RESEARCH ARTICLE OPEN ACCESS

Physical and Cognitive Activities and Trajectories of AD Neuroimaging Biomarkers

Longitudinal Analysis in the Mayo Clinic Study of Aging

Janina Krell-Roesch,[1,2] Jeremy A. Syrjanen,[2] Allison L. Hansen,[3] Prashanthi Vemuri,[4] Eugene L. Scharf,[5] Julie A. Fields,[6] Walter K. Kremers,[2] Val J. Lowe,[4] Jonathan Graff-Radford,[5] Clifford R. Jack, Jr.,[4] Ronald C. Petersen,[5] Susan B. Racette,[7] Alexander Woll,[1] Maria Vassilaki,[2] and Yonas E. Geda[8]

Correspondence
Dr. Krell-Roesch
janina.krell-roesch@kit.edu

Neurology® 2025;105:e214405. doi:10.1212/WNL.0000000000214405

Abstract

Background and Objectives

Engagement in physical and cognitive activities is associated with a decreased risk of mild cognitive impairment (MCI) and dementia, but the association with Alzheimer disease (AD) neuroimaging biomarkers is less clear. We thus examined associations of physical and cognitive activities with longitudinal trajectories of AD neuroimaging biomarkers among older adults free of dementia.

Methods

We conducted a longitudinal study within the population-based Mayo Clinic Study of Aging (mean follow-up durations 1.3–3.4 years). Participants were aged 50 years or older and were cognitively unimpaired or had MCI at baseline. Engagement in physical and cognitive activities during 12 months before baseline was assessed through questionnaires. Participants underwent AD neuroimaging biomarker assessments at 1 or more time points. We ran linear mixed-effect models to examine associations between physical and cognitive activity composite scores and trajectories of individual yearly change in amyloid deposition (Pittsburgh compound B [PiB]-PET centiloid), tau burden (tau-PET standardized uptake value ratio [SUVR]), and regional glucose hypometabolism (fluorodeoxyglucose [FDG]-PET SUVR), adjusted for age, sex, *APOE* ε4 carrier status, and medical comorbidity.

Results

We included 1,176 participants (47% female; mean [SD] age, 68.7 [9.6] years) for PiB-PET trajectories, 399 participants (49% female; mean [SD] age, 71.9 [11.0] years) for tau-PET trajectories, and 983 participants (46% female; mean [SD] age, 67.9 [9.2] years) for FDG-PET trajectories. PiB-PET and tau-PET measures increased during follow-up (3.4 [SD 4.0] and 1.3 [SD 2.1] years, respectively), whereas FDG-PET values decreased over 2.9 (SD 3.5) years of follow-up. Participants with higher total physical activity (interaction estimate 0.0017; 95% CI 0.0003–0.0031; $p = 0.021$) and higher moderate-to-vigorous physical activity (interaction estimate 0.0015; 95% CI 0.0001–0.0029; $p = 0.040$) had a less pronounced decrease in FDG-PET over time. Participants with higher cognitive activity experienced a less pronounced increase in PiB-PET (interaction estimate −0.2253; 95% CI −0.4437 to −0.0070; $p = 0.043$) and a smaller decrease in FDG-PET (interaction estimate 0.0015; 95% CI 0.0001–0.0028; $p = 0.038$) over time.

[1]Institute of Sports and Sports Science, Karlsruhe Institute of Technology, Germany; [2]Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN; [3]Department of Radiology, Creighton University School of Medicine, Phoenix, AZ; [4]Department of Radiology, Mayo Clinic, Rochester, MN; [5]Department of Neurology, Mayo Clinic, Rochester MN; [6]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN; [7]College of Health Solutions, Arizona State University, Phoenix; and [8]Department of Neurology and the Franke Barrow Global Neuroscience Education Center, Barrow Neurological Institute, Phoenix, AZ.

The article processing charge was funded by the Institute of Sports and Sports Science at Karlsruhe Institute of Technology.

Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **AIBL** = Australian Imaging, Biomarkers and Lifestyle; **FDG** = fluorodeoxyglucose; **MCI** = mild cognitive impairment; **MET** = metabolic equivalents of task; **MVPA** = moderate-to-vigorous physical activity; **PiB** = Pittsburgh compound B; **SUVR** = standardized uptake value ratio.

Discussion

Physical activity was associated with less synaptic dysfunction and cognitive activity with less synaptic dysfunction and lower amyloid burden over time, albeit effect sizes were small. Further research is needed to validate findings and clarify causal inference between physical and cognitive activities and AD neuroimaging biomarkers.

Introduction

Engagement in physical activity,[1-3] as well as cognitive or mentally stimulating activities,[4-7] is associated with a decreased risk of mild cognitive impairment (MCI) and dementia. Recently, studies have aimed to understand the underlying mechanism for the relationships between lifestyle factors, including physical or cognitive activities, and biomarkers of Alzheimer disease (AD) pathophysiology, such as amyloid plaque and tau neurofibrillary tangles.

While animal model studies have shown relationships between increased physical activity and decreased levels of amyloid and tau within the brain, human studies have not shown the same consistent relationship.[8] A systematic review that included 40 observational studies reported that there were only limited associations between physical activity and CSF-derived AD biomarkers or neuroimaging AD biomarkers (e.g., amyloid deposition based on PET and brain glucose metabolism using fluorodeoxyglucose [FDG]-PET).[9] A recent meta-analysis of observational studies found no evidence for an association between physical activity and amyloid deposition as measured by PET, but there was a positive association between physical activity and CSF-derived β-amyloid (Aβ).[10]

Only a few longitudinal studies examined both physical and cognitive activities as independent variables when evaluating AD biomarker outcomes. While these studies showed no associations of physical or cognitive activities with AD neuroimaging[11] or CSF-derived biomarkers,[12] they were limited by sample sizes of 70 and 464 participants, respectively. A longitudinal analysis of 393 participants in the Mayo Clinic Study of Aging[13] aged 70 years or older and free of dementia examined associations between midlife cognitive and physical activities and AD neuroimaging biomarkers derived from 3 imaging modalities, that is, Pittsburgh compound B (PiB)-PET, FDG-PET, and MRI. The study showed that in *APOE* ε4 carriers with high education, engagement in higher midlife cognitive activity was associated with lower amyloid deposition, whereas physical activity was not related to AD biomarkers.[13]

The aim of this longitudinal study was to build and expand on previous research by examining associations between self-reported engagement in physical and cognitive activities (independent variables) performed in the 12 months before baseline assessment and trajectories of AD neuroimaging biomarkers, namely PiB-PET centiloid, tau-PET standardized uptake value ratio (SUVR), and FDG-PET SUVR (dependent variables), in a large sample of more than 1,000 community-dwelling adults aged 50 years or older and free of dementia enrolled in the Mayo Clinic Study of Aging.

