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# The Effect of Midlife Physical Activity on Cognitive Function Among Older Adults: AGES—Reykjavik Study

Milan Chang,[1] Palmi V. Jonsson,[1,2] Jon Snaedal,[1,2] Sigurbjorn Bjornsson,[1] Jane S. Saczynski,[3] Thor Aspelund,[4,5] Gudny Eiriksdottir,[4] Maria K. Jonsdottir,[1,6] Oscar L. Lopez,[7] Tamara B. Harris,[8] Vilmundur Gudnason,[2,4] and Lenore J. Launer[8]

[1]Geriatric Research Center, Landspitali University Hospital, Reykjavik, Iceland.
[2]Faculty of Medicine, University of Iceland, Reykjavik.
[3]Division of Geriatric Medicine and Meyers Primary Care Institute, University of Massachusetts Medical School, Worcester.
[4]Icelandic Heart Association, Kopavogur.
[5]Faculty of Science and [6]Faculty of Psychology, University of Iceland, Reykjavik.
[7]Department of Psychiatry and Neurology, University of Pittsburgh, Pennsylvania.
[8]Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, National Institutes of Health, Bethesda, Maryland.

Address correspondence to Lenore J. Launer, PhD, Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, National Institutes of Health, Gateway Building, 3C309, 7201 Wisconsin Avenue, Bethesda, MD 20892-9205. Email: launerl@nia.nih.gov

***Background***. There are few studies on the long-term associations of physical activity (PA) to cognition. Here, we examine the association of midlife PA to late-life cognitive function and dementia.

***Methods***. The sample consisted of a population-based cohort of men and women (born in 1907–1935) participating in the Age Gene/Environment Susceptibility—Reykjavik Study. The interval between the midlife ascertainment of PA and late-life cognitive function was 26 years. Composite scores of speed of processing, memory, and executive function were assessed with a battery of neuropsychological tests, and dementia was diagnosed according to international guidelines. There were 4,761 nondemented participants and 184 (3.7%) with a diagnosis of dementia, with complete data for the analysis.

***Results***. Among the participants, no midlife PA was reported by 68.8%, ≤5 hours PA by 26.5%, and >5 hours PA by 4.5%. Excluding participants with dementia compared with the no PA group, both PA groups had significantly faster speed of processing (≤5 hours, β = .22; >5 hours, β = .32, *p* trend < .0001), better memory (≤5 hours, β = .15; >5 hours, β = .18, *p* trend < .0001), and executive function (≤5 hours, β = .09; >5 hours, β = .18, *p* trend< .0001), after controlling for demographic and cardiovascular factors. The ≤5 hours PA group was significantly less likely to have dementia in late life (odds ratio: 0.6, 95% confidence interval: 0.40–0.88) after adjusting for confounders.

***Conclusion***. Midlife PA may contribute to maintenance of cognitive function and may reduce or delay the risk of late-life dementia.

***Key Words:*** Physical activity—Cognitive function—Longitudinal study.

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REGULAR physical activity (PA) provides benefits for cardiovascular health and helps improve or maintain physical function among older adults (1–3). Numerous epidemiological studies suggest that regular PA may reduce the risk of cognitive decline and dementia in older adults (4–6). This may reflect lifestyle factors (7–10) or underlying modulation of neurotrophic and vascular health factors demonstrated in clinical and experimental research (1,10).

Although the evidence suggests that PA is beneficial for maintaining cognitive function and reducing risk of dementia in later life, most previous epidemiological studies report data on PA collected close to the time at which cognitive function was assessed or dementia diagnosed (5,6,9,11). With short intervals between PA and dementia, it is difficult to determine whether what is reported regarding PA is a risk factor for cognitive decline and dementia or an indicator of incipient disease. Findings from two studies that examined midlife PA and risk of dementia were mixed (12,13). Furthermore, most previous studies examined either global cognitive performance (11,14,15) or dementia risk related to PA (5,6,9,12,13) but not both.

