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Timing of Physical Activity, Apolipoprotein E (APOE) ϵ 4 Genotype, and the Risk of Incident Mild Cognitive Impairment

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Abstract

Objectives—To investigate the timing (mid- vs. late life) of physical activity, APOE ϵ 4 and the risk of incident mild cognitive impairment (MCI) in a population-based setting.

Design—Prospective cohort study.

Setting—The Mayo Clinic Study of Aging in Olmsted County, Minnesota.

Participants—We followed 1830 cognitively normal elderly persons (median age: 78 years, 50.2% females) for a median of 3.2 years.

Measurements—Light, moderate and vigorous physical activities in mid- and late life were assessed by a validated questionnaire. MCI was measured by an expert consensus panel based on published criteria. We used Cox proportional hazards models to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) with age as a time scale, after adjusting for sex, education, medical comorbidity, and depression.

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Results—Light (HR [95% CI], 0.58 [0.43 to 0.79]) and vigorous (0.78 [0.63 to 0.97]) physical activity in midlife were associated with a decreased risk of incident MCI. The association between moderate activity and incident MCI was marginally significant (0.85 [0.67–1.09]). In late life, light (0.75 [0.58 to 0.97]) and moderate (0.81 [0.66 to 0.99]), but not vigorous physical activity were associated with a decreased risk of incident MCI. We also observed a synergistic interaction between mid- and late life activity in reducing the risk of incident MCI. Furthermore, Apolipoprotein E (APOE) ε4 carriers who did not exercise had a higher risk of incident MCI as compared to APOE ε4 non-carriers who reported physical activity.

Conclusion—Physical activity reduced the risk of incident MCI. Exercising in both mid- and late life, had an additive synergistic interaction in further reducing the risk of MCI.

Keywords

Physical Activity; APOE ε4; Mild Cognitive Impairment

INTRODUCTION

Mild cognitive impairment (MCI) is the intermediate stage between normal cognitive aging and dementia.^{1,2} MCI has high prevalence^{3,4} and incidence rates^{5,6} in old age and constitutes a high-risk state for dementia. Therefore, the identification of potential protective factors against new onset MCI is of great importance.

Growing evidence indicates that physical activity is associated with decreased risk of cognitive decline and dementia.^{7–11} Various research groups have reported the outcome of incident dementia as predicted by baseline exposure to physical activity.^{12–17} However, only few studies have examined the outcome of incident MCI or similar constructs.^{13,18} Furthermore, little is known about the timing of physical activity (mid- vs. late life) and the risk of incident MCI in a large-scale, population-based setting.

We sought to determine the association between mid- vs. late life physical activity and the risk of incident MCI. Additionally, we investigated the interaction between mid- and late life physical activity, and the risk of incident MCI in a population-based setting. Since Apolipoprotein E (APOE) ε4 is a well-known risk factor for MCI and dementia we conducted a stratified analysis of the role of physical activity by APOE genotype.

METHODS

Design and Setting

We conducted a prospective cohort study that was 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 elsewhere.¹⁹ Briefly, a stratified random sampling was used to recruit participants from the target population of 9953 elderly individuals residing in Olmsted County, Minnesota, on October 1, 2004.²⁰ 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 2207 cognitively normal participants who had completed a validated physical activity questionnaire at baseline; 377 individuals were excluded (222 withdrew prior to follow-up, 118 had no follow-up visit, and 37 died). Therefore, the final cohort consisted of 1830 cognitively normal persons who were followed to the outcome of incident MCI (Figure 1).

Assessment of Physical Activity

Details of the measurement of physical activity in the MCSA have been reported elsewhere.^{21,22} Briefly, physical activity was measured using a self-reported questionnaire.^{21–24} As we reported previously^{21,22}, we used questions from two validated instruments: the 1985 National Health Interview Survey²³ and the Minnesota Heart Survey intensity codes²⁴. The questionnaire was designed to assess the intensity and frequency of physical activity at 2 different time points: (1) the year prior to the date of cognitive assessment (late life physical activity; participants were aged ≥ 70 years at cognitive assessment), and (2) between 50 and 65 years of age (midlife physical activity). Participants provided information about intensity (light, moderate, and vigorous) and frequency of activity (1 time per month, 2–3 times per month, 1–2 times per week, 3–4 times per week, 5–6 times per week, and daily). Light physical activity included activities such as leisurely walking, slow dancing, or stretching. Moderate physical activity included activities such as hiking, brisk walking, swimming, or yoga. Vigorous physical activity included activities such as jogging, tennis singles, or bicycling uphill.