Methods

Study Sample and Design

This study was conducted within the population-based Mayo Clinic Study of Aging in Olmsted County, MN.[14] In brief, the Mayo Clinic Study of Aging is a prospective cohort study established in 2004, which was designed to examine cognitive aging. Participants aged 30 years or older are randomly selected from the Olmsted County population using a stratified sampling approach based on age and sex and leveraging the Rochester Epidemiology Project medical records–linkage system.[15] On providing informed consent, participants undergo an initial baseline assessment, followed by follow-up evaluations at approximately 15-month intervals. During each study visit, participants undergo a comprehensive face-to-face evaluation including a neurologic examination and medical history review by a physician, a study coordinator interview, and cognitive testing by a psychometrist covering 4 domains (i.e., memory, attention, language, and visuospatial skills). Participants are classified as having MCI, dementia, or being cognitively unimpaired by a consensus expert panel of a study coordinator, a nurse, a physician, and a neuropsychologist, after reviewing all information available for each participant and based on published criteria. For this study, we included participants aged 50 years or older, with valid information on self-reported engagement in physical activities and/or cognitive activities in the 12 months before baseline assessment, who had undergone at least 1 AD neuroimaging biomarker assessment at baseline (approximately half had at least 1 follow-up assessment) and were either cognitively unimpaired or had MCI at baseline. Mean follow-up durations

ranged from 1.3 years for the outcome of tau-PET trajectories to 3.4 years for the outcome of PiB-PET trajectories.

Assessment of Independent Variables

Engagement in physical activities in the 12 months before baseline assessment was reported by participants using a questionnaire derived from validated instruments, that is, 1985 National Health Interview Survey[16] and Minnesota Heart Survey intensity codes.[17] The questionnaire inquired about 3 different intensities of nonexercise physical activity (i.e., light intensity such as laundry or vacuuming, moderate intensity such as scrubbing floors or gardening, and vigorous intensity such as digging or carrying heavy objects), as well as exercise-related physical activity (i.e., light intensity such as leisurely walking or slow dancing, moderate intensity such as brisk walking or swimming, and vigorous intensity such as jogging or tennis singles). Participants were asked about the frequency at which they performed each of these activities, that is, ≤1 time per month, 2–3 times per month, 1–2 times per week, 3–4 times per week, 5–6 times per week, or daily. For statistical analysis, we assigned the following metabolic equivalents of task (MET) to the intensity categories based on published MET values for different physical activities[18]: light physical activity (2.5 MET), moderate physical activity (4.0 MET), heavy physical activity (6.5 MET), light physical exercise (3.0 MET), moderate physical exercise (5.5 MET), and vigorous physical exercise (8.0 MET). We then calculated 2 scores: (1) a composite total physical activity score by multiplying the MET values for light, moderate, and heavy/vigorous physical activities and exercise by the frequency (days per week) at which the corresponding activities were performed and then summing the values to derive an overall score, and (2) a moderate-to-vigorous physical activity (MVPA) score by adding the MET values multiplied by frequency (days per week) for moderate physical exercise and vigorous physical exercise only. Both the composite total physical activity score and the MVPA score were converted to *z*-scores for use in the statistical models. A higher score reflects a higher level of physical activity, similar to our previous publications.[19]

Engagement in cognitive activities in the 12 months before baseline assessment was reported by participants using a questionnaire derived from previously validated instruments.[20-22] The questionnaire assessed engagement in 10 cognitive activities, that is, artistic activities, playing games, reading books, reading magazines, reading newspapers, playing music, computer activities, craft activities, group activities, and social activities. Participants were asked about the frequency at which they performed each of these activities, that is, ≤1 time per month, 2–3 times per month, 1–2 times per week, 3–4 times per week, 5–6 times per week, or daily. For statistical analysis, we calculated a composite score for cognitive activities (possible range 0–70) by first expressing the frequency of each of the 10 cognitive activities as days per week (0–7) and then summing the days per week of the 10 cognitive activities. The composite score was then converted to *z*-score for use in the statistical models. A higher score reflects higher engagement in cognitive activities.

Assessment of Dependent Variables

Neuroimaging biomarkers of AD included amyloid deposits assessed using PiB-PET, tau burden assessed using flortaucipir tau-PET, and brain glucose metabolism assessed using FDG-PET. Neuroimaging was conducted at baseline for all participants and at 1 or more follow-up visits for approximately half the sample. All PET scans were conducted using a 3-dimensional mode PET/CT scanner (GE or Siemens). The PiB-PET and tau-PET scans consisted of four 5-minute dynamic frames and were acquired from 40 to 60 minutes (PiB-PET) and 80 to 100 minutes (tau-PET) after intravenous injections. The FDG-PET scan consisted of four 2-minute dynamic frames and was performed approximately 30 minutes after intravenous injection. Analysis was conducted using an in-house automated image-processing pipeline.[23] A global cortical PiB SUVR was calculated from prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus regions of interest normalized to the cerebellar crus gray matter, without partial volume correction, and then calibrated to the centiloid scale using established conversion equations.[24] The tau-PET temporal meta-region of interest included the amygdala, entorhinal cortex, fusiform gyrus, parahippocampal gyrus, and inferior temporal and middle temporal gyri, without partial volume correction. The FDG-PET meta-region of interest consisted of bilateral angular gyri, posterior cingulate/precuneus, and inferior temporal cortical regions of interest from both hemispheres normalized to the pons and the cerebellar vermis, without partial volume correction. Atlas and image recognition steps were based on a 3D T1-weighted volume MRI sequence.[23] The reader is referred to the detailed descriptions of the methodology of AD neuroimaging biomarker ascertainment in previous Mayo Clinic Study of Aging publications on amyloid (PiB-PET) and tau-PET imaging,[23,25-27] as well as FDG-PET.[25,27-31]

Assessment of Confounding Variables

In addition to traditional covariates (i.e., age and biological sex), we adjusted the analyses for *APOE* ε4 genotype status, which was determined using standard methods for DNA extracted from blood and medical comorbidity through the weighted Charlson Index. Models on cognitive activities were also adjusted for years of education.

