Timing of Physical Activity, Apolipoprotein E ε4 Genotype, and Risk of Incident Mild Cognitive Impairment

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OBJECTIVES: To investigate the timing (mid- vs late life) of physical activity, apolipoprotein (APO)E ε4, and risk of incident mild cognitive impairment (MCI).

DESIGN: Prospective cohort study.

SETTING: Mayo Clinic Study of Aging (Olmsted County, MN).

PARTICIPANTS: Cognitively normal elderly adults (N = 1,830, median age 78, 50.2% female).

MEASUREMENTS: Light, moderate, and vigorous physical activities in mid- and late life were assessed using a validated questionnaire. An expert consensus panel measured MCI based on published criteria. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) with age as a time scale after adjusting for sex, education, medical comorbidity, and depression.

RESULTS: Light (HR = 0.58, 95% CI = 0.43–0.79) and vigorous (HR = 0.78, 95% CI = 0.63–0.97) physical activity in midlife were associated with lower risk of incident MCI. The association between moderate activity and incident MCI was not significant (HR = 0.85, 95% CI = 0.67–1.09). In late life, light (HR = 0.75, 95% CI = 0.58–0.97) and moderate (HR = 0.81, 95% CI = 0.66–0.99) but not vigorous physical activity were associated with lower risk of incident MCI. A synergistic interaction was also observed between mid- and late-life activity in reducing risk of incident MCI. Furthermore, APOE ε4 carriers who did not exercise had a higher risk of incident MCI than noncarriers who reported physical activity.

CONCLUSION: Physical activity reduced the risk of incident MCI. Exercising in mid- and late life had an additive synergistic interaction in reducing the risk of MCI. **J Am Geriatr Soc 2016.**

Key words: physical activity; APOE e4; mild cognitive impairment

Mild cognitive impairment (MCI) is the intermediate stage between normal cognitive aging and dementia.[1,2] MCI has high prevalence[3,4] and incidence[5,6] rates 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 lower risk of cognitive decline and dementia.[7–11] Various research groups have reported the outcome of incident dementia as predicted according to baseline exposure to physical activity,[12–17] although only a few studies have examined the outcome of incident MCI or similar constructs.[13,18] Furthermore, little is known about the association between timing of physical activity (mid- vs late life) and the risk of incident MCI as investigated in a large-scale, population-based sample.

The current study was designed to determine the association between mid- and late-life physical activity and risk of incident MCI. In addition, the interaction between mid- and late-life physical activity and risk of incident MCI was investigated in a population-based setting. Because the apolipoprotein E (APOE) ε4 allele is a well-known risk factor for MCI and dementia, a stratified analysis was conducted of the role of physical activity according to APOE genotype.

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METHODS

Design and Setting

This was a prospective cohort study derived from the population-based Mayo Clinic Study of Aging (MCSA)—an ongoing study of normal cognitive aging and MCI in individuals aged 70 and older. The details of the MCSA have been reported elsewhere.[19] Briefly, stratified random sampling was used to recruit participants from the target population of 9,953 elderly individuals residing in Olmsted County, Minnesota, on October 1, 2004.[20] The institutional review boards of the Mayo Clinic and Olmsted Medical Center (Rochester, MN) approved the MCSA protocols. All participants provided written informed consent.

Study Sample

A cohort was assembled of 2,207 cognitively normal participants who had completed a validated physical activity questionnaire at baseline; 377 individuals were excluded (222 withdrew before follow-up, 118 had no follow-up visit, 37 died), leaving a final cohort of 1,830 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 reported previously,[21,22] questions were used from two validated instruments: the 1985 National Health Interview Survey[23] and the Minnesota Heart Survey.[24] The questionnaire was designed to assess the intensity and frequency of physical activity at two time points: the year before the date of cognitive assessment (late-life physical activity; participants aged ≥70 at cognitive assessment) and between 50 and 65 years of age (midlife physical activity). Participants provided information about intensity (light, moderate, 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, daily). Light physical activity included activities such as leisurely walking, slow dancing, and stretching. Moderate physical activity included activities such as hiking, brisk walking, swimming, and yoga. Vigorous physical activity included activities such as jogging, tennis singles, and bicycling uphill.

