 cognitively normal participants 70 years or older were followed for approximately 4 years. The following activities were associated with significant decreased risk of new-onset mild cognitive impairment: computer use, craft activities, social activities, and playing games.

Meaning Engaging in a mentally stimulating activity even in late life may decrease the risk of mild cognitive impairment.

Methods

Design and Setting

We conducted a prospective cohort study derived from the population-based Mayo Clinic Study of Aging (MCSA). The MCSA is an ongoing study of normal cognitive aging and MCI among persons 70 years or older. Details of the MCSA have been reported elsewhere.[19] Briefly, from the target population of 9953 elderly individuals residing in Olmsted County, Minnesota, on October 1, 2004, we recruited study participants by stratified random sampling.[20] The MCSA protocols were approved by the institutional review boards of the Mayo Clinic and Olmsted Medical Center in Rochester, Minnesota. All participants provided written informed consent.

Study Sample

We assembled a cohort of 2213 cognitively normal participants who had completed a questionnaire on engaging in mentally stimulating activities, as well as a valid cognitive assessment at baseline. Neurocognitive assessment at baseline was followed by evaluations at 15-month intervals. In total, 284 individuals were excluded (242 withdrew before follow-up, 3 had no follow-up visit, and 39 died before follow-up). Therefore, the final cohort consisted of 1929 cognitively normal persons who were followed up to the outcome of incident MCI.

Assessment of Mentally Stimulating Activities

Details of the measurement of mentally stimulating activities in the MCSA have been reported elsewhere.[12,21] Briefly, we modified previously validated instruments to measure these activities.[8,22,23] We defined the following activities as exposures of interest based on the results from our group's cross-sectional study[12]: reading books, craft activities, computer use, playing games, and social activities (eg, going out to movies and theaters). A research nurse or psychometrist assessed the frequency at which each participant engaged in each mentally stimulating activity by using a structured survey with ordinal responses (once per month or less, 2-3 times per month, 1-2 times per week, 3-4 times per week, 5-6 times per week, or daily). Participants were asked to provide information about engagement in these activities in the year before study participation (late-life mentally stimulating activities).

Cognitive Evaluation

The cognitive assessment in the MCSA is described in detail elsewhere.[12,19] Briefly, a face-to-face evaluation was completed among all study participants and included the following 3 assessment components: (1) a neurological evaluation, which included a neurological history review, the administration of the Short Test of Mental Status,[24] and a neurological examination; (2) a risk factor assessment interview, which was conducted by a nurse or study coordinator and included the Clinical Dementia Rating Scale; and (3) neuropsychological testing, which was administered by a psychometrist to assess performance in 4 cognitive domains. These 4 domains were (1) memory (delayed recall trials from the Auditory Verbal

Learning Test[25] and Wechsler Memory Scale-Revised[26] logical memory and visual reproduction subtests), (2) language (Boston Naming Test[27,28] and category fluency[29]), (3) visuospatial skills (Wechsler Adult Intelligence Scale-Revised[30] picture completion and block design subtests), and (4) executive functions (Trail Making Test B[31] and Wechsler Adult Intelligent Scale-Revised[30] digit symbol substitution subtest).

An expert consensus panel made the classifications of normal cognition and MCI after reviewing the results acquired from the clinical and neuropsychological evaluation.[19] Individuals were considered cognitively normal at baseline according to published normative data developed on this community.[32-35] For MCI, the following revised Mayo Clinic criteria for MCI[36,37] were used: (1) cognitive concern expressed by a physician, informant, participant, or nurse; (2) impairment in 1 or more cognitive domains (memory, language, visuospatial skills, or executive functions); (3) essentially normal functional activities; and (4) absence of dementia. Participants with MCI had a Clinical Dementia Rating Scale score of 0 or 0.5; however, the final diagnosis of MCI was based on all available data.