Statistical Analysis

Descriptive statistics were calculated and are presented as mean values with SD for continuous variables or frequencies (N) and percentages (%) for categorical variables. We ran linear mixed-effect models with random, correlated subject-specific intercepts and slopes for years since baseline, adjusted for age, sex, *APOE* ε4 carrier status, and medical comorbidity, to examine the associations of baseline physical activity scores and cognitive activity scores (all *z*-scored, continuous variables) with longitudinal changes in neuroimaging biomarkers. Models on cognitive activities were also further adjusted for

education. We ran the models separately for total physical activity, MVPA, and cognitive activities, and for each of the AD neuroimaging biomarker outcomes (i.e., PiB-PET centiloid, tau-PET SUVR, and FDG-PET SUVR). All models included physical activities or cognitive activities at baseline as independent variables, time in years from baseline, and interactions between time and physical activities or cognitive activities, as well as between time and age. Age was scaled per decade and centered (i.e., subtract mean) so that the longitudinal results can be interpreted for those at the average age. Furthermore, we also examined whether cognitive diagnosis at baseline (i.e., cognitively unimpaired vs MCI) modified the effect of physical and cognitive activities on longitudinal AD biomarkers by further running models including 3-way interactions (i.e., diagnosis × physical or cognitive activity × time). β Coefficients, 95% CIs, and *p* values were computed for each model. All analyses were conducted using the conventional 2-tailed α level of 0.05 and performed with SAS 9.4 (SAS Institute, Inc., Cary, NC) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Standard Protocol Approvals, Registrations, and Participant Consents

The Mayo Clinic Study of Aging protocols have been approved by the institutional review boards of the Mayo Clinic and Olmsted Medical Center in Rochester, MN. All study participants provided written informed consent. In participants with cognitive impairment sufficient to interfere with capacity, a legally authorized representative provided assent.

Data Availability

Data from this study are available on reasonable request.

Results

A total of 1,181 participants (46.7% female) out of 7,437 unique individuals enrolled in the Mayo Clinic Study of Aging (15.9%) were included in the analyses. Participants in this study had a mean (SD) age of 68.68 (9.64) years and a mean (SD) of 14.85 (2.47) years of education; 28.5% were *APOE* ε4 carriers, 89.9% were cognitively unimpaired, and 10.1% had MCI. Baseline demographics for the sample as categorized by the neuroimaging outcomes of interest (i.e., PiB-PET trajectories, tau-PET trajectories, and FDG-PET trajectories) are given in Table 1.

Cross-sectionally, at baseline, participants with higher total physical activity and MVPA had higher FDG-PET SUVRs and those with higher total physical activity also had marginally significantly lower PiB-PET SUVRs (Table 2). Longitudinally, as expected, participants showed an increase in PiB-PET and tau-PET and a decrease in FDG-PET over time, on average, as indicated by positive β estimates for PiB-PET and tau-PET and negative β estimates for FDG-PET (Table 2).

Participants with higher total physical activity and MVPA had less pronounced decreases in FDG-PET over time (Table 2). In addition, participants with higher cognitive activities experienced less pronounced increase in PiB-PET and less pronounced decrease in FDG-PET over time. To put into context with an example, in those with average age and average total physical activity, FDG-PET SUVR decreased, on average, annually by 0.0116 (time effect; Table 2) whereas those with 1 SD above the mean total physical activity level showed a decrease annually, on average, by 0.0099 (time effect + interaction effect = −0.0115 + 0.0017). No statistically significant associations were observed related to tau-PET (Table 2).

In the models including 3-way interactions between cognitive diagnosis, physical or cognitive activities, and time, none of the interactions was statistically significant (data not shown), suggesting that cognitive diagnosis does not modify our observed associations between physical or cognitive activities and longitudinal AD biomarker trajectories.

Discussion

We observed that participants with higher composite scores in physical or cognitive activities during the 12 months before the baseline assessment had less synaptic dysfunction, as indicated by a smaller decrease in brain glucose metabolism based on FDG-PET, and those with higher mentally stimulating activities also had less amyloid burden as indicated by a less pronounced increase in PiB-PET over time; however, the effect sizes were small and possibly not clinically meaningful. We did not observe any associations with tau protein accumulation based on tau-PET.

The literature regarding the associations between physical activity and cognitive or mentally stimulating activity and AD biomarkers is mixed. Several cross-sectional studies examined associations between physical activity[32-35] or a combination of lifestyle factors, that is, physical and cognitive activities,[36-39] and AD-related neuroimaging biomarkers and have reported inconsistent results. For example, a study in a volunteer sample of 65 cognitively unimpaired older individuals, 10 persons with AD, and 11 younger controls revealed an association between engagement in cognitively stimulating activities, particularly in early and middle life, and reduced PiB-PET uptake, reflective of lower Aβ deposition, but engaging in physical activity was not related to Aβ deposition.[38] Other studies have reported favorable associations between higher physical activity and fewer neuroimaging biomarker alterations,[32,33,40,41] suggesting lower levels of neurodegeneration. By contrast, 2 studies showed no association between engagement in physical or cognitive stimulating activities and AD biomarkers based on PiB-PET, FDG-PET, or MRI.[36,37]

Compared with cross-sectional research, there are only few longitudinal studies. A longitudinal analysis derived from the Australian Imaging, Biomarkers and Lifestyle (AIBL) Study of Aging did not find associations between physical activity and Aβ, as measured by PET imaging in 731 cognitively