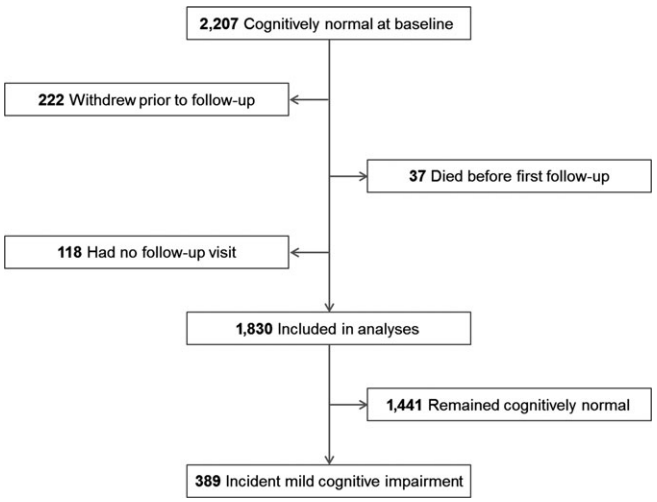

Figure 1. Study flowchart.

Cognitive Evaluation

The cognitive assessment in the MCSA has been described in detail elsewhere[19,21] and is briefly described here. A face-to-face evaluation was completed of all study participants and included three assessment components: a neurological evaluation (neurological history review, administration of Short Test of Mental Status,[25] neurological examination); a risk factor assessment interview, which a nurse or study coordinator conducted and included the Clinical Dementia Rating Scale (CDR); and neuropsychological testing, which a psychometrist administered to assess performance in four cognitive domains: memory (delayed recall trials from Auditory Verbal Learning Test,[26] Wechsler Memory Scale-Revised,[27] Logical Memory and Visual Reproduction subtests), language (Boston Naming Test,[28,29] category fluency[30]); visuospatial skills (Wechsler Adult Intelligence Scale, Revised,[31] Picture Completion and Block Design subtests); and executive function (Trail-Making Test Part B,[32] 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 of the clinical and neuropsychological evaluation.[19] Individuals were considered to be cognitively normal at baseline according to published normative data developed on this community.[33–36] The following revised Mayo Clinic criteria for MCI[2,37] were used: concern about cognition expressed by a physician, informant, participant, or nurse; impairment in one or more cognitive domains (executive function, memory, language, visuospatial skills); essentially normal functional activities; and absence of dementia. Participants with MCI had a CDR score of 0 or 0.5, although the final diagnosis of MCI was based on all available data.

APOE Genotyping

Blood was drawn from study participants after they provided informed consent. Deoxyribonucleic acid was amplified using polymerase chain reaction, and APOE genotype was determined using standard methods.[38] Laboratory technicians who were unaware of clinical characteristics determined genotypes.

Statistical Analysis

To investigate the association between mid- and late-life physical activity and incident MCI, hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated using Cox proportional hazards models with age as a time scale after adjusting for sex, education, medical comorbidity (weighted Charlson index range 0–33),[39] and depression (Beck Depression Inventory).[40]

Analyses were conducted separately for physical activity (any vs none) in midlife (aged 50–65) and late life

(within 1 year of the cognitive assessment) and for the three different levels of activity intensity (light, moderate, vigorous). Any physical activity was compared with none. Any physical activity was defined as engaging in physical activity at least twice per month. No physical activity (reference) was defined as physical activity once per month or less. Central tendency was measured using medians and associated interquartile ranges; Kaplan-Meier survival curves were prepared for the visual display of data. A stratified analysis was also conducted according to the timing of physical activity (mid- and late life), and possible interaction effects between activity in mid- and late life were investigated using multivariate models to test for additive interactions. A stratified analysis was also conducted according to APOE ε4 genotype. Statistical testing was performed at the conventional two-tailed alpha level of .05. All analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

At baseline, there were 1,830 cognitively normal persons (50% female) with a valid physical activity assessment and cognitive evaluation. This cohort was followed for a median of 3.2 years (interquartile range (IQR) 1.9–4.7 years), by which time 389 participants had developed new-onset MCI (Figure 1). Median age at baseline was 78 (IQR 74–83), and median level of education was 14 years (IQR 12–16 years). Four hundred seventy-four participants were APOE ε4 carriers, and 1,347 participants were APOE ε4 noncarriers. APOE ε4 carrier status data were missing for nine participants. Detailed demographic characteristics are displayed in Table 1.