Cognitive Evaluation

The cognitive assessment in the MCSA was described in detail elsewhere^{19,21} and is briefly described here. A face-to-face evaluation was completed among all study participants and included 3 assessment components: (1) a neurological evaluation which included a neurological history review, the administration of the Short Test of Mental Status,²⁵ 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 Test²⁶ and Wechsler Memory Scale-Revised,²⁷ Logical Memory and Visual Reproduction subtests); Language (Boston Naming Test^{28,29} and category fluency³⁰); Visuospatial Skills (Wechsler Adult Intelligence Scale-Revised,³¹ Picture Completion and Block Design subtests); and Executive Functions (Trail Making Test B³² and Wechsler Adult Intelligent Scale-Revised,³¹ 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 as cognitively normal at baseline according to published normative data developed on this community.^{33–36} For MCI, the following revised Mayo Clinic criteria for MCI^{2,37} were used: (1) cognitive concern expressed by a physician, an informant, a participant, or a 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 methods.³⁸ The genotypes were determined by laboratory technicians who were kept unaware of clinical characteristics.

Statistical Analysis

To investigate the association between mid- and late life physical activity 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 ranging from 0 to 33),³⁹ and depression (Beck Depression Inventory score <13 vs ≥13).⁴⁰

Analyses were conducted separately for physical activity (any vs. none) in midlife (between the ages of 50 to 65 years) and late life (within 1 year of the cognitive assessment) and for the three different levels of activity intensity (light, moderate, and vigorous). In our analyses, we compared any physical activity versus none. Any physical activity was defined as engaging in physical activity at least 2–3 times/month. No physical activity (reference) was defined as physical activity carried out less than or equal to 1 time/month. We measured central tendency using medians and associated interquartile ranges. Furthermore, we prepared Kaplan-Meier survival curves for the visual display of data. We also conducted a stratified analysis by the timing of physical activity (mid- and late life) and additionally investigated possible interaction effects between activity in mid- and late life by using multivariate models to test for additive interactions. Additionally, we conducted a stratified analysis by APOE ε4 genotype. 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, there were 1830 cognitively normal persons (about 50% females) with a valid physical activity assessment and cognitive evaluation. We followed this cohort forward in time for a median of 3.2 years (interquartile range [IQR], 1.9–4.7 years), at which time 389 participants developed new onset MCI (Figure 1). The median age at baseline was 78 years (IQR, 74–83 years) and the median level of education was 14 years (IQR, 12–16 years). 474 participants were APOE ε4 carriers and 1,347 participants were APOE ε4 non-carriers. APOE ε4 carrier status data is missing on 9 participants. The detailed demographic characteristics are displayed in Table 1.

After adjusting for age, sex, and years of education we observed that light and vigorous physical activity in midlife were associated with a decreased risk of incident MCI, whereas the association between moderate activity and incident MCI was marginally significant (light: HR [95% CI], 0.58 [0.43 to 0.79]; moderate: HR [95% CI], 0.85 [0.67–1.09]);

vigorous: HR [95% CI], 0.78 [0.63 to 0.97]). Additional adjustment for medical comorbidity and depression did not significantly alter the results (Model 2). For late life, light (Model 1: HR [95% CI], 0.75 [0.58–0.97]) and moderate (Model 1: HR [95% CI], 0.81 [0.66–0.99]) but not vigorous (Model 1: HR [95% CI], 0.90 [0.66–1.25]) physical activity was significantly associated with a decreased risk of incident MCI. After additionally adjusting the late life model for medical comorbidity and depression (Model 2), only light intensity activity was significantly associated with a decreased risk of incident MCI (HR [95% CI], 0.76 [0.58–0.98]). (Table 2) Please refer to Figure 2 for visual display of data.

We also conducted additional analyses (Supplemental table 1) in which we defined “physical activity” as engaging in physical activity at a frequency of at least 1–2 times per week. The results are slightly different as compared to our analysis comparing “any vs. none” physical activity. We observed that light intensity activity in midlife was associated with a decreased risk of incident MCI, whereas the association was marginally significant for moderate intensity activity and not significant for vigorous intensity activity. For late life, moderate activity was significantly associated with a decreased risk of incident MCI but not light or vigorous intensity. It must be noted that there was no significant effect of late life physical activity on incident MCI when we additionally adjusted the model for medical comorbidity and depression. It is reassuring to know that using various definitions of activity (2–3 times per month vs. 1 time a week) still indicated that activity is associated with a decreased risk of incident MCI regardless of the categories used to define activity.

