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Associations of Physical Activity and β-Amyloid With Longitudinal Cognition and Neurodegeneration in Clinically Normal Older Adults

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IMPORTANCE In the absence of disease-modifying therapies for Alzheimer disease, there is a critical need to identify modifiable risk factors that may delay the progression of Alzheimer disease.

OBJECTIVE To examine whether physical activity moderates the association of β-amyloid (Aβ) burden with longitudinal cognitive decline and neurodegeneration in clinically normal individuals and to examine whether these associations are independent of vascular risk.

DESIGN, SETTING, AND PARTICIPANTS This longitudinal observational study included clinically normal participants from the Harvard Aging Brain Study. Participants were required to have baseline Aβ positron emission tomography data, baseline medical data to quantify vascular risk, and longitudinal neuropsychological and structural magnetic resonance imaging data. Data were collected from April 2010 to June 2018. Data were analyzed from August to December 2018.

MAIN OUTCOMES AND MEASURES Baseline physical activity was quantified with a pedometer (mean steps per day). Baseline Aβ burden was measured with carbon 11–labeled Pittsburgh Compound B positron emission tomography. Cognition was measured annually with the Preclinical Alzheimer Cognitive Composite (PACC; median [interquartile range] follow-up, 6.0 [4.3-6.3] years). Neurodegeneration was assessed with longitudinal structural magnetic resonance imaging (2 to 5 scans per participant; median [interquartile range] follow-up, 4.5 [3.0-5.0] years), with a focus on total gray matter volume and regional cortical thickness. Physical activity and Aβ burden were examined as interactive predictors of PACC decline and volume loss in separate linear mixed models, adjusting for age, sex, education, apolipoprotein E ε*4* status, and, where appropriate, intracranial volume. Secondary models adjusted for vascular risk and its interaction with Aβ burden.

RESULTS Of the 182 included participants, 103 (56.6%) were female, and the mean (SD) age was 73.4 (6.2) years. In models examining PACC decline and volume loss, there was a significant interaction of physical activity with Aβ burden, such that greater physical activity was associated with slower Aβ-related cognitive decline (β, 0.03; 95% CI, 0.02-0.05; $P < .001$) and volume loss (β, 482.07; 95% CI, 189.40-774.74; $P = .002$). Adjusting for vascular risk did not alter these associations. In these models, lower vascular risk was independently associated with slower Aβ-related PACC decline (β, −0.04; 95% CI, −0.06 to −0.02; $P < .001$) and volume loss (β, −483.41; 95% CI, −855.63 to −111.20; $P = .01$).

CONCLUSIONS AND RELEVANCE Greater physical activity and lower vascular risk independently attenuated the negative association of Aβ burden with cognitive decline and neurodegeneration in asymptomatic individuals. These findings suggest that engaging in physical activity and lowering vascular risk may have additive protective effects on delaying the progression of Alzheimer disease.

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Supplemental content

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The pathophysiological process of Alzheimer disease (AD) begins decades before clinical symptoms emerge and is characterized by early accumulation of β-amyloid (Aβ).[1,2] This preclinical stage of AD provides an opportunity to intervene prior to substantial neuronal loss and clinical impairment.[3] However, there are currently no available disease-modifying therapies for AD, and several recent trials targeting Aβ in the symptomatic phase of the disease have yielded disappointing results.[4] Accordingly, there is a critical need to identify potentially modifiable risk factors that may delay the progression of AD.

Physical activity has garnered significant attention as a potentially effective strategy for maintaining brain health and cognition in the aging population. Animal and human studies suggest that greater engagement in physical activity may preserve cortical gray matter structure[5-9] and slow the accumulation of Aβ and tau burden.[8,10-13] Human studies further report that higher levels of physical activity may attenuate cognitive decline and reduce the risk of dementia, including dementia due to AD.[14-20] However, it should be noted that most of these AD studies lacked assessment of Aβ burden.

In the present study, we examined whether baseline physical activity is protective against Aβ-related cognitive decline and neurodegeneration in a cohort of older adults who were clinically normal at baseline. To do this, we used baseline Aβ burden and objectively measured physical activity as interactive predictors of longitudinal change in cognition and structural magnetic resonance imaging (MRI) in older adults participating in the Harvard Aging Brain Study (HABS). Given the association of physical activity with vascular health,[21] along with the association of vascular risk with cognitive decline in this[22] and other cohorts,[23,24] we also examined whether the associations of physical activity with Aβ-related cognitive decline and neurodegeneration were independent of vascular risk.