Table 1 Baseline Characteristics of the Study Sample (Stratified by Outcome of Interest)

	PiB-PET (N = 1,176)	Tau-PET (N = 399)	FDG-PET (N = 983)
Age, y, mean (SD)	68.68 (9.63)	71.94 (10.98)	67.93 (9.15)
Female sex, n (%)	550 (46.8)	195 (48.9)	450 (45.8)
Cognitive status, n (%)			
Cognitively unimpaired	1,057 (89.9)	349 (87.5)	889 (90.4)
Mild cognitive impairment	119 (10.1)	50 (12.5)	94 (9.6)
***APOE* ε4 carriers, n (%)**	333 (28.3)	115 (28.8)	280 (28.5)
Education, y, mean (SD)	14.85 (2.47)$^{\{2\}}$	15.01 (2.43)$^{\{2\}}$	14.82 (2.47)$^{\{1\}}$
Charlson Index score, mean (SD)	2.75 (2.87)	3.33 (3.12)	2.58 (2.78)
Physical activity score, mean (SD)			
Total PA	55.31 (32.50)$^{\{4\}}$	53.53 (35.31)$^{\{2\}}$	55.25 (31.45)$^{\{3\}}$
MVPA	17.52 (18.99)$^{\{2\}}$	16.41 (19.63)$^{\{1\}}$	17.58 (18.45)$^{\{2\}}$
Cognitive activity score, mean (SD)	22.32 (9.27)$^{\{3\}}$	22.41 (10.07)$^{\{2\}}$	22.26 (9.03)$^{\{2\}}$
PiB-PET centiloid, mean (SD)	22.53 (28.52)	—	—
Tau-PET SUVR, mean (SD)	—	1.20 (0.13)	—
FDG-PET SUVR, mean (SD)	—	—	1.58 (0.15)
Follow-up, y, mean (SD)	3.44 (4.03)	1.32 (2.10)	2.89 (3.52)
% Proportion of all MCSA participants (N = 7,437)	15.8	5.4	13.2

Abbreviations: FDG = fluorodeoxyglucose; MCSA = Mayo Clinic Study of Aging; MVPA = moderate-vigorous physical activity; PA = physical activity; PiB = Pittsburgh compound B; SUVR = standardized uptake value ratio.
Data are presented as mean (SD) or n (%), as indicated. {n} indicates number missing for the corresponding variable.

unimpaired adults aged 60 years or older.[42] Another study from Washington University in St. Louis found that higher levels of questionnaire-assessed physical activity over a 10-year period were associated with less decline in processing speed but were not related to any AD biomarkers including PiB-PET.[43] Similarly, a longitudinal study from the New York City area among 70 cognitively unimpaired persons aged 30–60 years reported that engagement in neither physical nor cognitive activities was related to AD neuroimaging biomarker trajectory.[11] Furthermore, a previous study using the Mayo Clinic Study of Aging data looked at the associations between intellectual enrichment and trajectories of PiB-PET, FDG-PET, and MRI biomarkers and found that higher education levels combined with higher midlife cognitive activity were associated with lower longitudinal amyloid deposition in participants who were *APOE* ε4 carriers.[13] Finally, a longitudinal study of 464 individuals in Europe also found no association between cognitively stimulating activities and AD biomarkers, including hippocampal volume measured on MRI.[12]

By contrast, in our study, we demonstrated an association between higher physical and cognitive activities in the 12 months before baseline assessment and less prominent decrease in glucose metabolism identified on FDG-PET over time, as well as an association between higher cognitive activities, but not physical activity, and lower amyloid burden identified on PiB-PET over time. However, we did not observe any associations between physical or cognitive activities and tau protein biomarkers based on tau-PET.

While there are a fair number of studies investigating associations between physical or cognitive activities and AD biomarkers using PiB-PET or FDG-PET, as outlined above, fewer studies used tau-PET. One cross-sectional study using data from the AIBL study included 43 cognitively unimpaired individuals and categorized them as engaging in low-moderate or high physical activity based on International Physical Activity Questionnaire scores.[40] The researchers found a higher tau burden among individuals in the low-moderate physical activity group when compared with the high physical activity group. Another cross-sectional study of 354 middle-aged participants enrolled in the Framingham Heart Study revealed that a higher total physical activity score was associated with lower tau-PET binding levels in the entorhinal cortex.[41]

These results, albeit derived from cross-sectional studies, differ from ours because we did not observe any longitudinal associations between either physical or cognitive activities and tau-PET SUVRs in our sample, although we need to

Table 2 Association Between Baseline Physical and Cognitive Activities and Longitudinal Change in AD Neuroimaging Biomarkers

	IV β (95% CI)	*p* Value	Time β (95% CI)	*p* Value	IV × time interaction β (95% CI)	*p* Value
PiB-PET						
Total PA	−1.4143 (−2.8690 to 0.0404)	0.057	2.5355 (2.3197 to 2.7513)	<0.001	−0.0048 (−0.2211 to 0.2115)	0.965
MVPA	−0.9640 (−2.4116 to 0.4836)	0.192	2.5378 (2.3227 to 2.7529)	<0.001	0.1314 (−0.0842 to 0.3470)	0.232
Cognitive activities	−0.8232 (−2.3657 to 0.7193)	0.295	2.5439 (2.3288 to 2.7591)	<0.001	−0.2253 (−0.4437 to −0.0070)	0.043
Tau-PET						
Total PA	0.0110 (−0.0019 to 0.0240)	0.093	0.0046 (0.0019 to 0.0074)	0.001	−0.0007 (−0.0034 to 0.0021)	0.625
MVPA	0.0086 (−0.0041 to 0.0212)	0.180	0.0048 (0.0021 to 0.0076)	<0.001	0.0011 (−0.0020 to 0.0041)	0.487
Cognitive activities	0.0010 (−0.0126 to 0.0146)	0.880	0.0047 (0.0020 to 0.0075)	<0.001	0.0009 (−0.0020 to 0.0038)	0.554
FDG-PET						
Total PA	0.0086 (0.0004 to 0.0168)	0.040	−0.0116 (−0.0130 to −0.0102)	<0.001	0.0017 (0.0003 to 0.0031)	0.021
MVPA	0.0133 (0.0052 to 0.0213)	0.001	−0.0116 (−0.0130 to −0.0102)	<0.001	0.0015 (0.0001 to 0.0029)	0.040
Cognitive activities	0.0006 (−0.0081 to 0.0093)	0.889	−0.0117 (−0.0131 to −0.0103)	<0.001	0.0015 (0.0001 to 0.0028)	0.038