APOE ε4 Genotyping

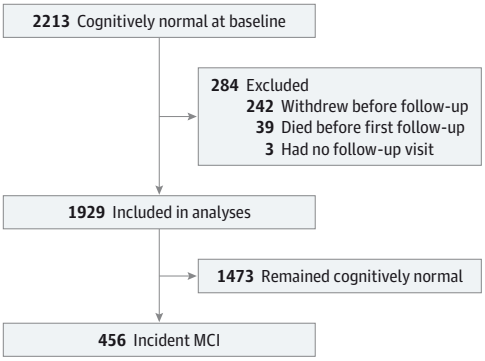
Blood was drawn from the study participants after receiving written informed consent. DNA was amplified by means of polymerase chain reaction, and *APOE* ε4 genotyping was determined by standard methods.[38] The genotypes were assessed by laboratory technicians who were kept unaware of clinical characteristics.

Statistical Analysis

To investigate the association between late-life mentally stimulating activities and the outcome of incident MCI, we calculated hazard ratios (HRs) and 95% CIs. We used Cox proportional hazards regression models, with age as a timescale and after adjusting for sex, educational level, medical comorbidity (weighted Charlson Comorbidity Index),[39] depression (Beck Depression Inventory-II score <13 vs ≥13),[40] and *APOE* ε4 carrier status.

Hypotheses were generated from our group's previous cross-sectional study.[12] Therefore, the analyses were conducted separately for the following 5 types of mentally stimulating activities in late life (within 1 year of the cognitive assessment): reading books, playing games, craft activities, computer use, and social activities (eg, going out to movies and theaters). In our analyses, we compared mentally stimulating activities performed at least 1 to 2 times per week vs mentally stimulating activities performed 2 to 3 times per month or less (reference group) in predicting the risk of incident MCI. We measured central tendency using medians and associated interquartile ranges (IQRs). Furthermore, we conducted analyses stratified by MCI subtype (amnestic vs nonamnestic), as well as *APOE* ε4 carrier status to investigate possible interactions between this genetic risk factor for Alzheimer disease (AD) and mentally stimulating activities in late life. Fitting all the data, we also tested for multiplicative interactions on the HR scale, as well as for additive interactions. Statistical testing was performed at the conventional 2-tailed α = .05. All analyses were performed using statistical software (SAS, version 9.3; SAS Institute Inc).

Figure 1. Study Flowchart



We conducted a prospective cohort study derived from the population-based Mayo Clinic Study of Aging, which is an ongoing study of normal cognitive aging and mild cognitive impairment (MCI) among persons 70 years or older.

Results

At baseline, we included 1929 cognitively normal persons 70 years or older (50.4% [n = 973] female) who had completed a valid assessment of mentally stimulating activities and a cognitive evaluation. We followed up this cohort for a median of 4.0 years (IQR, 2.3-6.4 years), at which time 456 participants had developed new-onset MCI (**Figure 1**). The median age at baseline was 77 years (IQR, 74-82 years), and the median educational level was 14 years (IQR, 12-16 years). In total, 512 participants (26.7%) were *APOE* ε4 carriers; *APOE* ε4 genotype data were missing for 9 participants. The detailed demographic characteristics are listed in **Table 1**.

After adjusting for sex, age, and educational level, we observed that playing games (HR, 0.78; 95% CI, 0.65-0.95) and engaging in craft activities (HR, 0.72; 95% CI, 0.57-0.90), computer use (HR, 0.70; 95% CI, 0.57-0.85), and social activities (HR, 0.77; 95% CI, 0.63-0.94) were associated with a decreased risk of incident MCI. The association between reading books (HR, 0.83; 95% CI, 0.68-1.01) and a decreased risk of incident MCI approached significance. Additional adjustment for medical comorbidity, depression, and *APOE* ε4 genotype did not significantly alter the results (model 2). **Table 2** summarizes these results.

We also conducted stratified analyses by MCI subtype (amnestic vs nonamnestic). We observed significant associations between craft activities (HR, 0.76; 95% CI, 0.58-1.00), computer use (HR, 0.75; 95% CI, 0.59-0.95), and social activities (HR, 0.74; 95% CI, 0.58-0.95) and a decreased risk of incident amnestic MCI. However, we observed a significant association only between computer use (HR, 0.42; 95% CI, 0.26-0.67) and a decreased risk of incident nonamnestic MCI. The results of this analysis are summarized in eTable 1 in the Supplement.