Key Points

Question Does physical activity moderate the associations of β-amyloid (Aβ) burden with longitudinal cognitive decline and neurodegeneration in clinically normal older adults?

Findings In this study of 182 individuals, greater baseline physical activity attenuated Aβ-related cognitive decline and gray matter volume loss. In models adjusting for vascular risk, physical activity remained significant, and lower vascular risk was independently associated with slower Aβ-related cognitive decline and gray matter volume loss.

Meaning Interventional approaches that target both physical activity and vascular risk factors may have additive beneficial effects on delaying the progression of Alzheimer disease.

Methods

Participants

A total of 182 clinically normal older adults were recruited from HABS. The Partners Institutional Review Board approved the HABS protocol, and participants provided written informed consent before undergoing any procedures.

As previously described,[25] all participants underwent a comprehensive medical and neurological evaluation and were screened for major medical, psychiatric, or neurological conditions as well as recent history of alcohol use disorder or drug use disorder. At study entry, all participants had a global Clinical Dementia Rating score of 0,[26] a Geriatric Depression Scale score less than 11,[27] and a Mini-Mental State Examination score of 27 or greater with adjustment for education[28] and performed normally within education-adjusted norms on Logical Memory delayed recall.[29] Exclusionary criteria included a modified Hachinski ischemic score greater than 4, a history of stroke with residual deficits, and evidence of cortical infarcts or strategically placed lacunar infarcts.

Included participants were required to have baseline Aβ positron emission tomography (PET) imaging, baseline physical activity data, at least 2 cognitive and MRI data points, and the necessary demographic and medical information to calculate an aggregate measure of vascular risk at baseline. Note that the baseline assessments in HABS (clinical, medical history, MRI and PET scans, and cognitive assessments) take place over the course of several visits during the first year of participation, a period spanning 3 to 4 months.

Physical Activity

Physical activity was measured at baseline using a waistband-mounted pedometer (HJ-720ITC; Omron Healthcare). Participants were asked to wear the pedometer on their waist for 7 consecutive days during waking hours. Mean steps per day was used as the primary measure of daily physical activity. Using previously published cutoffs for pedometer data quality,[30] days that registered less than 100 or greater than 30 000 steps were excluded. Included participants were required to have at least 5 days of recorded activity within these cutoffs.

Cardiovascular Disease Risk

Vascular risk was quantified at baseline using the office-based Framingham Heart Study cardiovascular disease risk score (FHS-CVD).[31] The FHS-CVD represents a weighted sum of age, sex, antihypertensive treatment (yes or no), systolic blood pressure, body mass index (calculated as weight in kilograms divided by height in meters squared), history of diabetes (yes or no), and current cigarette smoking status (yes or no). The FHS-CVD provides a 10-year probability of future cardiovascular events (defined as coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and heart failure). In our sample, the FHS-CVD ranged from 4% to 76% (mean FHS-CVD, 32%), with higher scores indicating greater risk of sustaining cardiovascular events.

PET Imaging

β-Amyloid burden data used in the present study were obtained at baseline using carbon 11-labeled Pittsburgh Compound B PET. Positron emission tomography imaging was carried out at the Massachusetts General Hospital PET facility using the ECAT EXACT HR+ scanner (Siemens). Detailed Aβ PET protocols in HABS have been previously described.[32] As in prior studies from our group,[32] Aβ PET measurements were represented

as a distribution volume ratio across a composite of frontal, lateral temporal and parietal, and retrosplenial regions. Cerebellar gray matter (as defined by FreeSurfer software version 6.0 [http://surfer.nmr.mgh.harvard.edu/]) served as the reference region. Positron emission tomography data were corrected for partial volume effects using the geometric transfer matrix method.[33]

Cognitive Measures

At the time of analysis, cognitive data were available for 182 participants from baseline through follow-up year 4, for 173 through follow-up year 5, for 128 through follow-up year 6, and for 96 through follow-up year 7 (median [interquartile range] follow-up, 6.0 [4.3-6.3] years). The Preclinical Alzheimer Cognitive Composite (PACC)[34,35] was used as the primary measure of cognitive change over time. The PACC consists of the Mini-Mental State Examination,[28] Wechsler Adult Intelligence Scale–Revised Digit Symbol Coding,[36] Wechsler Memory Scale–Revised Logical Memory delayed recall,[29] and the Free and Cued Selective Reminding Test (free recall plus total recall).[37] Raw scores were *z*-transformed based on the mean and SD from the baseline data and averaged together. Higher PACC scores indicate better performance.