We also examined a possible interaction between mid- and late life physical activity in predicting the risk of incident MCI. We defined the reference group as participants who did not exercise in both mid- and late life. Compared with the reference group, participants who exercised at moderate intensity in mid- but not in late life had an HR of 0.94 (95% CI = 0.68–1.28) for incident MCI, participants who exercised in late but not in midlife had an HR of 0.88 (95% CI = 0.55–1.42), and participants who exercised in both mid- and late life had an HR of 0.76 (95% CI = 0.57–1.02). A test for additive interaction between mid- and late life moderate activity in decreasing the risk of new-onset MCI was significant ($P < .001$). Additional adjustment for medical comorbidity and depression did not alter the results. The frequency for participants who did not exercise in both mid- and late life was about 26%, and the frequency for those who exercised in both mid- and late life was approximately 18%. This implies an 8% risk reduction for participants who exercised in both mid- and late life as compared to those who did not. We conducted the same analysis for light and vigorous intensity activity and also observed the lowest HR for participants who exercised in both mid- and late life as compared to participants who exercised in either mid- or late life. However, a test for additive interaction was significant only for light intensity but not vigorous intensity activity. (Table 3)

Furthermore, we conducted analyses stratified by APOE $\epsilon 4$ genotype for both mid- and late life physical activity in predicting the risk of incident MCI. The analyses were conducted separately for the three intensity levels and were adjusted for age, sex, and education. We defined the reference group as participants who did not engage in any physical activity and who did not carry an APOE $\epsilon 4$ allele. In both mid- and late life, we observed the highest risk for incident MCI among APOE $\epsilon 4$ carriers who did not engage in any intensity of physical

activity be it in midlife or late life (Supplemental table 2). In contrast, participants who were APOE ϵ 4 non-carriers and engaged in physical activity consistently showed the lowest risk of MCI, even though only light activity intensity in midlife reached statistical significance.

We also conducted additional analyses on the interaction between mid- and late life activity stratified by APOE carrier status (Supplemental table 3). We observed that, regardless of APOE ϵ 4 carrier status, the point estimates for exercising at any intensity in both mid- and late life together were consistently lower than the point estimates for exercising in either mid- or late life alone; though it lacked statistical significance which in part could be related to the chopping of data into several categories by APOE ϵ 4 status and intensity of activity.

DISCUSSION

In this population-based, prospective cohort study, we observed that engaging in physical activity in mid- and late life was associated with a decreased risk of incident MCI. Especially light but not vigorous physical activity significantly reduced the risk of incident MCI. This suggests a potential protective effect of light intensity activity such as a leisurely walk after a dinner. Even though the point estimate for moderate intensity physical activity in midlife suggested a protective effect, it did not reach statistical significance. Additional adjustment for medical comorbidity and depression did not alter the results for light and vigorous activity; only moderate activity in late life lost significance after additionally adjusting for medical comorbidity and depression. As expected, not many elderly individuals engaged in vigorous physical activity (e.g. jogging and uphill biking) in late life which may explain the absence of an association between late life vigorous activity and incident MCI.

We observed an additive interaction between mid- and late life activity in reducing the risk of MCI. The significant p-value for the additive interaction indicates that the combined effect of exercising in both midlife and late life is greater than the expected arithmetic sum of the independent benefits of midlife activity or late life activity. As APOE ϵ 4 is a well-known risk factor for MCI and Alzheimer's dementia, we also conducted a stratified analysis by APOE ϵ 4 status in predicting the outcome of incident MCI. The data overall points towards a reduced risk of incident MCI in participants who exercise and are APOE ϵ 4 non-carriers, but an increased risk of MCI for those who do not exercise and carry an APOE ϵ 4 allele. However, not all point estimates reached significance, which may be due to reduced statistical power as the data had to be divided into smaller groups for the stratified analysis. In the past, we have reported decreased odds of MCI for moderate intensity physical activity in mid- and late life in a population-based, case-control study.²¹ However, we considered those findings as preliminary until confirmed by a prospective cohort study which we are now reporting.