We conducted the same analyses stratified by *APOE* ε4 carrier status. Among *APOE* ε4 noncarriers, craft activities (HR, 0.65; 95% CI, 0.49-0.85) and computer use (HR, 0.73; 95% CI, 0.58-0.93) were significantly associated with a decreased risk of incident MCI. The associations approached significance for reading books (HR, 0.81; 95% CI, 0.64-1.02) and playing games (HR, 0.81; 95% CI, 0.64-1.02). Among *APOE* ε4 carriers, only computer use (HR, 0.65; 95% CI, 0.46-0.92) and social activities (HR, 0.62; 95% CI, 0.43-0.89) were associated with a decreased risk of incident MCI (**Table 3**).

We also examined a possible interaction between late-life mentally stimulating activities and *APOE* ε4 genotype in predicting the risk of incident MCI. We defined the reference group as participants who did not engage in late-life mentally stimulating activities and were *APOE* ε4 noncarriers. We consistently observed the lowest risk of incident MCI in participants who engaged in any type of mentally stimulating activity and were *APOE* ε4 noncarriers compared with the reference group. In contrast, participants who were *APOE* ε4 carriers and did not engage in mentally stimulating activities tended to have the highest risk for incident MCI, with the exception of engaging in craft activities. None of the results of tests for additive interactions between late-life mentally stimulating activities and the *APOE* ε4 genotype on the risk of new-onset MCI were significant. However, the model on additive interaction approached significance for social activities. Additional adjustment for medical comorbidity and depression did not alter the results. eTable 2 in the Supplement summarizes these results, and **Figure 2** shows an HR plot of the data.

Table 1. Demographic Characteristics of 1929 Study Participants

Variable	Value
Female, No. (%)	973 (50.4)
Age at baseline, y	
Median (IQR)	77 (74-82)
70-79, No. (%)	1154 (59.8)
80-93, No. (%)	775 (40.2)
Educational level, y	
Median (IQR)	14 (12-16)
>12, No. (%)	1203 (62.4)
Beck Depression Inventory-II score	
Grand total, median (IQR)	3 (1-7)[a]
Depression, total ≥13, No. (%)	106 (5.5)
Charlson Comorbidity Index, median (IQR)	3 (2-5)

Abbreviation: IQR, interquartile range.

[a] Information was missing on 4 participants.

Table 2. Mentally Stimulating Activities and Risk of Incident Mild Cognitive Impairment (MCI)[a]

Variable	No. at Risk	No. With Incident MCI	Median Follow-up, y	HR (95% CI)[b]	*P* Value	HR (95% CI)[c]	*P* Value
Reading books	1083	240	4.1	0.83 (0.68-1.01)	.06	0.86 (0.71-1.05)	.14
Playing games	1108	245	4.1	0.78 (0.65-0.95)	.01	0.83 (0.69-1.01)	.06
Craft activities	502	104	4.1	0.72 (0.57-0.90)	.004	0.78 (0.62-0.98)	.03
Computer use	1077	193	4.1	0.70 (0.57-0.85)	<.001	0.74 (0.61-0.90)	.002
Social activities	767	154	4.1	0.77 (0.63-0.94)	.009	0.79 (0.64-0.96)	.02

Abbreviation: HR, hazard ratio.

[a] No. at Risk refers to the number of participants (of the total sample size of 1929) who reported mentally stimulating activities performed at least 1 to 2 times per week. No. With Incident MCI refers to the number of participants (of the total sample size of 1929) who developed incident MCI.

[b] The model was adjusted for sex, age (scale), and educational level.

[c] The model was also adjusted for medical comorbidity, depression, and *APOE* ε4 carrier status.

