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Association Between Mentally Stimulating Activities in Late Life and the Outcome of Incident Mild Cognitive Impairment, With an Analysis of the APOE ϵ 4 Genotype

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Abstract

Importance—We and others have reported cross-sectional associations between mentally stimulating activities and decreased odds of having mild cognitive impairment (MCI) or Alzheimer’s disease. However, little is known about the longitudinal outcome of incident MCI as predicted by late life (age $\geq$ 70 years) mentally stimulating activities.

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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: Krell-Roesch, Roberts, Christianson, Knopman, Petersen, Geda.

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Conflict of Interest Disclosures

Dr. Knopman serves as Deputy Editor for *Neurology*®; serves on a Data Safety Monitoring Board for Lundbeck Pharmaceuticals and for the Dominantly Inherited Alzheimer’s Disease Treatment Unit. He has served on a Data Safety Monitoring Board for Lilly Pharmaceuticals; served as a consultant to Tau RX, was an investigator in clinical trials sponsored by Baxter and Elan Pharmaceuticals in the past 2 years; and receives research support from the NIH.

Dr. Petersen reports being a consultant to GE Healthcare and Elan Pharmaceuticals; serving on a data safety monitoring board in clinical trials sponsored by Pfizer Incorporated and Janssen Alzheimer Immunotherapy; and gave a CME lecture at Novartis Incorporated.

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Objective—To test our hypothesis on the association between mentally stimulating activities in late life and the risk of incident MCI and additionally evaluate the impact of APOE ε4 genotype.

Design—Prospective cohort study.

Setting—Population-based Mayo Clinic Study of Aging in Olmsted County, Minnesota.

Participants—We followed 1929 participants aged 70 years who were cognitively normal at baseline to the outcome of incident MCI.

Main Outcome and Measures—At baseline, participants provided information about mentally stimulating activities within a year prior to enrolment into the study. Neurocognitive assessment was conducted at baseline and 15 month interval evaluations. Cognitive diagnosis was made by an expert consensus panel based on published criteria. We calculated hazard ratios (HR) and 95% confidence intervals (95% CI) using Cox proportional hazards models after adjusting for age, sex and education.

Results—Over a median follow-up period of 4 years, we observed that playing games (HR [95% CI], 0.78 [0.65–0.95]), and engaging in craft activities (0.72 [0.57–0.90]), computer use (0.70 [0.57–0.85]), and social activities (0.77 [0.63–0.94]) were associated with a decreased risk of incident MCI. In a stratified analysis by APOE ε4 status, the data points towards the lowest risk of incident MCI for APOE ε4 non-carriers who engage in mentally stimulating activities and towards the highest risk of incident MCI for APOE ε4 carriers who do not engage in mentally stimulating activities.

Conclusion 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.

Dementia has become a global epidemic causing significant burden not only for societies but also for caregivers and patient families¹. 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 decline² and dementia^{3–10}. To date, only few studies investigated whether cognitive activities are related to the outcome of mild cognitive impairment (MCI) which is the intermediate zone between normal cognitive aging and dementia¹¹. Our group has reported a cross-sectional association between mentally stimulating activities and decreased odds of having mild cognitive impairment (MCI)¹². A cohort study involving a convenience sample of community-dwelling elderly found an association between cognitive activities and a decreased risk of amnesic MCI¹³ as well as vascular cognitive impairment¹⁴.

In the current 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 aged 70 years and above. We have made rigorous efforts to ensure that our study participants were cognitively normal at baseline and we also had a well-

established research infrastructure to follow the cohort forward in time to the outcomes of incident MCI. Such an undertaking minimizes the potential for reverse causality though theoretically it may not completely eliminate it. We hypothesize that elderly persons who report engaging in mentally stimulating activities at least 1–2 times per week have a significantly decreased risk of developing new onset of MCI as compared to persons that report less mentally stimulating activities. Since Apolipoprotein E (APOE) ϵ 4 is a well-known risk factor for MCI and dementia^{15–18}, we also conducted a stratified analysis by APOE genotype. We hypothesize that 1) APOE ϵ 4 carriers have a higher risk of developing incident MCI as compared to APOE ϵ 4 non-carriers regardless of engaging in mentally stimulating activities; 2) APOE ϵ 4 carriers who report engaging in mentally stimulating activities have a decreased risk of developing incident MCI as compared to APOE ϵ 4 carriers who do not report engaging in mentally stimulating activities.