Abbreviations: β = beta coefficient; FDG = fluorodeoxyglucose; IV = independent variable; MVPA = moderate-to-vigorous physical activity; PA = physical activity; PiB = Pittsburgh compound B; SUVR = standardized uptake value ratio.
Dependent variables (outcomes) are PiB-PET centiloid, tau-PET SUVR, and FDG-PET SUVR. IVs are total PA, MVPA, and cognitive activities. Time reflects the annual change in outcome for participants with average IV. Interaction = difference in slopes over time for each 1 SD increase in value for the IV. PiB-PET: each row represents a unique model adjusted for age, sex, *APOE* ε4 carrier status, and medical comorbidity (and education for the models on cognitive activities), including age × time interaction (significant [$p < 0.001$] for all models; not shown). Tau-PET: each row represents a unique model adjusted for age, sex, *APOE* ε4 carrier status, and medical comorbidity (and education for the models on cognitive activities), including age × time interaction (not significant [$p > 0.05$] for all models; not shown). FDG-PET: each row represents a unique model adjusted for age, sex, *APOE* ε4 carrier status, and medical comorbidity (and education for the models on cognitive activities), including age × time interaction (not significant [$p > 0.05$] for all models; not shown). Age was scaled per decade and centered (i.e., subtract mean).

acknowledge the shorter follow-up period between the independent variables and the tau-PET SUVR assessed. We are not aware of another longitudinal study that examined associations between lifestyle activities and tau burden as indicated by PET imaging; more research is thus needed to examine whether lifestyle factors such as the ones included in our study are longitudinally related to tau burden in community-dwelling older adults.

We did not examine potential mechanisms explaining associations between lifestyle factors and AD biomarker trajectories. One possibility for the limited level of evidence or lack of associations between lifestyle factors and AD biomarkers could be that physical activity recorded in many studies may not have been rigorous enough or span a long enough time frame. In addition, preclinical stages of AD can begin decades before clinical symptoms manifest.[8] It is possible that many human studies do not encompass the preclinical "window of opportunity" during which physical activity may have a greater impact on signs and symptoms of the disease. In our study of individuals who were cognitively unimpaired or with MCI, we observed associations between physical and cognitive activities performed within the past 12 months and neuroimaging biomarker trajectories. More research is needed to explore the potential differential effects of midlife vs late-life lifestyle factors on AD pathophysiologic changes. Meaningful insights into the associations between lifestyle factors and AD neuroimaging biomarkers, in addition to observational research as outlined above, can also be derived from interventional research. To this end, systematic reviews of intervention studies[44,45] showed only a few effects of physical activity on neurotrophic and inflammatory biomarkers but not AD pathophysiology, while also acknowledging that only a small number of original studies could be identified. Similarly, a nonsystematic review of interventional studies found overall no convincing evidence of a relationship between physical activity and AD biomarkers but identified studies that showed significant associations in specific populations, for example, between physical activity and blood-based Aβ levels in women with obesity, prediabetes, or depression, and between physical activity and CSF-derived Aβ in *APOE* ε4 carriers with AD.[46] Furthermore, promising clinical trials have recently been conducted or are still ongoing; for example, the EXERT trial examined the effects of an 18-month physical exercise intervention on cognitive function and other brain function measures in persons with MCI,[47] and the US POINTER trial examined the effects of multidomain lifestyle interventions including physical and cognitive activities on cognitive function in older adults at risk of cognitive decline and dementia.[48] Results from such trials will also be valuable in further understanding the mechanisms linking physical activity and brain health in older adults.

Regarding the clinical significance of our observed associations, it is informative to consider findings from a publication by the Mayo Clinic Study of Aging team.[49] The study showed that an increase of 1 interquartile range in plasma %p-tau217 was associated with a 0.5-unit increase in PiB centiloid slope over time. Our models suggest a protective effect of approximately half that magnitude (−0.23) per SD increase in cognitive activity. Furthermore, in our sample, the average PiB centiloid value was 22.53, and the slope over time for individuals with average age and activity was approximately 2.5. Given that the Mayo Clinic Study of Aging team uses a PiB centiloid cutoff of 25 to determine amyloid positivity, we can assume that the average participant in our data is approximately 1 year away from amyloid positivity. The protective effect of a SD increase in cognitive activity translates to a delay of approximately 1 month in reaching amyloid positivity ([0.23/2.5] × 12 = 1.1 month), which is a modest effect. However, considering the large SD of PiB centiloid in our sample (28.52), an individual 1 SD below the mean would need to increase by approximately 31 centiloids to reach the positivity threshold, equating to roughly 12.4 years for someone with average age and cognitive activity. For an individual 1 SD above the mean in cognitive activity, the protective effect accumulates to approximately 1 additional year below the cutoff of 25. Individuals with higher levels of cognitive activity could extend their amyloid-negative status even further.