After adjusting for age, sex, and years of education, light and vigorous physical activity in midlife were found to be associated with lower risk of incident MCI, whereas the association between moderate activity and incident MCI was not significant (light: HR = 0.58, 95% CI = 0.43–0.79; moderate: HR = 0.85, 95% CI = 0.67–1.09; vigorous: HR = 0.78, 95% CI = 0.63–0.97). Additional adjustment for medical comorbidity and depression did not significantly alter the results (Model 2). For late life, light (Model 1: HR = 0.75, 95% CI = 0.58–0.97) and moderate (Model 1: HR = 0.81, 95% CI = 0.66–0.99) but not vigorous (Model 1: HR = 0.90, 95% CI = 0.66–1.25) physical activity were significantly associated with lower 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 lower risk of incident MCI (HR = 0.76 m 95% CI = 0.58–0.98) (Table 2). Please refer to Figure 2 for visual display of data.

Table 1. Demographic Characteristics (N = 1,830)

Variable	Value
Female, n (%)	919 (50.2)
Age, median (IQR)	78 (74–83)
Age, n (%)	
70–79	1,060 (57.9)
80–93	770 (42.1)
Education, years, median (IQR)	14 (12–16)
>12 years education, n (%)	1,130 (61.7)
BDI-II score, median (IQR)	3 (1–7)[a]
Depressed (BDI-II score ≥13)	102 (5.6)
Charlson Comorbidity Index score	3 (2–5)

[a]Data missing from three participants.
IQR = interquartile range; BDI-II = Beck Depression Inventory, Second Edition.

Additional analyses (Table S1) were conducted in which physical activity was defined as engaging in physical activity at least once per week. The results were slightly different from the analysis comparing any with no physical activity. Light-intensity activity in midlife was associated with lower risk of incident MCI, whereas the association was not significant for moderate-intensity activity and not significant for vigorous intensity activity. For late life, moderate- but not light- or vigorous-intensity activity was significantly associated with lower risk of incident MCI. There was no significant effect of late-life physical activity on incident MCI when the model was additionally adjusted for medical comorbidity and depression. It is reassuring to know that using various definitions of activity (twice per month or more vs once per week or more) still indicated that activity was associated with lower risk of incident MCI regardless of the categories used to define activity.

A possible interaction between mid- and late-life physical activity was also examined in predicting the risk of incident MCI. The reference group was participants who did not report being physically active in mid- or late life. Participants who exercised at moderate intensity were slightly less likely than the reference group to have incident MCI (physical activity in mid- but not late life: HR = 0.94, 95% CI = 0.68–1.28; physical activity in late but not in midlife: HR = 0.88, 95% CI = 0.55–1.42; physical activity in mid- and late life: HR = 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 percentage of participants who did not exercise in mid- or late life and developed incident MCI was approximately 26%, and the percentage of those who exercised in mid- and late life and developed incident MCI was approximately 18%, indicating that the risk of MCI was 8 percentage points lower for participants who exercised in mid- and late life than for those who did not. The same analysis was conducted for light- and vigorous-intensity activity and showed the lowest risk for participants who exercised in mid- and late life, although a test for additive interaction was significant for light- but not vigorous-intensity activity (Table 3).

Additional analyses stratified according to APOE ε4 genotype status were conducted to investigate the risk of incident MCI as predicted according to mid- and late-life physical activity. The analyses were conducted separately for the three intensity levels and were adjusted for age, sex, and education. The reference group was participants who did not engage in any physical activity and did not carry an APOE ε4 allele. In mid- and late life, the highest risk for incident MCI was observed in APOE ε4 carriers who did not engage in any physical activity in mid- or late life (Table S2). In contrast, participants who were APOE

Table 2. Mid- and Late-Life Physical Activity and Risk of Incident Mild Cognitive Impairment (MCI)

Variable	At Risk, n (n = 1,830)	Incident MCI, n (n = 389)	Time to Outcome, Median, Years	Model 1 Hazard Ratio (95% Confidence Interval) *P*-Value	Model 2 Hazard Ratio (95% Confidence Interval) *P*-Value
Midlife physical activity (any vs none)					
Light	1,685[a]	341	3.3	0.58 (0.43–0.79) <.001	0.59 (0.43–0.80) <.001
Moderate	1,495[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) .03	0.79 (0.63–0.98) .03
Late-life physical activity (any vs none)					
Light	1,576	318	3.3	0.75 (0.58–0.97) .03	0.76 (0.58–0.98) .03
Moderate	1,149	217	3.4	0.81 (0.66–0.99) .04	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

Any activity defined as engaging in physical activity at least twice a 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 (Beck Depression Inventory-II score).