A recent meta-analysis of longitudinal studies indicated that higher levels of physical activity as compared to lower ones are significantly associated with reduced risk of cognitive decline or dementia⁴¹. However, to date, only few cohort studies have investigated the risk of incident MCI or similar constructs by baseline exposure to physical activity. In contrast to our findings, a prospective cohort study involving 437 community-dwelling elderly individuals failed to detect a significant association between physical activity and the risk of

new onset amnesic MCI.⁴² However, the point estimate in this study suggested a potential protective effect of physical activity but lacking statistical significance. Middleton and Yaffe examined the cross-sectional association between the timing of physical activity and cognitive impairment in old age involving 9344 women. They reported that physical activity carried out at any time during life, but especially during teenage years, was associated with a lower risk of cognitive impairment in late life.⁴³ The similarity between their study and ours is that both investigated the timing of physical activity. However, their study sample consisted of women only, whereas our study had about 50% women. Additionally, the outcomes of interest and the study designs are different. Our study extends their findings by showing that physical activity in both mid- and late life, as opposed to mid- or late life only, further reduced the risk of incident MCI.

In addition, only few studies investigated the effect of APOE ε4 carrier status on the association between physical activity and the risk of Alzheimer's disease (AD) and dementia. Whereas APOE ε4 genotype did not alter the association between physical activity and the risk of AD in one study,¹² Finnish and Swedish researchers reported an effect of APOE ε4 on the association between midlife physical activity and the risk of AD and dementia. Interestingly, midlife physical activity was associated with a reduced risk of AD and dementia at a follow-up of 20 years later, especially in APOE ε4 carriers⁴⁴ but at a 30-year follow-up, this association was significant only for APOE ε4 non-carriers.⁴⁵ Similarly, we report the lowest risk of MCI in those who exercised and were APOE ε4 non-carriers. In addition to the cohort studies mentioned above, there are few other studies that have assessed the interaction between physical activity or fitness level and APOE ε4 with cognitive performance and decline^{46–48}, amyloid deposition⁴⁹, memory performance^{50,51}, white matter tract diffusivity⁵², glucose metabolism⁵³, and hippocampal volume⁴⁸.

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 1830 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.

One limitation pertains to potential recall bias that stems from the self-reported physical activity questionnaire.^{54,55} However, this is less likely as we have indicated in the past that our questionnaire had an internal consistency of a moderate to good range.²¹ Furthermore, the questionnaire used in this study did not assess the number of years of physical activity in either mid- or late life. Also, it would have been informative had there been continuous data for the frequency of physical activity. This could have potentially allowed us to compare the mean (standard deviation) of the frequency of physical activity between participants who remained cognitively normal and those who developed incident MCI (please refer to supplemental table 4 for the frequencies of the response categories of the physical activity questionnaire). Additionally, only a few people engaged in vigorous activity in late life which limited the statistical power for this analysis. Another limitation of our study is that even though the majority of Olmsted County population is of Caucasian decent, a recent publication has indicated that the data is generalizable to the US population⁵⁶.

In this study, we did not investigate possible mechanisms that might underlie or cause the association between timing of engaging in physical activity and the risk of incident MCI. However, we can speculate from published research that physical activity may be protective against cognitive decline via several mechanisms including increased cerebral blood flow,⁵⁷ increased production of neurotrophic factors,⁵⁸ increased neurogenesis and neuronal plasticity, as well as enhanced neuronal survival,⁵⁹ and a decreased risk of cardiovascular and cerebrovascular diseases.⁶⁰

In conclusion, we observed that physical activity, even of light intensity, in mid- and late life was associated with a decreased risk of incident MCI. Activity in both mid- as well as late life may have a substantially beneficial effect. Overall, APOE ε4 non-carriers who exercised showed the lowest risk of MCI, while APOE ε4 carriers who did not exercise had the highest risk of MCI. Future research is needed to understand the mechanisms linking physical activity and cognition in elderly human individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Ronald C. Petersen: Consultant to Roche Incorporated, Merck and Genentech; Serves as chair of data monitoring committees of Pfizer Incorporated and Janssen Alzheimer Immunotherapy;

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Figure 1.
Study Flowchart

Figure 2.

Survival Free of Incident Mild Cognitive Impairment among Cognitively Normal Subjects Stratified by Mid- and Late Life Physical Activity

Y-axes: Survival free of incident MCI (%); X-axes: age (years); A–C: Midlife physical activity; A, no activity (solid) vs light intensity (dashed); B, no activity (solid) vs moderate intensity (dashed); C, no activity (solid) vs vigorous intensity (dashed). D–E: Late life physical activity; D, no activity (solid) vs light intensity (dashed); E, no activity (solid) vs moderate intensity (dashed); F, no activity (solid) vs vigorous intensity (dashed).