The strengths of our study include the large sample size, consideration of engagement in physical and/or cognitive activities, and repeated AD neuroimaging measurements on a large sample of community-dwelling older adults. Limitations of the study are that both physical and cognitive activities were assessed through self-reported questionnaires; thus, as in any questionnaire-based assessment, recall bias may be present and may limit the validity of study findings. Future research is warranted that uses objective measurements such as accelerometry for physical activities, or ecological momentary assessment or digital monitoring for cognitive activities, or that obtains confirmation of a participant's responses from study partners such as spouses or caregivers. In addition, owing to the observational study design, we cannot conclude about the cause and effect in the association between physical and cognitive activities and AD neuroimaging biomarker changes, and reverse causality is possible. Thus, it is biologically plausible that persons with healthier brains (that is, less amyloid deposition and higher FDG-PET uptake) were more cognitively and physically active at baseline and were the ones who accumulated amyloid at a slower rate (as indicated by less pronounced increase in PiB-PET) and had better FDG-PET outcomes (as indicated by less pronounced decrease in FDG-PET uptake over time); thus, lower levels of physical and cognitive activities at baseline are clinical markers of incipient disease. Furthermore, while we adjusted our analyses for age, sex, *APOE* ε4 carrier status, and medical comorbidity (and education for models on cognitive activities), adjustments for additional confounders may be needed in future analyses and residual confounding is possible. Our study sample is relatively highly educated, and approximately 98% of participants are White older adults; thus, the results may have limited generalizability to other populations.[50] In addition, the effect sizes we observed are small, and pathologic significance of the amplitude of change in neuroimaging biomarker trajectories is unclear. It is possible that our study was overpowered, given its large sample size. In addition, the follow-up period of 1–3 years (depending on the outcome of interest) may have been too short to reveal changes in neuroimaging biomarker trajectories among cognitively unimpaired participants, albeit our analyses showed that cognitive diagnosis does not modify the observed associations between physical or cognitive activities and longitudinal AD biomarker trajectories. Furthermore, when considering a PiB centiloid cutoff of 25 for determining amyloid positivity (A+), 17% of cognitively unimpaired participants in our sample were A+ at the first visit and 36% were A+ at the last visit. In the MCI sample, 37% were A+ at the first visit and 53% were A+ at the last visit. Similarly, using a tau-PET SUVR cutoff of 1.29 for determining tau positivity (T+), 12% of cognitively unimpaired participants in our sample were T+ at the first visit and 17% were T+ at the last visit. In the MCI sample, 26% were T+ at the first visit and 32% were T+ at the last visit. Therefore, both cognitively unimpaired participants and those with MCI progressed on neuroimaging. Of note, these numbers are based on participants with multiple visits, and participants that only had a single visit do not contribute to these numbers. In addition, censoring and attrition could be an additional limitation because we only get an incomplete trajectory over time for those participants who drop out. However, if we assume that participants lost to follow-up are more likely those experiencing more physical or cognitive decline, then our study estimates may even be conservative (underestimated); however, the pattern of attrition is not known. Another limitation is a possible nonlinear association between physical and cognitive activities and neuroimaging biomarkers, but this was somewhat addressed by including interactions between baseline age and time, which allowed trajectory over time to vary by age in our models.

In conclusion, our study provides limited evidence of associations between higher physical activity and less synaptic dysfunction as indicated by FDG-PET, as well as higher cognitive activities with less synaptic dysfunction and lower amyloid burden as indicated by PiB-PET over time in community-dwelling older adults free of dementia. We also examined associations with Tau-PET, but no significant associations were observed. Overall, the number of associations was small, as were the observed effect sizes. Thus, more research is needed to explore the associations between physical and cognitive activities with AD pathology.

Acknowledgment

The authors thank the participants and staff of the Mayo Clinic Study of Aging.

Author Contributions

J. Krell-Roesch: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. J.A. Syrjanen: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. A.L. Hansen: drafting/revision of the manuscript for content, including medical writing for content. P. Vemuri: drafting/revision of the manuscript for content, including medical writing for content. E.L. Scharf: drafting/revision of the manuscript for content, including medical writing for content. J.A. Fields: drafting/revision of the manuscript for content, including medical writing for content. W.K. Kremers: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. V.J. Lowe: drafting/revision of the manuscript for content, including medical writing for content. J. Graff-Radford: drafting/revision of the manuscript for content, including medical writing for content. C.R. Jack: drafting/revision of the manuscript for content, including medical writing for content. R.C. Petersen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S.B. Racette: drafting/revision of the manuscript for content, including medical writing for content. A. Woll: drafting/revision of the manuscript for content, including medical writing for content. M. Vassilaki: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. Y.E. Geda: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

Study Funding

Support for this research was provided by NIH grants: National Institute on Aging (R01 AG057708, U01 AG006786, P30 AG062677, R37 AG011378, R01 AG041851, R01 NS097495); the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program; the GHR Foundation; the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Clinic; the Liston Award; the Schuler Foundation; the Mayo Foundation for Medical Education and Research; the Arizona Alzheimer's Consortium; and the Barrow Neurological Foundation. Resources were provided by the Rochester Epidemiology Project (REP) medical records–linkage system, which is supported by the National Institute on Aging (AG 058738), the Mayo Clinic Research Committee, and by fees paid annually by REP users.

Disclosure

P. Vemuri receives research support from the NIH. J. Fields reports grants from NIH and grants from the Mangurian Foundation outside the submitted work. V.J. Lowe serves as a consultant for Bayer Schering Pharma, Piramal Life Sciences, Life Molecular Imaging, Eisai Inc., AVID Radiopharmaceuticals, Eli Lilly and Company, PeerView Institute for Medical Education, and Merck Research; and receives research support from GE Healthcare, Siemens Molecular Imaging, AVID Radiopharmaceuticals, and the NIH (NIA, NCI). J. Graff-Radford serves on the DSMB for the National Institute of Neurological Disorders and Stroke; is an associate editor for *JAMA Neurology;* and acts as the site PI for trials sponsored by Eisai and Cognition Therapeutics. C.R. Jack receives no personal compensation from any commercial entity; he receives research support from NIH and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Clinic. R.C. Petersen is a consultant for Roche, Genentech, Eli Lilly and Co., Eisai, Novartis, and Novo Nordisk; receives research funding from the NIH; and receives royalties from Oxford University Press and UpToDate. S.B. Racette receives research support from NIH and the Barrow Neurological Foundation; and serves on the scientific advisory board for Pritikin Intensive Cardiac Rehab. M. Vassilaki consulted for F. Hoffmann-La Roche Ltd., unrelated to this manuscript; she currently has equity ownership in Amgen, Johnson and Johnson, and Merck. Y.E. Geda receives funding from Roche and served on the Lundbeck advisory board. All other authors report no financial relationships with commercial interests. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology*® May 20, 2025. Accepted in final form September 25, 2025. Submitted and externally peer reviewed. The handling editor was Associate Editor Linda Hershey, MD, PhD, FAAN.