[a]Data missing from two participants.

[b]Data missing from one participant.

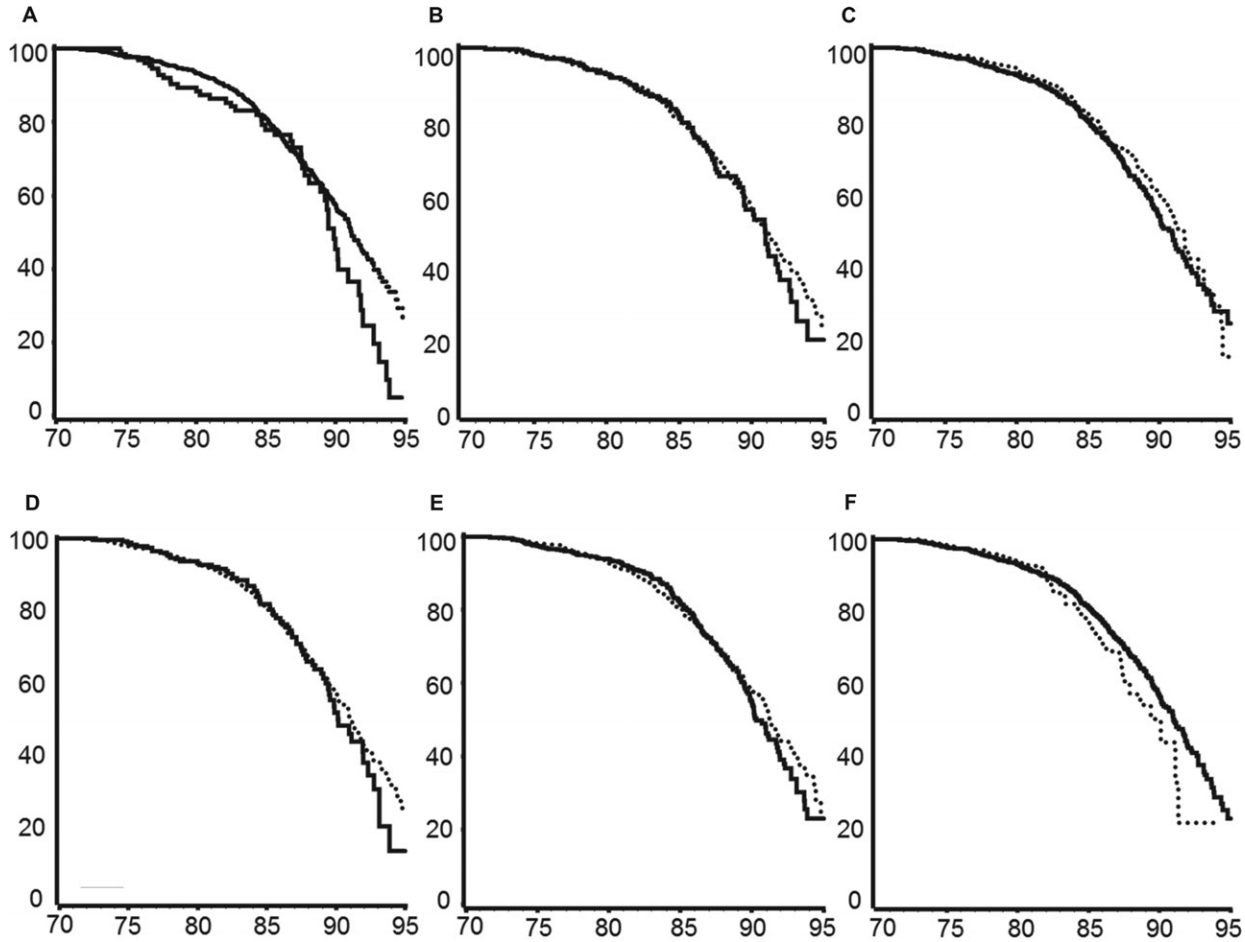

Figure 2. Survival free of incident mild cognitive impairment (MCI) in cognitively normal subjects stratified according to mid- and late-life physical activity. *Y*-axes: Survival free of incident MCI (%); *X*-axes: age. Midlife physical activity: (A) no activity (solid) vs light intensity (dashed); (B) no activity (solid) vs moderate intensity (dashed); (C) no activity (solid) vs vigorous intensity (dashed). 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).