In the current study, we examine the association of midlife PA and to late-life domain-specific cognitive performance and dementia. Following reports of *APOE* ε4 allele, a risk factor for Alzheimer's disease, modifying the association between PA and dementia (6,11,12), we examined the interaction of PA and *APOE* ε4 allele on dementia in a sub sample of the total cohort.

## Methods

### *Study Population*

Participants are from the cohort of men and women born in 1907–1935 living in Reykjavik. The cohort was followed as a part of the Reykjavik Study (RS) initiated in 1967 by the Icelandic Heart Association. Since its inception, cohort members have participated in up to six examinations and have been under continuous surveillance for cardiac and vital events. The RS has been described in previous publications (16). In 2002, cohort members were reinvited to participate in the Age Gene/Environment Susceptibility—Reykjavik Study (AGES-Reykjavik), which included a structured survey instrument, cognitive testing, and brain magnetic resonance imaging. Details on the study design and the baseline AGES—Reykjavik assessments have been described elsewhere (17). Mean age of the participants at midlife RS examination was 51 years, and mean age of the participants at current AGES—Reykjavik examination was 76 years.

The AGES—Reykjavik was approved by the Icelandic National Bioethics Committee (VSN 00-063) and by the Institutional Review Board of the U.S. National Institute on Aging, National Institutes of Health. Informed consent was signed by all participants.

### *Assessment of Midlife PA*

At the midlife RS interview, participants were asked two questions related to PA. First, participants were asked about whether they had ever regularly participated in sports or exercised at any time during their adult life. Participants who answered "yes" to this question were then asked a second question about how many hours per week they exercised during winter and summer time (three categories to answer, [1] none, [2] ≤5 hours, and [3] >5 hours). Hours of PA per week were calculated from the total sum of hours in winter and summer. The midlife PA groups were defined as (a) reported no PA (none), (b) ≤5 hours of PA per week, and (c) >5 hours or more of PA per week.

### *Assessment of Cognitive Function and Dementia*

As a part of AGES-Reykjavik, all participants were administered a battery of cognitive tests that included multiple tests of three cognitive domains. From these tests, we constructed composite scores for speed of processing (SP), memory (MEM), and executive function (EF) based on a theoretical grouping of tests similar to other population-based studies (7). The SP composite includes digit symbol substitution test (18), Figure Comparison (19), and a modified Stroop Test (20) part I (Word Reading) and part II (Color Naming). The MEM composite includes a modified version of the California Verbal Learning Test, immediate and delayed recall (21). The EF composite includes Digits Backward (18), a shortened version of the CANTAB Spatial Working Memory test (22) and the Stroop Test part III (23) (Word–Color Interference). All tests were normally distributed in the cohort, and interrater reliability was excellent (Spearman correlations range from .96 to .99 for all the tests). Composite measures were computed by converting raw scores on each test to standardized $z$ scores and averaging the $z$ scores across the tests in each composite. Details have been described elsewhere (24).

A three-step protocol was used to identify dementia cases in our cohort. First, the digit symbol substitution test (18) and the Mini-Mental State Examination (25) were administered to the total sample. Participants who scored 23 or lower on the Mini-Mental State Examination or had a raw score of 17 or lower on the digit symbol substitution test were administered a second diagnostic cognitive test battery. Participants who scored 8 or more on Trails B (26) that was the ratio of time taken for "Trails B/Trails A" (corrected for the number correct: [{time Trails B/number correct Trails B}/{time Trails A/number correct Trails A}]) or had lower than total score of 19 for the four immediate recall trials of the Rey Auditory Verbal Learning (27) went on to a third step. This step included a neurological test and a proxy interview regarding medical history, social, cognitive, and daily functioning changes of the participant. A consensus diagnosis of dementia was made according to international guidelines, *Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition* (*DSM-IV*) (28) by a geriatrician, neurologist, neuropsychologist, and neuroradiologist.