Table 1

Demographic Characteristics

Variable	Total (n = 1830)
Female, No. (%)	919 (50.2)
Age, y ^a	78 [74, 83]
70–79	1060 (57.9)
80–93	770 (42.1)
Education, y ^a	14 [12, 16]
>12	1130 (61.7)
BDI-II grand total ^a	3 [1, 7] ^b
Depression (total 13)	102 (5.6)
Charlson Comorbidity Index score ^a	3 [2, 5]

BDI-II, Beck Depression Inventory, second edition; y, years.

^aMedian [interquartile range].

^bData from 3 participants is missing.

Mid- and Late Life Physical Activity and the Risk of Incident Mild Cognitive Impairment

Table 2

Variable	No. at Risk (n = 1830)	No. With Incident MCI (n = 389)	Median Time to Outcome (y)	Model 1		Model 2	
				HR (95% CI)	P Value	HR (95% CI)	P Value
Midlife physical activity (any vs none)							
Light	1685 ^a	341	3.3	0.58 (0.43–0.79)	<.001	0.59 (0.43–0.80)	<.001
Moderate	1495 ^b	303	3.3	0.85 (0.67–1.09)	.19	0.87 (0.68–1.11)	.25
Vigorous	712 ^b	126	3.7	0.78 (0.63–0.97)	.028	0.79 (0.63–0.98)	.031
Late Life physical activity (any vs none)							
Light	1576	318	3.3	0.75 (0.58–0.97)	.029	0.76 (0.58–0.98)	.035
Moderate	1149	217	3.4	0.81 (0.66–0.99)	.040	0.85 (0.69–1.05)	.13
Vigorous	262	44	3.7	0.90 (0.66–1.25)	.54	0.88 (0.64–1.21)	.44

CI, confidence interval; HR, hazard ratio; MCI, mild cognitive impairment; y, years. NOTE: Any activity = Engaging in physical activity at least 2–3 times/month (reference: none = 1 time/month). Model 1: Calculated using Cox proportional hazards models with incident MCI as outcome, age as time scale, and adjustments for sex and years of education. Model 2: Calculated using Cox proportional hazards models with incident MCI as outcome, age as time scale, and adjustments for sex, years of education, medical comorbidity (weighted Charlson index), and depression (BDI-II score <13 vs ≥13).

^aData from 2 participants is missing.

^bData from 1 participant is missing.

Table 3

Investigation of the Interaction Between Physical Activity in Mid- and Late Life and the Outcome of Incident Mild Cognitive Impairment

Sample or Stratum	No. at Risk (n = 1830)	No. With Incident MCI (n = 389)	Median Time to Outcome (y)	HR (95% CI)	P Value	Mult. Int. P	Add. Int. P
Light intensity							
No activity in late life and midlife	75	22	2.7	1.00 (ref. group)		.33	.041
No activity in late life but activity in midlife	179	49	2.9	0.75 (0.45–1.24)	.26		
Activity in late life but no activity in midlife	68	26	2.9	1.08 (0.61–1.91)	.79		
Activity in late life and midlife	1506	292	3.3	0.59 (0.38–0.90)	.016		
Moderate							
No activity in late life and midlife	231	62	2.7	1.00 (ref. group)		.76	<.001
No activity in late life but activity in midlife	449	110	3.0	0.94 (0.68–1.28)	.68		
Activity in late life but no activity in midlife	103	24	2.7	0.88 (0.55–1.42)	.60		
Activity in late life and midlife	1046	193	3.6	0.76 (0.57–1.02)	.07		
Vigorous							
No activity in late life and midlife	1065	245	3.0	1.00 (ref. group)		.021	.47
No activity in late life but activity in midlife	502	100	3.7	0.86 (0.68–1.09)	.20		
Activity in late life but no activity in midlife	52	18	3.6	1.60 (0.99–2.59)	.05		
Activity in late life and midlife	210	26	3.8	0.64 (0.42–0.97)	.035		

Add. Int., additive interaction; CI, confidence interval; HR, hazard ratio; MCI, mild cognitive impairment; Mult. Int., multiple interaction; y, years. NOTE: Calculated using Cox proportional hazards models considering incident MCI as outcome, with age as time scale and with adjustment for sex and education.