Structural Imaging

Magnetic resonance imaging scanning was completed at the Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston, on a 3T MAGNETOM Trio TIM scanner with a 12-channel head coil (Siemens). High-resolution 3-dimensional T1-weighted multiecho magnetization-prepared rapid acquisition with gradient echo anatomical images were collected with the following parameters: TR = 6400 milliseconds; TE = 2.8 milliseconds; flip angle = 8°; and voxel size = 1 × 1 × 1.2 mm. Magnetic resonance imaging structural data in HABS are acquired at baseline, year 3, and year 5. At the time of analysis, MRI data were available for 182 participants at baseline, 175 at follow-up year 3, and 98 at follow-up year 5. Some participants received an additional scan at follow-up year 1.5 (n = 34) and/or follow-up year 3 (n = 43). The number of MRI scans per participant ranged from 2 to 5 (median [interquartile range] number of scans, 3.0 [2.0-3.0]; median [interquartile range] follow-up, 4.5 [3.0-5.0] years). Estimation of cortical thickness and subcortical volumetric segmentation was performed with FreeSurfer software (version 6.0).[38,39] Following previously described cross-sectional quality control measures,[25] MRI scans were grouped by participant and further processed together using the FreeSurfer longitudinal processing stream,[40] a temporally unbiased segmentation approach that decreases noise in longitudinal analyses. Change in total gray matter volume was selected a priori as the primary measure of neurodegeneration. This primary measure was supplemented by regional cortical thickness measures in follow-up analyses. Familywise error correction was used in analyses of regional cortical thickness to maintain an α of .005 or less.

Statistical Analysis

Statistical analyses were performed using R version 3.5.1 (The R Foundation). We used partial Pearson correlations to examine the cross-sectional associations of physical activity with Aβ burden and FHS-CVD, adjusting for age and sex. We used linear mixed-effects models (nlme package) to assess whether greater physical activity at baseline attenuates the negative association of Aβ burden with longitudinal PACC decline and gray matter volume loss. This was tested using separate models for PACC (model 1) and gray matter volume (model 2). In these models, the measure of interest was the 3-way interaction between physical activity, Aβ, and time. All models included baseline age, sex, years of education, and apolipoprotein E (*APOE*) *ε4* status (carrier vs noncarrier) as baseline covariates as well as their interactions with time. When the outcome variable was gray matter volume, we additionally adjusted for intracranial volume and its interaction with time. Both models included lower-order terms. A random intercept and slope were included for each participant. Time was operationalized as years from baseline for each participant. The following equations were used for the models: Model 1: PACC ~ Physical Activity × Aβ × Time + Covariates × Time; Model 2: Gray Matter Volume ~ Physical Activity × Aβ × Time + Covariates × Time. All continuous variables were *z*-transformed prior to model entry. In linear mixed-effects models, 2-sided *P* values less than .05 were considered statistically significant.

In secondary analyses, we assessed whether the associations remained significant after adjusting for vascular risk. To do so, we added the 3-way interaction of FHS-CVD, Aβ, and time as well as the lower-order terms to model 1 and model 2.

In follow-up analyses, we examined the regional specificity of the neurodegeneration effect in model 2. To do so, we carried out an exploratory whole-brain analysis examining the interaction of physical activity, Aβ, and time on cortical thinning in FreeSurfer-defined regions (averaged across right and left hemispheres), adjusting for age, sex, years of education, *APOE ε4* status, and their interactions with time. Given previously reported associations of physical activity with hippocampal volume,[7,9,41,42] we also examined the association of physical activity with Aβ-related hippocampal volume loss, adjusting for covariates, including intracranial volume.

Results

Of the 182 included participants from HABS, 103 (56.6%) were female, and the mean (SD) age was 73.4 (6.2) years. The baseline demographic and clinical characteristics of the sample are summarized in **Table 1.** Prior to longitudinal analyses, we first examined the cross-sectional associations of physical activity with Aβ burden and FHS-CVD. As expected, after adjusting for age and sex, there was a negative association of physical activity with FHS-CVD (partial $r = -0.27$; $P < .001$), such that greater physical activity was associated with lower vascular risk. There was no association of physical activity with Aβ burden after adjusting for age and sex (partial $r = 0.01$; $P = .85$).