### *Assessment of Covariates*

We controlled for potential confounders that may influence the association between PA and cognition, including several demographic and health factors. Measures based on midlife RS included age at the time of examination, blood pressure (millimeter of mercury), body mass index (kilograms per square meter), serum cholesterol (millimoles per liter ), self reported smoking status (never smoker/ever smoker), and resting heart rate. Blood pressure was measured in a recumbent position using mercury sphygmomanometer and a large cuff on the right arm (with a few exemptions) after participants had rested for 5 minutes. Heart rate per minute was also measured in a resting position. Body mass index was calculated from measured height (meters) and weight (kilograms). Serum cholesterol level was measured from a blood sample drawn at the in-person examination. We also used several measures from the AGES-Reykjavik (late-life) examination, including high depressive symptoms, defined by participants scoring 6 or greater on the 15-item Geriatric Depression Scale (29) and education categorized into four levels (elementary school, high school, undergraduate, and more than undergraduate education). *APOE* alleles were genotyped on a subsample of 2,113 using standard methods (30). Basic characteristics of this subsample did not differ with the remaining sample. *APOE* genotypes were grouped as *APOE* ε4 carrier (ε3/4 and ε4/4 genotypes) and *APOE* ε4

Table 1. Demographic and Health Characteristics by Level of Weekly Midlife PA

| Characteristics | Total ($n$ = 4,945) | | | $p$ Value | $P$ Value* |
|---|---|---|---|---|---|
| | None, ($n$ = 3,413) | ≤5 h, ($n$ = 1,309) | >5 h, ($n$ = 223) | | |
| Follow-up time, mean (*SD*), y | 26.1 (4.0) | 24.9 (4.4) | 25.7 (4.3) | <.0001 | <.0001 |
| Female, *n* (%) | 1,998 (58.5) | 777 (59.4) | 77 (34.5) | <.0001 | <.0001 |
| Elementary education, *n* (%) | 881 (25.8) | 209 (16.0) | 25 (11.2) | <.0001 | <.0001 |
| *APOE* ε4 carriers†, *n* (%) | 425 (27.9) | 137 (27.4) | 21 (23.6) | .68 | .57 |
| Midlife examination | | | | | |
| Age, mean (*SD*), y | 50.9 (6.5) | 51.6 (7.1) | 51.1 (6.6) | .003 | |
| Body mass index, mean (*SD*) | 25.2 (3.7) | 25.2 (3.2) | 25.1 (2.8) | .77 | <.0001 |
| Systolic blood pressure, mean (*SD*), mmHg | 131.2 (19.4) | 129.5 (18.3) | 133.8 (18.1) | .002 | <.0001 |
| Cholesterol, mean (*SD*), mmol/L | 6.4 (1.1) | 6.3 (1.1) | 6.3 (1.0) | .66 | <.0001 |
| Pulse, mean (*SD*), beat/s | 68.5 (8.6) | 67.4 (8.7) | 65.8 (7.7) | <.0001 | <.0001 |
| Smoking status, *n* (%) | | | | <.0001 | <.0001 |
| Never | 1,338 (39.2) | 586 (44.8) | 70 (31.4) | | |
| Previous | 720 (21.1) | 309 (23.6) | 66 (29.6) | | |
| Current | 1,355 (39.7) | 414 (31.6) | 87 (39.0) | | |
| Late-life examination | | | | | |
| MMSE, mean (*SD*) | 26.5 (2.8) | 27.2 (2.3) | 27.0 (2.3) | <.0001 | <.0001 |
| Speed of processing, mean (*SD*) | –0.06 (0.86) | 0.22 (0.87) | 0.25 (0.79) | <.0001 | <.0001 |
| Memory, mean (*SD*) | –0.02 (0.89) | 0.19 (0.93) | 0.08 (0.93) | <.0001 | <.0001 |
| Executive function, mean (*SD*) | –0.03 (0.72) | 0.10 (0.75) | 0.16 (0.77) | <.0001 | <.0001 |
| Depression‡, *n* (%) | 240 (7.0) | 78 (6.0) | 12 (5.4) | .30 | .36 |
| Prevalent dementia, *n* (%) | 145 (4.2) | 32 (2.4) | 7 (3.1) | .01 | .03 |

*Notes*: PA = physical activity; MMSE = Mini-Mental State Examination.
* Age and sex adjusted.
† Among 2,113 people.
‡ 15-item Geriatric Depression Scale score ≥6.

noncarrier (ε2/2, ε2/3, and ε3/3). Participants with ε2/4 ($n$ = 32) were excluded from the analysis because the ε2 and ε4 alleles have opposite effects on the risk for cognitive impairment and dementia (30–32).