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 elderly persons aged 70 years and older. The details of the MCSA study have been reported elsewhere¹⁹. 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 sampling²⁰. The MCSA study protocols have been 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. 284 individuals were excluded (242 withdrew prior to follow-up, 3 had no follow-up visit, and 39 died prior to follow-up). Therefore, the final cohort consisted of 1929 cognitively normal persons who were followed 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 results from our cross-sectional study¹²: Reading books, craft activities, computer activities, playing games, and social activities (e.g., 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 a month or less, 2–3 times a month, 1–2 times per week, 3–4 times per week, 5–6 times per week, and daily). Participants were asked to provide information about engagement in these activities in the year prior to study participation (late life mentally stimulating activities).

Cognitive Evaluation

The cognitive assessment in the MCSA was described in detail elsewhere^{12,19} and is briefly described here. A face-to-face evaluation was completed among all study participants and included three assessment components: (1) a neurological evaluation which included a neurological history review, the administration of the Short Test of Mental Status²⁴, 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 (CDR); and (3) neuropsychological testing which was administered by a psychometrist to assess performance in 4 cognitive domains: Memory (delayed recall trials from the Auditory Verbal Learning Test²⁵ and Wechsler Memory Scale-Revised²⁶, Logical Memory and Visual Reproduction subtests); Language (Boston Naming Test^{27,28} and category fluency²⁹); Visuospatial Skills (Wechsler Adult Intelligence Scale-Revised³⁰, Picture Completion and Block Design subtests); and Executive Functions (Trail Making Test B³¹ and Wechsler Adult Intelligent Scale-Revised³⁰, 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 evaluation¹⁹. Individuals were considered as 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 (executive functions, memory, language, or visuospatial skills); (3) essentially normal functional activities; and (4) absence of dementia. Participants with MCI had a CDR score of 0 or 0.5; however, the final diagnosis of MCI was based on all available data.

APOE Genotyping

Blood was drawn from the study participants after receiving informed consent. DNA was amplified by means of polymerase chain reaction, and APOE genotyping was determined by standard methods³⁸. The genotypes were determined 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 (HR) and 95% confidence intervals (95% CI) by using Cox proportional hazards models with age as a time scale and after adjusting for sex, education, medical comorbidity (weighted Charlson index)³⁹, depression (Beck Depression Inventory score <13 vs ≥13)⁴⁰, and APOE genotype status.

Our hypotheses were generated from our previous cross-sectional study. Thus, the analyses were conducted separately for five different types of mentally stimulating activities in late life (within 1 year of the cognitive assessment): reading books, craft activities, computer activities, playing games, and social activities (e.g., going out to movies and theaters). In our analyses, we compared mentally stimulating activities carried out at least 1–2 times per week vs. mentally stimulating activities carried out 2–3 times a month or less (reference group) in predicting the risk of incident MCI. We measured central tendency using medians

and associated interquartile ranges. Furthermore, we conducted analyses stratified by MCI subtype (amnesic vs. non-amnesic) as well as APOE $\epsilon 4$ status to investigate possible interactions between this genetic risk factor for AD and mentally stimulating activities in late life. Fitting all the data, we also tested for multiplicative interactions on the hazard ratio scale as well as for additive interactions. Statistical testing was performed at the conventional 2-tailed alpha level of 0.05. All analyses were performed using SAS[®] System, version 9.3 software (SAS Institute, Cary, North Carolina).

RESULTS

At baseline, we included 1929 cognitively normal persons aged 70 years and older (50.4% females) who had completed a valid mentally stimulating activities assessment and cognitive evaluation. We followed this cohort forward in time for a median of 4.0 years (interquartile range [IQR], 2.3–6.4 years), at which time 456 participants developed new onset MCI (Figure 1). The median age at baseline was 77 years (IQR, 74–82 years) and the median level of education was 14 years (IQR, 12–16 years). 512 participants (26.7%) were APOE $\epsilon 4$ carriers. APOE genotype data were missing for 9 participants. The detailed demographic characteristics are displayed in Table 1.

After adjusting for age, sex, and years of education, we observed that playing games (HR [95% CI], 0.78 [0.65 to 0.95]), engaging in craft activities (HR [95% CI], 0.72 [0.57 to 0.90]), computer activities (HR [95% CI], 0.70 [0.57 to 0.85]), and social activities (HR [95% CI], 0.77 [0.63 to 0.94]) were associated with a decreased risk of incident MCI. The association between reading books (HR [95% CI], 0.83 [0.68 to 1.01]) and a decreased risk of incident MCI was marginally significant. Additional adjustment for medical comorbidity, depression and APOE genotype did not significantly alter the results (Model 2). Please refer to Table 2 for a summary of results.