Table 3. Mentally Stimulating Activities and Risk of Incident Mild Cognitive Impairment (MCI) Stratified by *APOE* ε4 Carrier Status[a]

Variable	No. at Risk	No. With Incident MCI	Median Follow-up, y	HR (95% CI)[b]	*P* Value	HR (95% CI)[c]	*P* Value
***APOE* ε4$^+$**							
Reading books	283	77	3.4	0.91 (0.63-1.29)	.59	1.02 (0.71-1.46)	.94
Playing games	288	75	3.5	0.72 (0.51-1.01)	.06	0.78 (0.55-1.10)	.15
Craft activities	123	33	3.0	1.02 (0.69-1.51)	.92	1.08 (0.73-1.61)	.70
Computer use	276	61	3.7	0.65 (0.46-0.92)	.01	0.71 (0.50-1.00)	.05
Social activities	194	45	3.9	0.62 (0.43-0.89)	.009	0.64 (0.45-0.92)	.02
***APOE* ε4$^-$**							
Reading books	792	162	4.2	0.81 (0.64-1.02)	.07	0.82 (0.64-1.04)	.09
Playing games	815	169	4.2	0.81 (0.64-1.02)	.07	0.85 (0.68-1.08)	.18
Craft activities	378	71	4.5	0.65 (0.49-0.85)	.002	0.67 (0.51-0.88)	.004
Computer use	795	132	4.2	0.73 (0.58-0.93)	.01	0.75 (0.59-0.95)	.02
Social activities	571	108	4.2	0.83 (0.66-1.06)	.13	0.86 (0.68-1.09)	.22

Abbreviation: HR, hazard ratio.

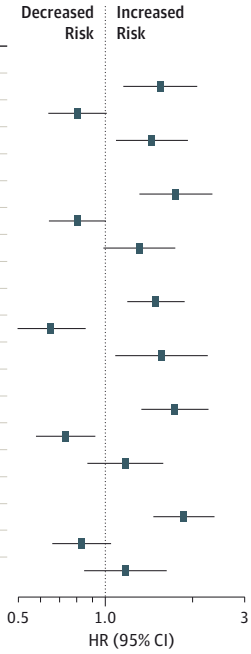
[a] No. at Risk refers to the number of participants (of the total sample size of 1929) who reported mentally stimulating activities performed at least 1 to 2 times per week. No. With Incident MCI refers to the number of participants (of the total sample size of 1929) who developed incident MCI.

[b] The model was adjusted for sex, age (scale), and educational level.

[c] The model was also adjusted for medical comorbidity and depression.

Figure 2. Hazard Ratio (HR) Plot of Interactions Between Mentally Stimulating Activities and *APOE* ε4 Carrier Status on the Risk of Incident Mild Cognitive Impairment

Interaction	HR (95% CI)
APOE ε4⁻ × Reading Books⁻	1 [Reference]
APOE ε4⁺ × Reading Books⁻	1.55 (1.16-2.07)
APOE ε4⁻ × Reading Books⁺	0.80 (0.63-1.93)
APOE ε4⁺ × Reading Books⁺	1.45 (1.09-1.93)
APOE ε4⁻ × Playing Games⁻	1 [Reference]
APOE ε4⁺ × Playing Games⁻	1.76 (1.31-2.35)
APOE ε4⁻ × Playing Games⁺	0.80 (0.64-1.01)
APOE ε4⁺ × Playing Games⁺	1.31 (0.99-1.74)
APOE ε4⁻ × Craft Activities⁻	1 [Reference]
APOE ε4⁺ × Craft Activities⁻	1.50 (1.19-1.88)
APOE ε4⁻ × Craft Activities⁺	0.65 (0.50-0.85)
APOE ε4⁺ × Craft Activities⁺	1.56 (1.08-2.26)
APOE ε4⁻ × Computer Use⁻	1 [Reference]
APOE ε4⁺ × Computer Use⁻	1.74 (1.33-2.27)
APOE ε4⁻ × Computer Use⁺	0.73 (0.58-0.92)
APOE ε4⁺ × Computer Use⁺	1.55 (1.16-2.07)
APOE ε4⁻ × Social Activities⁻	1 [Reference]
APOE ε4⁺ × Social Activities⁻	1.86 (1.46-2.38)
APOE ε4⁻ × Social Activities⁺	0.83 (0.66-1.05)
APOE ε4⁺ × Social Activities⁺	1.17 (0.85-1.63)



In our analyses, we compared mentally stimulating activities performed at least 1 to 2 times per week vs mentally stimulating activities performed 2 to 3 times per month or less (reference group) in predicting the risk of incident mild cognitive impairment. The model was adjusted for sex, age (scale), and educational level. Additional adjustment for medical comorbidity and depression did not significantly alter the results.