### *Statistical Analysis*

The total study cohort consisted of 5,764 participants. Of these, 819 individuals had missing data from the composite cognitive performance tests and were excluded from the analysis. Among those with missing cognitive data, 345 were men and 474 were women, including people who participated only in a home visit examination (101 men and 181 women). The final study population for analysis was 4,945 participants (2,093 men and 2,852 women), including 184 prevalent dementia cases.

We used $\chi^2$ test for categorical variables and general linear regression for continuous variables to compare participant characteristics by midlife PA level. For the three cognitive composite scores, linear regression analysis was used to examine the difference in performance among the three activity groups. The reference group was those who reported no PA in midlife. Model 1 was adjusted for age, sex, and education. The fully adjusted Model 2 further included cholesterol level, systolic blood pressure, education, smoking, and body mass index measured at midlife. Demented individuals were excluded from the analysis of cognitive function, giving a total sample of 4,761 (women = 2,006 and men = 2,755). The relation of midlife PA with late-life dementia was separately examined using a logistic regression model comparing the odds of having dementia in late life among midlife PA levels.

To examine whether *APOE* ε4 moderates the association of midlife PA to dementia, we created combination groups of presence or absence of *APOE* ε4 and midlife PA. The group of *APOE* ε4 carriers who did not report midlife PA was the reference as they were hypothesized to have the highest risk for cognitive impairment and dementia. Statistical analyses were performed using SAS software, version 8.02 (SAS Institute Inc., Cary, NC).

## Results

There were an average of 26 years between mid- and late-life examinations. Compared with those who reported no midlife PA ($n$ = 3,413, 69%), those who were physically active at midlife (≤5 hours, $n$ = 1,309, 26%; >5 hours, $n$ = 223, 5%) were older, were more often male, and had higher education. They also had higher Mini-Mental State Examination scores and better cognitive performance in the three domains tested at current AGES-Reykjavik examination (Table 1). All cognitive test scores within each domain according to midlife PA level are provided in the supplementary material, which is available online.

In a fully adjusted model (Table 2) compared with those who never exercised at midlife, the two groups that were physically active at midlife had significantly faster SP ($p$ < .0001), better MEM ($p$ < .0001), and EF ($p$ < .0001); the associations were strongest for SP. Compared with the group that never exercised at midlife, those who reported

Table 2. Association of Cognitive Function and Dementia to Midlife PA Levels

| | None, ($n$ = 3,268) | ≤5 h, ($n$ = 1,277) | | >5 h, ($n$ = 216) | |
|---|---|---|---|---|---|
| Adjusted mean differences of cognitive performance scores by midlife PA levels | | | | | |
| Cognitive performance* | Reference | Beta (95% CI) | $p$ Value | Beta (95% CI) | $p$ Value |
| Speed of processing | | | | | |
| Model 1 | — | 0.23 (0.18–0.27) | <.0001 | 0.32 (0.22–0.42) | <.0001 |
| Model 2 | — | 0.22 (0.17–0.26) | <.0001 | 0.32 (0.22–0.41) | <.0001 |
| Memory | | | | | |
| Model 1 | — | 0.16 (0.11–0.21) | <.0001 | 0.18 (0.07–0.29) | <.0001 |
| Model 2 | — | 0.15 (0.10–0.20) | .001 | 0.18 (0.07–0.29) | .001 |
| Executive function | | | | | |
| Model 1 | — | 0.10 (0.10–0.15) | <.0001 | 0.18 (0.09–0.27) | <.0001 |
| Model 2 | — | 0.09 (0.10–0.14) | .001 | 0.18 (0.09–0.27) | .001 |
| Odds ratio of having dementia among physically active groups compared with none PA group | | | | | |
| Dementia† | Reference | OR (95% CI) | | OR (95% CI) | |
| Model 1 | 1 | 0.59 (0.40–0.87) | | 0.74 (0.34–1.62) | |
| Model 2 | 1 | 0.59 (0.40–0.88) | | 0.76 (0.34–1.63) | |

*Notes*: Model 1 = adjusted for age, sex, and education. Model 2 = additionally adjusted for midlife body mass index, systolic blood pressure, smoking, and cholesterol. Beta = β coefficient; CI = confidence interval; OR = odds ratio; PA = physical activity.