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

We conducted the same analyses stratified by APOE $\epsilon 4$ status. We observed that among APOE $\epsilon 4$ non-carriers, craft activities (HR [95% CI], 0.65 [0.49 to 0.85]), and computer activities (HR [95% CI], 0.73 [0.58 to 0.93]) were significantly associated with a decreased risk of incident MCI and the associations were marginally significant for reading books (HR [95% CI], 0.81 [0.64 to 1.02]) and playing games (HR [95% CI], 0.81 [0.64 to 1.02]). Among APOE $\epsilon 4$ carriers, only computer activities (HR [95% CI], 0.65 [0.46 to 0.92]) and social activities (HR [95% CI], 0.62 [0.43 to 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 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 also APOE ϵ 4 non-carriers. We consistently observed the lowest risk of incident MCI in participants who engaged in any type of mentally stimulating activity and were APOE non-carriers as compared with the reference group. In contrast, participants who were APOE ϵ 4 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 tests for additive interactions between late life mentally stimulating activities and APOE genotype on the risk of new-onset MCI were significant. However, the model on additive interaction was marginally significant for social activities ($p = 0.088$). Additional adjustment for medical comorbidity and depression did not alter the results. Please refer to eTable 2 for a summary of results and to Figure 2 for visual display of data (HR plot).

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, engaging in craft, computer, and social activities significantly reduced the risk of incident MCI. In the past, we have reported decreased odds of MCI for engagement in mentally stimulating activities in late life in a population-based, case-control study¹². However, we considered those findings as preliminary until confirmed by a prospective cohort study, which we are now reporting.

When comparing MCI subtypes (amnesic vs. non-amnesic MCI), we observed more associations between mentally stimulating activities and a decreased risk of amnesic MCI as compared to non-amnesic MCI. This could be explained by a limited power due to smaller sample size for the analysis on non-amnesic MCI.

As APOE ϵ 4 is a well-known risk factor for MCI and AD^{15–18}, we also conducted stratified analyses by APOE ϵ 4 status in predicting the outcome of incident MCI. As expected, the data points towards a reduced risk of incident MCI for APOE ϵ 4 non-carriers who engage in mentally stimulating activities. However, we observed fewer associations between mentally stimulating activities and a decreased risk of incident MCI for APOE ϵ 4 carriers as compared to non-carriers. This finding may in part be explained by a lower sample size of APOE ϵ 4 carriers which limits the statistical power of this analysis.

Our study is in line with previous research that reported a potentially protective effect of mentally stimulating activities on cognitive decline², dementia^{3–10} and MCI^{13,21}. Additionally, a recent study involving persons aged 85 years and 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 MCI²¹. To our knowledge, our study might be one of the few if not the first population-based cohort study to examine the risk of incident MCI in persons 70 years and older as predicted by engagement in mentally stimulating activities in late life.

Our study could not disentangle why some mentally stimulating activities (e.g., computer activities) had a larger effect size on the decreased risk of incident MCI than other activities (e.g., reading books). However, we can speculate the following. Perhaps, a particular mental activity, for example, the use of a computer requires 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. Studies involving mouse models of Alzheimer's disease (AD) showed a protective effect of enriched environments on neuropathological changes associated with AD such as prevention of neuronal dysfunction and increased synaptic recovery⁴¹. So far, only few studies investigated the associations between mental or cognitive activities and pathological changes associated with cognitive decline and AD in humans. For example, researchers from UC Berkley reported a significant association between cognitive activities and a decreased beta amyloid deposition in the cortex⁴². An Australian group reported that complex mental activity across the lifespan was associated with decreased hippocampal atrophy⁴³. A recent report indicated that higher cognitive reserve was associated with decreased age-related changes in CSF biomarkers⁴⁴. Additionally, one can hypothesize that engagement in mentally stimulating activities may also 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 decline¹². 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 pathologies on cognitive function⁴⁵. The reader is referred to our previous manuscript¹² 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 exercise⁴⁸ and low caloric intake⁴⁹ are associated with a lower risk of MCI.

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 that we followed over several years. In addition, MCI was assessed using face-to-face evaluations and based on a consensus panel at a center that has a well-known reputation in the field. A limitation pertains to potential recall bias that stems from the self-reported mentally stimulating activities questionnaire. Also, we did not control for mentally stimulating activities carried out in early or midlife. We can assume that individuals who engaged in mentally stimulating activities in early and/or midlife are more likely to engage in these activities in late life as compared to persons who did not engage in these activities during the lifespan. Furthermore, an observational study like ours only allows investigating associations and does not allow drawing conclusions about cause and effect. This can only

be done by interventional (experimental) studies. Therefore, we cannot exclude a ‘reverse causality’ explanation, i.e. 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, it should be noted that the majority of the population in Olmsted County, Minnesota is of Caucasian descent. However, it has been indicated that the data is generalizable to the population of the United States⁵⁰.