Discussion

In this population-based prospective cohort study, we observed that engaging in mentally stimulating activities in late life was associated with a decreased risk of incident MCI. More specifically, playing games and engaging in craft activities, computer use, and social activities significantly reduced the risk of incident MCI. In the past, our group has reported decreased odds of MCI associated with engagement in mentally stimulating activities in late life in a population-based case-control study.[12] However, those findings were considered preliminary until confirmed by a prospective cohort study, which we are reporting herein.

When comparing MCI subtypes (amnestic vs nonamnestic), we observed more associations between mentally stimulating activities and a decreased risk of amnestic MCI than nonamnestic MCI. This finding could be explained by limited power because of smaller sample size for the analysis on nonamnestic MCI.

Because the *APOE* ε4 genotype is a well-known risk factor for MCI and AD,[15-18] we also conducted stratified analyses by *APOE* ε4 carrier status in predicting the outcome of incident MCI. As expected, the data point toward a reduced risk of incident MCI for *APOE* ε4 noncarriers who engage in mentally stimulating activities. However, we observed fewer associations between mentally stimulating activities and a decreased risk of incident MCI for *APOE* ε4 carriers compared with noncarriers. This finding may in part be explained by a smaller sample size of *APOE* ε4 carriers, which limits the statistical power of this analysis.

Our study findings are in line with previous research that reported a potentially protective effect of mentally stimulating activities on cognitive decline,[2] dementia,[3-10] and MCI.[13,21] In addition, a recent study[21] involving persons 85 years or older reported a list of risk and protective factors for advanced aging, one of which was an association between cognitive activities and a decreased risk of MCI. To our knowledge, the present study may be one of few population-based cohort studies (if not the first) to examine the risk of incident MCI in persons 70 years or older as predicted by engagement in mentally stimulating activities in late life.

Our study could not disentangle why some mentally stimulating activities (eg, computer use) had a larger effect size on the decreased risk of incident MCI than other activities (eg, reading books). However, we speculate that a particular mental activity (eg, computer use) may require specific technical and manual skills and that these could be the factors that might be associated with a decreased risk of cognitive decline. Future studies may need to examine the specific mediation factors between a particular mentally stimulating activity and the decreased risk of incident MCI.

However, we did not investigate possible mechanisms that might underlie the association between engagement in mentally stimulating activities and the risk of incident MCI. Insights on these mechanisms can be derived from animal studies. Investigations involving mouse models of AD showed a protective effect of enriched environments on neuropathological changes associated with AD, such as prevention of neuronal dysfunction and increased synaptic recovery.[41] Thus far, few studies have investigated the associations between mental or cognitive activities and pathological changes associated with cognitive decline and AD in humans. For example, researchers at the University of California, Berkeley, reported a significant association between cognitive activities and a decreased β-amyloid deposition in the cortex.[42] An Australian group found that complex mental activity across the life span was associated with decreased hippocampal atrophy.[43] A recent report indicated that higher cognitive reserve was associated with decreased age-related changes in cerebrospinal fluid biomarkers.[44] In addition, one can hypothesize that engagement in mentally stimulating activities may be associated with other protective lifestyle factors, such as engagement in physical exercise. These activities might in sum lead to a decreased risk of cognitive decline.[12] Also, the cognitive reserve theory states that engagement in mentally stimulating activities or a high educational level may buffer the negative effects of abnormal brain pathological changes on cognitive function.[45] The reader is referred to our group's previous article[12] for a discussion of potential mechanisms of action.

In addition to mentally stimulating activities, several other risk and protective factors for MCI have been discussed in the literature. There is evidence that neuropsychiatric

symptoms[46,47] are associated with an increased risk of incident MCI. In contrast, lifestyle-related factors, such as physical exercise[48] and low caloric intake,[49] are associated with a lower risk of MCI.