Of primary interest was whether physical activity moderated the association of Aβ burden with prospective PACC decline (model 1) and gray matter volume loss (model 2). The interaction of physical activity, Aβ, and time was significant in both models, such that greater engagement in physical activity was associated with slower Aβ-related cognitive decline and gray matter volume loss (**Table 2; Figure 1** and **Figure 2**).

Table 1. Baseline Demographic and Clinical Characteristics of the Sample

Characteristic	Mean (SD)
Total, No.	182
Age, y	73.4 (6.2)
Education, y	16.0 (3.1)
Women, No. (%)	103 (56.6)
Aβ FLR partial volume-corrected DVR on PET	1.4 (0.4)
APOE ε4 carriers, No. (%)	54 (29.7)
Physical activity, No. of steps	5577 (2742)
Baseline total gray matter volume, mm^3	590 000 (54 000)
Geriatric Depression Scale score	3.2 (2.8)
FHS-CVD	31.7 (17.7)
Antihypertensive medication, No. (%)	90 (49.5)
SBP, mm Hg	138.7 (16.6)
BMI[a]	26.7 (4.7)
History of diabetes, No. (%)	18 (9.9)
Current smoker, No. (%)	6 (3.3)

Abbreviations: Aβ, β-amyloid; *APOE ε4*, apolipoprotein E *ε4*; BMI, body mass index; DVR, distribution volume ratio; FHS-CVD, Framingham Heart Study cardiovascular disease risk score; FLR, frontal, lateral temporal and parietal, and retrosplenial regions; PET, positron emission tomography; SBP, systolic blood pressure.

[a] Calculated as weight in kilograms divided by height in meters squared.

To examine whether the variance explained by physical activity in these models overlapped with the variance explained by systemic vascular risk, we re-ran models 1 and 2 and included the 3-way interaction of FHS-CVD, Aβ, and time. The associations remained significant, such that physical activity continued to be significantly associated with Aβ-related PACC decline (β, 0.03; 95% CI, 0.02-0.05; $P < .001$) and gray matter volume loss (β, 434.70; 95% CI, 148.30-721.10; $P = .004$). Interestingly, in these models, the interaction of FHS-CVD, Aβ, and time was also significant, both for PACC (β, −0.04; 95% CI, −0.06 to −0.02; $P < .001$) and gray matter volume loss (β, −483.41; 95% CI, −855.63 to −111.20; $P = .01$) (eTable 1 in the Supplement). These findings suggest that physical activity and vascular risk have independent and additive effects on Aβ-related cognitive decline and neurodegeneration.

To examine the anatomy underlying the significant association of physical activity with Aβ-related neurodegeneration (model 2), we carried out an exploratory whole-brain analysis examining the interaction of physical activity, Aβ, and time on regional cortical thinning. After adjusting for covariates and applying familywise error correction for multiple comparisons, we observed that greater engagement in physical activity was associated with slower Aβ-related cortical thinning in medial temporal (entorhinal cortex), insula, lateral temporal, and medial parietal regions (**Figure 3**). Given the previously reported association of physical activity with hippocampal volume,[7,41,42] we also examined the association of physical activity with Aβ-related hippocampal volume loss, adjusting for covariates, including intracranial volume. In this model, physical activity did not moderate the association of Aβ burden with hippocampal atrophy (β, 3.40; 95% CI, −0.27 to 7.07; $P = .07$). There was also no association of physical activity (physical activity × time) with hippocampal atrophy when the 3-way interaction was removed (β, −0.89; 95% CI, −5.12 to 3.34; $P = .68$).

In post hoc analyses, we decomposed the PACC into its constituent measures and assessed the longitudinal association of each measure with the 3-way interaction of physical activity, Aβ burden, and time, adjusting for covariates. Here we found that greater physical activity was significantly associated with slower Aβ-related decline in the Free and Cued Selective Reminding Test, Wechsler Memory Scale–Revised Logical Memory delayed recall, and Mini-Mental State Examination but not Wechsler Adult Intelligence Scale–Revised Digit Symbol Coding Test (eTable 2 in the Supplement).