References

1. Buchman AS, Boyle PA, Yu L, Shah RC, Wilson RS, Bennett DA. Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology*. 2012;78(17):1323-1329. doi:10.1212/WNL.0b013e3182535d35
2. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol*. 2001;58(3):498-504. doi:10.1001/archneur.58.3.498
3. Krell-Roesch J, Pink A, Roberts RO, et al. Timing of physical activity, apolipoprotein E ε4 genotype, and risk of incident mild cognitive impairment. *J Am Geriatr Soc*. 2016;64(12):2479-2486. doi:10.1111/jgs.14402
4. Wu Z, Pandigama DH, Wrigglesworth J, et al. Lifestyle enrichment in later life and its association with dementia risk. *JAMA Netw Open*. 2023;6(7):e2323690. doi:10.1001/jamanetworkopen.2023.23690
5. Krell-Roesch J, Syrjanen JA, Vassilaki M, et al. Quantity and quality of mental activities and the risk of incident mild cognitive impairment. *Neurology*. 2019;93(6):e548-e558. doi:10.1212/WNL.0000000000007897
6. Krell-Roesch J, Vemuri P, Pink A, et al. Association between mentally stimulating activities in late life and the outcome of incident mild cognitive impairment, with an analysis of the APOE ε4 genotype. *JAMA Neurol*. 2017;74(3):332-338. doi:10.1001/jamaneurol.2016.3822
7. Sattler C, Toro P, Schönknecht P, Schröder J. Cognitive activity, education and socioeconomic status as preventive factors for mild cognitive impairment and Alzheimer's disease. *Psychiatry Res*. 2012;196(1):90-95. doi:10.1016/j.psychres.2011.11.012
8. Brown BM, Peiffer J, Rainey-Smith SR. Exploring the relationship between physical activity, beta-amyloid and tau: a narrative review. *Ageing Res Rev*. 2019;50:9-18. doi:10.1016/j.arr.2019.01.003
9. Frederiksen KS, Gjerum L, Waldemar G, Hasselbalch SG. Physical activity as a moderator of Alzheimer pathology: a systematic review of observational studies. *Curr Alzheimer Res*. 2019;16(4):362-378. doi:10.2174/1567205016666190315095151
10. Rodriguez-Ayllon M, Solis-Urra P, Arroyo-Ávila C, et al. Physical activity and amyloid beta in middle-aged and older adults: a systematic review and meta-analysis. *J Sport Health Sci*. 2024;13(2):133-144. doi:10.1016/j.jshs.2023.08.001
11. Walters MJ, Sterling J, Quinn C, et al. Associations of lifestyle and vascular risk factors with Alzheimer's brain biomarker changes during middle age: a 3-year longitudinal study in the broader New York City area. *BMJ Open*. 2018;8(11):e023664. doi:10.1136/bmjopen-2018-023664
12. Reijs BLR, Vos SJB, Soininen H, et al. Association between later life lifestyle factors and Alzheimer's disease biomarkers in non-demented individuals: a longitudinal