*Adjusted mean differences of cognitive performance scores by midlife PA levels (dementia cases excluded, $n$ = 4,761).

†Odds ratio of having dementia among physically active groups compared with no PA group ($n$ = 4,945).

≤5 hours per week were less likely to have dementia in late life (odds ratio [OR]: 0.6, 95% confidence interval [CI]: 0.40–0.89) after full adjustment. The >5 hours group was also less likely to have dementia, but it did not reach statistical significance (OR: 0.8, 95% CI: 0.36–1.73). We conducted secondary analyses to investigate the impact on our midlife results of including in the model, late-life CVD. There was very small and not significant change in our estimates (data not shown).

Considering *APOE* ε4-related risk in the subsample ($n$ = 2,113), in a fully adjusted model, compared with those who reported no midlife PA and were *APOE* ε4 carriers ($n$ = 425), *APOE* ε4 noncarriers who reported midlife PA ($n$ = 431) had the lowest risk for late-life dementia (OR: 0.18, 95% CI: 0.07–0.45); *APOE* ε4 noncarriers who reported no midlife PA also had a significantly reduced risk for dementia ($n$ = 1,099, OR: 0.59, 95% CI: 0.36–0.98). Those who reported midlife PA, but were *APOE* ε4 carriers, did not have reduced risk for dementia ($n$ = 158, OR: 1.08, 95% CI: 0.50–2.25) compared with those who did not report any PA in midlife and were *APOE* ε4 carriers.

## Discussion

In this large longitudinal study of a community-based cohort, we found a strong association between midlife PA and cognitive function in late life. Scores of SP, MEM, and EF were all significantly higher among those who reported regular PA at midlife than those with no PA, adjusting for demographic and cardiovascular risk factors. Performance was best in those who reported more than 5 hours of PA per week. Furthermore, compared with participants who reported no PA, those who reported 5 hours or less of PA per week were less likely to develop dementia 26 years later. Those who reported more than 5 hours of PA per week were also less likely to have dementia, but the association was not statistically significant. The association between midlife PA and dementia was strongest in the non-*APOE* ε4 carriers.

Our study has several strengths. First, our results are from a large well-described population-based sample of men and women. Second, we investigated the long-term association of midlife PA to cognitive outcomes in late life. This 26-year long interval between the measure of exposure and outcome makes it less likely that cognitive disorders influenced PA at baseline and more likely that the risk for cognitive disorders is modulated by PA. Third, we ascertained three different cognitive abilities derived from various cognitive tests, and dementia was diagnosed according to internationally accepted guidelines. Previous studies mostly show cognitive outcomes as either dementia alone (12,13,33) or as a single global cognitive function measurement, such as the Mini-Mental State Examination (11). Ascertaining various cognitive abilities as well as clinically defined dementia in the same sample allows us to compare the degree to which PA may influence the trajectory of cognitive decline. Fourth, potential confounding health factors are well characterized in our study. Health-related factors were directly measured at the same time when PA was reported at the midlife RS examination average 26 years before measurement of cognitive performances and dementia. Therefore, those health characteristics evaluated at the same time as exposure allowed us to establish a well-adjusted statistical model.

Our study is limited by the detail in which PA is characterized. Although the questions are standard for the time the RS was started in 1967, the set of questions that were used were likely suitable to group individuals by those who did at least some PA over the winter and summer seasons when the daylight hours in Iceland vary significantly. However, further characterization of midlife PA is needed not only to understand how PA may modulate brain function but also to

develop guidelines for PA as a measure to maintain cognitive health. In this analysis, we did not take into account changes in PA during 26 years of interval time. Our study focused on the effect of midlife PA on late-life cognition for several reasons. There are few studies of the long-term effects of PA on late-life cognition; as discussed, most reports of PA are based on measures taken close in time to the measurements of cognitive function. In addition, this design informs us about the association between midlife PA and late-life cognition, regardless of intervening illness. This is important to understand in the context of prevention. Never theless, further study is needed to examine how the PA changes over 26 years influence on changes in cognitive function in later life.