ε4 noncarriers and engaged in physical activity consistently had the lowest risk of MCI, even though only light-intensity activity in midlife reached statistical significance.

Additional analyses were conducted of the interaction between mid- and late-life activity stratified according to APOE carrier status (Table S3). Regardless of APOE ε4

Table 3. Interaction Between Physical Activity in Mid- and Late Life and Incident Mild Cognitive Impairment (MCI)

Intensity	At Risk, n (n = 1,830)	Incident MCI, n (n = 389)	Median Time to Outcome, Years	Hazard Ratio (95% Confidence Interval)	*P*-Value	Multiple Interaction *P*-Value	Additive Interaction *P*-Value
Light							
No activity in late life and midlife	75	22	2.7	1.00 (reference)		.33	.04
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	1,506	292	3.3	0.59 (0.38–0.90)	.02		
Moderate							
No activity in late life and midlife	231	62	2.7	1.00 (reference)		.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	1,046	193	3.6	0.76 (0.57–1.02)	.07		
Vigorous							
No activity in late life and midlife	1,065	245	3.0	1.00 (reference)		.02	.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)	.03		

Calculated using Cox proportional hazards models considering incident MCI as outcome with age as time scale and adjustment for sex and education.

carrier status, the point estimates for exercising at any intensity in mid- and late life were consistently lower than the point estimates for exercising in mid- or late life, although this analysis lacked statistical significance, which in part could be related to the dividing of data into several categories according to APOE ε4 status and intensity of activity.

DISCUSSION

This population-based, prospective cohort study showed that engaging in physical activity in mid- and late life was associated with lower risk of incident MCI. In particular, light- but not vigorous-intensity physical activity significantly reduced the risk of incident MCI, suggesting a potential protective effect of light-intensity activity such as a leisurely walk after 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.

There was 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 mid- and late life is greater than the expected arithmetic sum of the independent benefits of m- or late life activity. Because APOE ε4 is a well-known risk factor for MCI and Alzheimer's disease (AD), a stratified analysis was also conducted according to APOE ε4 genotype status to predict incident MCI. The data overall point toward a lower risk of incident MCI in participants who exercise and are APOE ε4 noncarriers but a greater risk of MCI in those who do not exercise and have an APOE ε4 allele, although not all point estimates reached significance, which may be because of lack of statistical power because the data had to be divided into smaller groups for the stratified analysis. Lower odds of MCI were reported with moderate-intensity physical activity in mid- and late life in a population-based, case-control study,[21] but those findings were considered preliminary until a prospective cohort study, which is being reported herein, could confirm them.

A recent meta-analysis of longitudinal studies indicated that higher levels of physical activity are significantly associated with lower risk of cognitive decline or dementia than lower levels,[41] although only a few cohort studies have investigated the risk of incident MCI or similar constructs according to baseline exposure to physical activity. In contrast to the current findings, a prospective cohort

study involving 437 community-dwelling elderly individuals failed to detect a significant association between physical activity and risk of new-onset amnestic MCI,[42] although the point estimate in that study suggested a potential protective effect of physical activity albeit lacking in statistical significance. The cross-sectional association between the timing of physical activity and cognitive impairment in old age was examined in 9,344 women, and it was found that physical activity at any time during life, but especially during the teenage years, was associated with lower risk of cognitive impairment in late life.[43] The similarity between that study and the current one is that both investigated the timing of physical activity, although that study sample consisted of women only, whereas the current study had approximately 50% women. In addition, the outcomes of interest and the study designs were different. The current study extends the findings of the previous study by showing that physical activity in mid- and late life, as opposed to mid- or late life only, further reduced the risk of incident MCI.