Strengths and Limitations

The findings of our study should be interpreted within the context of its strengths and limitations. The major strength of our study pertains to its design. We conducted a population-based prospective cohort study with a large sample size of 1929 participants at baseline, whom we followed up for several years. In addition, MCI was assessed using face-to-face evaluations and was based on a consensus panel at the Alzheimer Disease Research Center at Mayo Clinic in Rochester, which has a well-known reputation in the field.

A limitation pertains to potential recall bias that stems from the questionnaire on self-reported mentally stimulating activities. Also, we did not control for mentally stimulating activities performed in early life or mid-life. We can assume that individuals who engaged in mentally stimulating activities in early life or mid-life are more likely to engage in these activities in late life compared with persons who did not engage in these activities during the life span. Furthermore, an observational study like ours allows investigating associations but does not permit drawing conclusions about cause and effect, which can only be done by interventional (experimental) studies. Therefore, we cannot exclude a "reverse causality" explanation (ie, it is possible that participants who are at higher risk for MCI are less likely to engage in mentally stimulating activities). However, given that we conducted a rigorous, time-intensive, large-scale population-based prospective cohort study, and considering similar findings from smaller studies in the past, we can conclude that the observed associations in our study are real. In addition, most of the population in Olmsted County is of white race. However, generalizability of the data to the population of the United States has been indicated.[50]

Conclusions

We observed that engaging in mentally stimulating activities even in late life may be protective against new-onset MCI. In addition, performing certain mentally stimulating activities may also lower the risk of incident MCI among *APOE* ε4 carriers. Future research is needed to understand the mechanisms linking mentally stimulating activities and cognition in late life.

ARTICLE INFORMATION

Accepted for Publication: August 8, 2016.

Published Online: January 30, 2017. doi:10.1001/jamaneurol.2016.3822

Author Affiliations: Mayo Clinic Translational Neuroscience and Aging Program, Mayo Clinic, Scottsdale, Arizona (Krell-Roesch, Pink, Geda); Department of Radiology, Mayo Clinic, Rochester, Minnesota (Vemuri); Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota (Roberts, Mielke, Petersen, Geda); Department of Neurology, Mayo Clinic, Rochester, Minnesota (Roberts, Knopman, Petersen); International Clinical Research Center, Brno, Czech Republic (Stokin); Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota (Christianson, Kremers); Department of Psychiatry and Psychology, Mayo Clinic, Scottsdale, Arizona (Geda); Department of Neurology, Mayo Clinic, Scottsdale, Arizona (Geda).

Author Contributions: Dr Geda had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Krell-Roesch, Roberts, Petersen, Geda.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Krell-Roesch, Geda.
Critical revision of the manuscript for important intellectual content: Vemuri, Pink, Roberts, Stokin, Mielke, Christianson, Knopman, Petersen, Kremers.
Statistical analysis: Christianson, Kremers.
Administrative, technical, or material support: Roberts, Petersen, Geda.
Study supervision: Geda.

Conflict of Interest Disclosures: Dr Knopman reported being deputy editor of *Neurology*; reported serving on data safety monitoring boards for Lundbeck Pharmaceuticals, the Dominantly Inherited Alzheimer's Disease Treatment Unit, and Lilly Pharmaceuticals; reported serving as a consultant to TauRx; reported being an investigator in clinical trials sponsored by Baxter and Elan Pharmaceuticals in the past 2 years; and reported receiving research support from the National Institutes of Health. Dr Petersen reported being a consultant to GE Healthcare and Elan Pharmaceuticals, reported serving on a data safety monitoring board in clinical trials sponsored by Pfizer Incorporated and Janssen Alzheimer Immunotherapy, and reported delivering a continuing medical education lecture at Novartis Incorporated. Dr Kremers reported receiving research funding from AstraZeneca. No other disclosures were reported.

Funding/Support: The study was supported by grants U01 AG006786 and R01 AG034676 from the National Institute on Aging and by grants K01 MH068351 and K01 AG028573 from the National Institute of Mental Health. Support for this research was also provided by the Robert Wood Johnson Foundation, the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program, the European Regional Development Fund–Project FNUSA-ICRC (No. CZ.1.05/1.1.00/02.0123), the Arizona Alzheimer's Consortium, and the Edli Foundation (the Netherlands) (Dr Geda).