This analysis of a large longitudinal sample extends the previous findings on the associations of PA to cognitive health. Although several studies suggest that regular PA may protect against cognitive impairment in late age (11,15), those studies are mostly based on short-term follow-up from the time when PA was measured (5,6,9,11). This limitation raises the critical issue of whether cognitive function of older participants had already declined among those who did not engage in regular PA.

There are only two previous studies that have provided results on the long-term relationship between midlife PA and late-life dementia (12,13). The Cardiovascular risk factors, Aging, and Incidence of Dementia study (12) found that older adults who were active at midlife had significantly lower odds of dementia and Alzheimer's disease compared with people who were sedentary at midlife. However, another longitudinal community-based Japanese study (13) did not find a significant association between midlife PA and dementia in late life. Our study found an association between midlife PA and dementia in late life but only among those who reported 5 hours or less of PA per week at midlife compared with those who never exercised at midlife. There was a tendency toward a reduced risk of dementia in late life by midlife PA level; however, it lacks a clear dose–response relationship because there were very few cases in the higher PA group (>5 hours, dementia = 3.1% [7/223]). Finally, our population had a slightly higher number of sedentary people (69%) compared with that reported in Cardiovascular risk factors, Aging, and Incidence of Dementia study (60%), which has a similar study setting. The modest difference in the number of sedentary people is probably caused by different definitions of PA used by the studies: Our study defined PA as a sport or an exercise, whereas the Cardiovascular risk factors, Aging, and Incidence of Dementia study defined PA as any activity causing breathlessness and sweating for 20–30 minutes (12).

Previous reports of the modification of the PA and cognition association by *APOE* ε4 are inconsistent (6,11,12,14). Our finding from analysis in a subsample of the joint effect of *APOE* ε4 and PA on dementia suggests that the effect was restricted to noncarriers of the APOE ε4 allele, which is similar to results from the Cardiovascular Health Study (6). However, these findings need replication in other studies.

The effect of PA on the risk for developing dementia has been emphasized intensively for the past decade. To our knowledge, this is the first study to examine the association between midlife PA and cognition using multiple cognitive domains in old age. The strongest association was shown for SP. Participants in an exercise setting need fast reactions and experience a constant change in direction of body movements (34,35). This type of activity could provide a cognitively stimulating environment to participants (36) that may be particularly related to SP. PA might alter the allocation of attention resources, speed of cognitive processing (34,37,38), and reflect a beneficial effect of fitness on both perceptual and central processing as well as response-related processing (39). Although not as strong as SP, MEM and EF were also associated with midlife PA. Our results confirm the previous findings from a short-term human intervention study, which reported that those who exercised had significantly greater improvements in speed, MEM, and executive control tasks compared with nonexercisers (34).

There are a number of mechanisms and hypotheses that might explain how midlife PA may be related to late-life cognition. Regular PA can reduce serum lipid levels and blood pressure and increase cardiovascular fitness (1,11), which could lead to a reduced risk of dementia (40). Generally, it is suggested that aerobic fitness reduces age-associated brain tissue loss (34,41,42). Studies provide evidence that PA stimulates neuronal growth, which provides some reserve for cognitive decline and dementia. Moreover, PA may be closely related to other healthy lifestyles and social/cognitive activities that could influence cognitive vitality.

In summary, our results suggests that midlife PA helps to maintain cognitive function and may reduce or delay the risk of dementia in late life. Our study strongly implies that regular PA at an early stage in life has a beneficial influence on various cognitive functions as long as 26 years later. Long-term clinical trials are needed to understand the efficacy of PA interventions on cognitive functions in older persons.

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### Supplementary Material

Supplementary material can be found at: http://biomed.gerontologyjournals.org/

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