descriptive cohort study. *J Alzheimers Dis*. 2017;60(4):1387-1395. doi:10.3233/JAD-170039
13. Vemuri P, Lesnick TG, Przybelski SA, et al. Effect of intellectual enrichment on AD biomarker trajectories: longitudinal imaging study. *Neurology*. 2016;86(12):1128-1135. doi:10.1212/WNL.0000000000002490
14. Roberts RO, Geda YE, Knopman DS, et al. The Mayo Clinic Study of Aging: design and sampling, participation, baseline measures and sample characteristics. *Neuroepidemiology*. 2008;30(1):58-69. doi:10.1159/000115751
15. St Sauver JL, Grossardt BR, Yawn BP, et al. Data resource profile: the Rochester Epidemiology Project (REP) medical records-linkage system. *Int J Epidemiol*. 2012;41(6):1614-1624. doi:10.1093/ije/dys195
16. Moss AJ, Parsons VL. Current estimates from the National Health Interview Survey, United States, 1985. *Vital Health Stat 10*. 1986;(160):i-iv, 1-182.
17. Folsom AR, Caspersen CJ, Taylor HL, et al. Leisure time physical activity and its relationship to coronary risk factors in a population-based sample. The Minnesota Heart Survey. *Am J Epidemiol*. 1985;121(4):570-579. doi:10.1093/oxfordjournals.aje.a114035
18. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc*. 2011;43(8):1575-1581. doi:10.1249/MSS.0b013e31821ece12
19. Krell-Roesch J, Syrjanen JA, Moeller T, et al. Self-reported physical activity and gait in older adults without dementia: a longitudinal study. *Health Sci Rep*. 2024;7(11):e70108. doi:10.1002/hsr2.70108
20. Verghese J, Lipton RB, Katz MJ, et al. Leisure activities and the risk of dementia in the elderly. *N Engl J Med*. 2003;348(25):2508-2516. doi:10.1056/NEJMoa022252
21. Wilson RS, Bennett DA, Beckett LA, et al. Cognitive activity in older persons from a geographically defined population. *J Gerontol B Psychol Sci Soc Sci*. 1999;54(3):P155-P160. doi:10.1093/geronb/54b.3.p155
22. Friedland RP, Fritsch T, Smyth KA, et al. Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. *Proc Natl Acad Sci USA*. 2001;98(6):3440-3445. doi:10.1073/pnas.061002998
23. Mielke MM, Dage JL, Frank RD, et al. Performance of plasma phosphorylated tau 181 and 217 in the community. *Nat Med*. 2022;28(7):1398-1405. doi:10.1038/s41591-022-01822-2
24. Klunk WE, Koeppe RA, Price JC, et al. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimers Dement*. 2015;11(1):1-15.e1-4. doi:10.1016/j.jalz.2014.07.003
25. Jack CR Jr, Lowe VJ, Senjem ML, et al. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment. *Brain*. 2008;131(pt 3):665-680. doi:10.1093/brain/awm336
26. Lowe VJ, Kemp BJ, Jack CR Jr, et al. Comparison of 18F-FDG and PiB PET in cognitive impairment. *J Nucl Med*. 2009;50(6):878-886. doi:10.2967/jnumed.108.058529
27. Jack CR Jr, Wiste HJ, Weigand SD, et al. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. *Alzheimers Dement*. 2017;13(3):205-216. doi:10.1016/j.jalz.2016.08.005
28. Minoshima S, Frey KA, Foster NL, Kuhl DE. Preserved pontine glucose metabolism in Alzheimer disease: a reference region for functional brain image (PET) analysis. *J Comput Assist Tomogr*. 1995;19(4):541-547. doi:10.1097/00004728-199507000-00006
29. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*. 2002;15(1):273-289. doi:10.1006/nimg.2001.0978
30. Jagust WJ, Bandy D, Chen K, et al. The Alzheimer's Disease Neuroimaging Initiative positron emission tomography core. *Alzheimers Dement*. 2010;6(3):221-229. doi:10.1016/j.jalz.2010.03.003
31. Landau SM, Harvey D, Madison CM, et al. Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. *Neurobiol Aging*. 2011;32(7):1207-1218. doi:10.1016/j.neurobiolaging.2009.07.002
32. Liang KY, Mintun MA, Fagan AM, et al. Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. *Ann Neurol*. 2010;68(3):311-318. doi:10.1002/ana.22096
33. Okonkwo OC, Schultz SA, Oh JM, et al. Physical activity attenuates age-related biomarker alterations in preclinical AD. *Neurology*. 2014;83(19):1753-1760. doi:10.1212/WNL.0000000000000964
34. Pedrini S, Chatterjee P, Nakamura A, et al. The association between Alzheimer's disease-related markers and physical activity in cognitively normal older adults. *Front Aging Neurosci*. 2022;14:771214. doi:10.3389/fnagi.2022.771214
35. Brown BM, Peiffer JJ, Taddei K, et al. Physical activity and amyloid-beta plasma and brain levels: results from the Australian Imaging, Biomarkers and Lifestyle Study of Ageing. *Mol Psychiatry*. 2013;18(8):875-881. doi:10.1038/mp.2012.107
36. Gidicsin CM, Maye JE, Locascio JJ, et al. Cognitive activity relates to cognitive performance but not to Alzheimer disease biomarkers. *Neurology*. 2015;85(1):48-55. doi:10.1212/WNL.0000000000001704
37. Vemuri P, Lesnick TG, Przybelski SA, et al. Effect of lifestyle activities on alzheimer disease biomarkers and cognition. *Ann Neurol*. 2012;72(5):730-738. doi:10.1002/ana.23665
38. Landau SM, Marks SM, Mormino EC, et al. Association of lifetime cognitive engagement and low beta-amyloid deposition. *Arch Neurol*. 2012;69(5):623-629. doi:10.1001/archneurol.2011.2748
39. Casaletto KB, Rentería MA, Pa J, et al. Late-life physical and cognitive activities independently contribute to brain and cognitive resilience. *J Alzheimers Dis*. 2020;74(1):363-376. doi:10.3233/JAD-191114
40. Brown BM, Rainey-Smith SR, Dore V, et al. Self-reported physical activity is associated with tau burden measured by positron emission tomography. *J Alzheimers Dis*. 2018;63(4):1299-1305. doi:10.3233/JAD-170998
41. Gonzales MM, Kojis D, Spartano NL, et al. Associations of physical activity engagement with cerebral amyloid-beta and tau from midlife. *J Alzheimers Dis*. 2024;100(3):935-943. doi:10.3233/JAD-240322
42. Slee MG, Rainey-Smith SR, Villemagne VL, et al. Physical activity and brain amyloid beta: a longitudinal analysis of cognitively unimpaired older adults. *Alzheimers Dement*. 2024;20(2):1350-1359. doi:10.1002/alz.13556
43. Stojanovic M, Jin Y, Fagan AM, et al. Physical exercise and longitudinal trajectories in alzheimer disease biomarkers and cognitive functioning. *Alzheimer Dis Assoc Disord*. 2020;34(3):212-219. doi:10.1097/WAD.0000000000000385
44. Frederiksen KS, Gjerum L, Waldemar G, Hasselbalch SG. Effects of physical exercise on Alzheimer's disease biomarkers: a systematic review of intervention studies. *J Alzheimers Dis*. 2018;61(1):359-372. doi:10.3233/JAD-170567
45. Moniruzzaman M, Kadota A, Akash MS, et al. Effects of physical activities on dementia-related biomarkers: a systematic review of randomized controlled trials. *Alzheimers Dement (NY)*. 2020;6(1):e12109. doi:10.1002/trc2.12109
46. Raffin J. Does physical exercise modify the pathophysiology of Alzheimer's disease in older persons? *JAR Life*. 2024;13:77-81. doi:10.14283/jarlife.2024.11
47. Baker LD, Pa JA, Katula JA, et al. Effects of exercise on cognition and Alzheimer's biomarkers in a randomized controlled trial of adults with mild cognitive impairment: the EXERT study. *Alzheimers Dement*. 2025;21(4):e14586. doi:10.1002/alz.14586
48. Baker LD, Espeland MA, Whitmer RA, et al. Structured vs self-guided multidomain lifestyle interventions for global cognitive function: the US POINTER randomized clinical trial. *JAMA*. 2025;334(8):681-691. doi:10.1001/jama.2025.12923
49. Cogswell PM, Wiste HJ, Weigand SD, et al. Plasma Alzheimer's disease biomarker relationships with incident abnormal amyloid PET. *Alzheimers Dement*. 2025;21(2):e14629. doi:10.1002/alz.14629
50. St Sauver JL, Grossardt BR, Leibson CL, Yawn BP, Melton LJ III, Rocca WA. Generalizability of epidemiological findings and public health decisions: an illustration from the Rochester Epidemiology Project. *Mayo Clin Proc*. 2012;87(2):151-160. doi:10.1016/j.mayocp.2011.11.009