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement*. 2007;3(3):186-191.

2. Vemuri P, Lesnick TG, Przybelski SA, et al. Association of lifetime intellectual enrichment with cognitive decline in the older population. *JAMA Neurol*. 2014;71(8):1017-1024.

3. Wilson RS, Mendes De Leon CF, Barnes LL, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *JAMA*. 2002;287(6):742-748.

4. Wilson RS, Bennett DA, Bienias JL, et al. Cognitive activity and incident AD in a population-based sample of older persons. *Neurology*. 2002;59(12):1910-1914.

5. Wilson RS, Barnes LL, Aggarwal NT, et al. Cognitive activity and the cognitive morbidity of Alzheimer disease. *Neurology*. 2010;75(11):990-996.

6. Akbaraly TN, Portet F, Fustinoni S, et al. Leisure activities and the risk of dementia in the elderly: results from the Three-City Study. *Neurology*. 2009;73(11):854-861.

7. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurol*. 2004;3(6):343-353.

8. Verghese J, Lipton RB, Katz MJ, et al. Leisure activities and the risk of dementia in the elderly. *N Engl J Med*. 2003;348(25):2508-2516.

9. Then FS, Luppa M, Schroeter ML, König HH, Angermeyer MC, Riedel-Heller SG. Enriched environment at work and the incidence of dementia: results of the Leipzig Longitudinal Study of the Aged (LEILA 75+). *PLoS One*. 2013;8(7):e70906. doi:10.1371/journal.pone.0070906

10. Marioni RE, Proust-Lima C, Amieva H, et al. Social activity, cognitive decline and dementia risk: a 20-year prospective cohort study. *BMC Public Health*. 2015;15:1089.

11. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999;56(3):303-308.

12. Geda YE, Topazian HM, Roberts LA, et al. Engaging in cognitive activities, aging, and mild cognitive impairment: a population-based study. *J Neuropsychiatry Clin Neurosci*. 2011;23(2):149-154.

13. Verghese J, LeValley A, Derby C, et al. Leisure activities and the risk of amnestic mild cognitive impairment in the elderly. *Neurology*. 2006;66(6):821-827.

14. Verghese J, Cuiling Wang, Katz MJ, Sanders A, Lipton RB. Leisure activities and risk of vascular cognitive impairment in older adults. *J Geriatr Psychiatry Neurol*. 2009;22(2):110-118.

15. Roses AD. Apolipoprotein E alleles as risk factors in Alzheimer's disease. *Annu Rev Med*. 1996;47:387-400.

16. Roses AD, Strittmatter WJ, Pericak-Vance MA, Corder EH, Saunders AM, Schmechel DE. Clinical application of apolipoprotein E genotyping to Alzheimer's disease. *Lancet*. 1994;343(8912):1564-1565.

17. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993;261(5123):921-923.

18. Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology*. 1993;43(8):1467-1472.

19. Roberts RO, Geda YE, Knopman DS, et al. The Mayo Clinic Study of Aging: design and sampling, participation, baseline measures and sample characteristics. *Neuroepidemiology*. 2008;30(1):58-69.

20. St Sauver JL, Grossardt BR, Yawn BP, Melton LJ III, Rocca WA. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester Epidemiology Project. *Am J Epidemiol*. 2011;173(9):1059-1068.

21. Roberts RO, Cha RH, Mielke MM, et al. Risk and protective factors for cognitive impairment in persons aged 85 years and older. *Neurology*. 2015;84(18):1854-1861.

22. Wilson RS, Bennett DA, Beckett LA, et al. Cognitive activity in older persons from a geographically defined population. *J Gerontol B Psychol Sci Soc Sci*. 1999;54(3):155-160.

23. Friedland RP, Fritsch T, Smyth KA, et al. Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. *Proc Natl Acad Sci U S A*. 2001;98(6):3440-3445.