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Study Flow Chart

Figure 2. Hazard ratio plot on interaction between mentally stimulating activities and APOE ϵ 4 status on the risk of incident MCI

Abbreviations: HR, hazard ratio; CI, confidence interval; APOE ϵ 4-/ APOE ϵ 4+, APOE ϵ 4 non-carrier/ carrier; Books+/Games+/Craft+/Computer+/Social+, reported engaging in reading books/playing games/craft activities/computer activities/social activities at least 1–2 times per week or more; Books-/Games-/Craft-/Computer-/Social-, reported not engaging in reading books/playing games/craft activities/computer activities/social activities (2–3 times a month or less).

Model adjusted for age (scale), sex, and education. Additional adjustment for medical comorbidity and depression did not significantly alter the results (data not shown).

Table 1

Demographic Characteristic of the Study Sample

Variable	Total (n = 1929)
Female, No. (%)	973 (50.4)
Age, yrs ^a	77 [74, 82]
70–79	1154 (59.8)
80–93	775 (40.2)
Education, yrs ^a	14 [12, 16]
>12	1203 (62.4)
BDI-II grand total ^a	3 [1, 7] ^I
Depression (total 13)	106 (5.5)
Charlson Comorbidity Index score ^a	3 [2, 5]

Abbreviations: BDI-II, Beck Depression Inventory.

^aMedian [interquartile range]

^IInformation missing on 4 participants.

Table 2**Mentally stimulating activities and risk of incident MCI**

Variable	No. at Risk	No. with incident MCI	Median Follow-up (yrs)	HR (95%CI) ¹	p-value	HR (95%CI) ²	p-value
Reading books	1083	240	4.1	0.83 (0.68, 1.01)	0.06	0.86 (0.71, 1.05)	0.14
Playing games	1108	245	4.1	0.78 (0.65, 0.95)	0.012	0.83 (0.69, 1.01)	0.06
Craft activities	502	104	4.1	0.72 (0.57, 0.90)	0.004	0.78 (0.62, 0.98)	0.030
Computer activities	1077	193	4.1	0.70 (0.57, 0.85)	<0.001	0.74 (0.61, 0.90)	0.002
Social activities	767	154	4.1	0.77 (0.63, 0.94)	0.009	0.79 (0.64, 0.96)	0.017

Abbreviations: HR, hazard ratio; CI, confidence interval.

¹Model adjusted for age (scale), sex, and education.²Model also adjusted for medical comorbidity, depression, and APOE ε4 status. No. at risk refers to the number of participants (of the total sample size of 1929) that reported engaging in a mentally stimulating activity with a frequency of at least 1–2 times per week or more. No. with incident MCI refers to the number of participants (of the total sample size of 1929) that developed incident MCI.

Table 3
Mentally stimulating activities and risk of incident MCI stratified by APOE ε4 carrier status

Variable	No. at Risk	No. with incident MCI	Median Follow-up (yrs)	HR (95%CI) ¹	p-value	HR (95%CI) ²	p-value
APOE ε4 carriers							
Reading books	283	77	3.4	0.91 (0.63, 1.29)	0.59	1.02 (0.71, 1.46)	0.94
Playing games	288	75	3.5	0.72 (0.51, 1.01)	0.06	0.78 (0.55, 1.10)	0.15
Craft activities	123	33	3.0	1.02 (0.69, 1.51)	0.92	1.08 (0.73, 1.61)	0.70
Computer activities	276	61	3.7	0.65 (0.46, 0.92)	0.014	0.71 (0.50, 1.00)	0.05
Social activities	194	45	3.9	0.62 (0.43, 0.89)	0.009	0.64 (0.45, 0.92)	0.017
APOE ε4 non-carriers							
Reading books	792	162	4.2	0.81 (0.64, 1.02)	0.07	0.82 (0.64, 1.04)	0.09
Playing games	815	169	4.2	0.81 (0.64, 1.02)	0.07	0.85 (0.68, 1.08)	0.18
Craft activities	378	71	4.5	0.65 (0.49, 0.85)	0.002	0.67 (0.51, 0.88)	0.004
Computer activities	795	132	4.2	0.73 (0.58, 0.93)	0.011	0.75 (0.59, 0.95)	0.017
Social activities	571	108	4.2	0.83 (0.66, 1.06)	0.13	0.86 (0.68, 1.09)	0.22

Abbreviations: HR, hazard ratio; CI, confidence interval.

¹Model adjusted for age (scale), sex, and education.

²Model also adjusted for medical comorbidity and depression. No. at risk refers to the number of participants (of the total sample size of 1929) that reported engaging in a mentally stimulating activity with a frequency of at least 1–2 times per week or more. No. with incident MCI refers to the number of participants (of the total sample size of 1929) that developed incident MCI.