In addition, only a few studies have investigated the effect of APOE ε4 carrier status on the association between physical activity and risk of 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 dementia. Midlife physical activity was associated with lower risk of dementia at follow-up 20 years later, especially in APOE ε4 carriers,[44] but at 30-year follow-up, this association was significant only for APOE ε4 noncarriers.[45] Similarly, the current study found the lowest risk of MCI in those who exercised and were APOE ε4 noncarriers. In addition to the cohort studies mentioned above, few other studies have assessed the interaction between physical activity or fitness level, APOE ε 4, and cognitive performance and decline,[46–48] amyloid deposition,[49] memory performance,[50,51] white matter tract diffusivity,[52] glucose metabolism,[53] and hippocampal volume.[48]

The findings of the current study should be interpreted within the context of its strengths and limitations. Its major strength pertains to its design. It was a population-based, prospective cohort study with a large sample size of 1,830 participants at baseline who were 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 good reputation.

One limitation pertains to potential recall bias that stems from the self-reported physical activity questionnaire,[54,55] although this is unlikely because the questionnaire had moderate to good internal consistency.[21] Furthermore, the questionnaire did not assess the number of years of physical activity in mid- or late life. Also, it would have been informative had there been continuous data for the frequency of physical activity. This might have allowed the mean and standard deviation of the frequency of physical activity of participants who remained cognitively normal and those who developed incident MCI to be compared. (See Table S4 for the frequencies of the response categories of the physical activity questionnaire.) In addition, only a few people engaged in vigorous activity in late life, which limited the statistical power for this analysis. Another limitation is that the majority of the population of Olmsted County is of Caucasian decent, which may raise concerns about the generalizability of the study findings, although a recent publication has indicated that the data are generalizable to the U.S. population.[56]

Possible mechanisms that might underlie or cause the association between timing of engaging in physical activity and risk of incident MCI were not investigated in the current study, but it can be extrapolated from published research that physical activity may be protective against cognitive decline through several mechanisms, including increased cerebral blood flow,[57] increased production of neurotrophic factors,[58] increased neurogenesis and neuronal plasticity, enhanced neuronal survival,[59] and decreased risk of cardiovascular and cerebrovascular diseases.[60]

In conclusion, physical activity, even light intensity, in mid- and late life was associated with lower risk of incident MCI. Mid- and late-life activity may have a substantially beneficial effect. Overall, APOE ε4 noncarriers who exercised had the lowest risk of MCI, whereas 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.

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Conflict of Interest: David S. Knopman is Deputy Editor of *Neurology* and an investigator in clinical trials sponsored by Baxter and Elan Pharmaceuticals in the past 2 years; receives research support from NIH; is a consultant to Tau RX; and serves on a Data Safety Monitoring Board for Lundbeck Pharmaceuticals and the Dominantly Inherited Alzheimer's Disease Treatment Unit. He has served on a Data Safety Monitoring Board for Lilly Pharmaceuticals. Ronald C. Petersen is a consultant to Roche, Inc., Merck, and Genentech and serves as chair of data monitoring committees of Pfizer, Inc. and Jannsen Alzheimer Immunotherapy.

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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. Krell-Roesch, Roberts, Petersen, Geda: study concept and design. Krell-Roesch, Pink, Roberts, stokin, Mielke, Christianson, Geda: acquisition, analysis, or interpretation of data. Krell-Roesch, Geda: drafting of the manuscript. Pink, Roberts, Stokin, Mielke, Spangehl, Bartley, Knopman, Petersen: critical revision of the manuscript for important intellectual content. Christianson: statistical analysis. Stokin, Petersen, Geda: obtained funding. Roberts, Stokin, Petersen, Geda: administrative, technical, or material support.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Mid- and Late-Life Physical Activity (Using Alternative Definition of Physical Activity) and Risk of Incident Mild Cognitive Impairment (MCI)

Table S2 Interaction Between Physical Activity, Apolipoprotein E Carrier Status, and Incident Mild Cognitive Impairment (MCI)

Table S3 Interaction Between Physical Activity in Mid- and Late Life, Apolipoprotein (APO)E Carrier Status and Outcome of Incident Mild Cognitive Impairment (MCI)

Table S4 Unadjusted (Crude) Frequencies for Response Categories of Physical Activity Questionnaire for Participants Who Remained Cognitively Normal (n = 1,441) and Those Who Developed Incident Mild Cognitive Impairment (MCI) (n = 389)

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