24. Kokmen E, Smith GE, Petersen RC, Tangalos E, Ivnik RC. The Short Test of Mental Status: correlations with standardized psychometric testing. *Arch Neurol*. 1991;48(7):725-728. Medline:

25. Rey A. *L'Examen Clinique en Psychologie*. Paris: Presses Universitaires de France; 1964.

26. Wechsler D. *Wechsler Memory Scale–Revised*. New York, NY: Psychological Corp; 1987.

27. Kaplan E, Goodglass H, Brand S. *Boston Naming Test*. Philadelphia, PA: Lea & Febiger; 1983.

28. Kaplan E, Goodglass H, Weintraub S. *Boston Naming Test*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.

29. Lucas JA, Ivnik RJ, Smith GE, et al. Mayo's Older Americans Normative Studies: category fluency norms. *J Clin Exp Neuropsychol*. 1998;20(2):194-200.

30. Wechsler D. *Wechsler Adult Intelligence Scale–Revised*. New York, NY: Psychological Corp; 1981.

31. Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills*. 1958;8(3):271-276.

32. Ivnik RJ, Malec JF, Smith GE, et al. Mayo's Older Americans Normative Studies: WAIS-R norms for ages 56 to 97. *Clin Neuropsychol*. 1992;6(suppl):1-30.

33. Ivnik RJ, Malec JF, Smith GE, et al. Mayo's Older Americans Normative Studies: WMS-R norms for ages 56 to 94. *Clin Neuropsychol*. 1992;6(suppl):49-82.

34. Ivnik RJ, Malec JF, Smith GE, et al. Mayo's Older Americans Normative Studies: updated AVLT norms for ages 56 to 97. *Clin Neuropsychol*. 1992;6(suppl):83-104.

35. Malec JF, Ivnik RJ, Smith GE, et al. Mayo's Older Americans Normative Studies: utility of corrections for age and education for the WAIS-R. *Clin Neuropsychol*. 1992;6(suppl):31-47.

36. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2004;256(3):183-194.

37. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment: beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med*. 2004;256(3):240-246.

38. Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with *Hha*I. *J Lipid Res*. 1990;31(3):545-548.

39. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.

40. Beck AT, Steer RA, Brown GK. *Beck Depression Inventory–II (BDI-II): Manual*. 2nd ed. San Antonio, TX: Pearson; 1996.

41. Nithianantharajah J, Hannan AJ. Enriched environments, experience-dependent plasticity and disorders of the nervous system. *Nat Rev Neurosci*. 2006;7(9):697-709.

42. Landau SM, Marks SM, Mormino EC, et al. Association of lifetime cognitive engagement and low β-amyloid deposition. *Arch Neurol*. 2012;69(5):623-629.

43. Valenzuela MJ, Sachdev P, Wen W, Chen X, Brodaty H. Lifespan mental activity predicts diminished rate of hippocampal atrophy. *PLoS One*. 2008;3(7):e2598. doi:10.1371/journal.pone.0002598

44. Almeida RP, Schultz SA, Austin BP, et al. Effect of cognitive reserve on age-related changes in cerebrospinal fluid biomarkers of Alzheimer disease. *JAMA Neurol*. 2015;72(6):699-706.

45. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol*. 2012;11(11):1006-1012.

46. Geda YE, Roberts RO, Mielke MM, et al. Baseline neuropsychiatric symptoms and the risk of incident mild cognitive impairment: a population-based study. *Am J Psychiatry*. 2014;171(5):572-581.

47. Geda YE, Roberts RO, Knopman DS, et al. Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: population-based study. *Arch Gen Psychiatry*. 2008;65(10):1193-1198.

48. Geda YE, Roberts RO, Knopman DS, et al. Physical exercise, aging, and mild cognitive impairment: a population-based study. *Arch Neurol*. 2010;67(1):80-86.

49. Geda YE, Ragossnig M, Roberts LA, et al. Caloric intake, aging, and mild cognitive impairment: a population-based study. *J Alzheimers Dis*. 2013;34(2):501-507.

50. St Sauver JL, Grossardt BR, Leibson CL, Yawn BP, Melton LJ III, Rocca WA. Generalizability of epidemiological findings and public health decisions: an illustration from the Rochester Epidemiology Project. *Mayo Clin Proc*. 2012;87(2):151-160.