Discussion

In this prospective study of clinically normal older adults, we observed that higher levels of daily physical activity attenuated the negative association of elevated Aβ burden with longitudinal cognitive decline and gray matter volume loss. Adjusting for vascular risk did not significantly change these associations. Notably, in these models, lower vascular risk was independently associated with slower Aβ-related cognitive decline and gray matter volume loss. Together, these findings suggest that greater engagement in physical activity may be protective against Aβ-related cognitive decline and neurodegeneration in asymptomatic older adults.

Our findings are consistent with a rich literature suggesting that greater engagement in physical activity is associated with a lower risk for dementia due to AD.[15,17,18,20] Importantly, these associations remained significant after adjusting for vascular risk, supporting the view that the protective effect of physical activity on cognitive decline and neurodegeneration does not solely occur via mechanisms related to vascular risk. The finding of independent associations of vascular risk and physical activity with Aβ-related cognitive decline and neurodegeneration suggest that interventional approaches that target both physical activity and management of vascular risk factors may have additive beneficial effects on delaying the progression of AD in asymptomatic individuals.

Follow-up regional analyses suggested that greater physical activity preferentially attenuated Aβ-related cortical thinning in the entorhinal cortex, lateral temporal cortex, insula, and medial parietal regions. Many of these regions have been implicated in episodic memory[43] and AD-related neurodegeneration.[44] Interestingly, when we decomposed the PACC into its constituent measures, we found significant associations with tests assessing memory but not processing speed. This regional pattern may reflect protection against Aβ-related tau deposition or perhaps regional variations in neurotrophic support. Further studies that address the spread of tau pathology and the regional variations in neurotrophin signaling are needed to help disentangle these possibilities. Despite prior studies suggesting that hippocampal volume is larger in those with greater physical activity,[7,9,41,42] we did not observe a significant association of physical activity with Aβ-related hippocampal volume loss. This may be because of the amount of follow-up data available or the known difficulty in accurately measuring hippocampal volume. Alternatively, it may be that associations are specific to hippocampal subregions[45] that were not examined in the present study.

Table 2. Associations of Physical Activity and β-Amyloid (Aβ) Burden With Longitudinal Cognitive Decline and Neurodegeneration

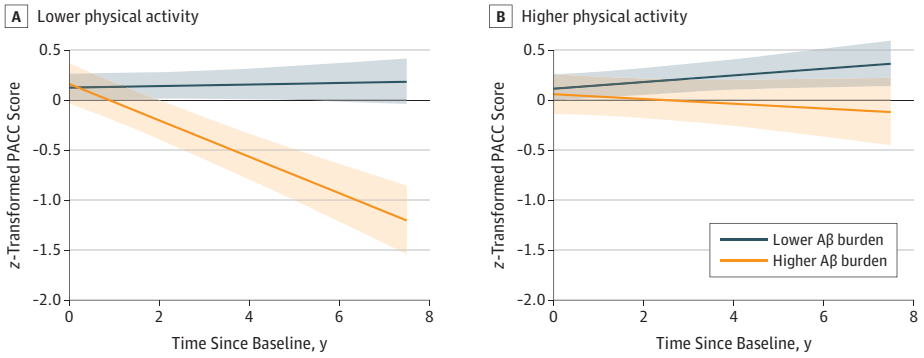
Covariate	β Estimate (95% CI)	*t* Statistic	*P* Value
Model 1[a]			
PA × Aβ × time	0.03 (0.02 to 0.05)	3.771	<.001
PA × time	0.03 (0.01 to 0.05)	2.615	.009
Aβ × time	−0.07 (−0.09 to −0.05)	−6.710	<.001
Age × time	−0.02 (−0.04 to −0.003)	−2.250	.02
Male sex × time	0.01 (−0.03 to 0.05)	0.427	.67
Education × time	−0.004 (−0.02 to 0.02)	−0.411	.68
APOE ε4 status × time	0.04 (−0.003 to 0.09)	1.821	.07
PA × Aβ	−0.02 (−0.09 to 0.06)	−0.395	.69
PA	0.01 (−0.08 to 0.09)	0.139	.89
Aβ	−0.06 (−0.14 to 0.03)	−1.222	.22
Age	−0.12 (−0.20 to −0.04)	−2.826	.005
Male sex	−0.21 (−0.37 to −0.04)	−2.457	.02
Education	0.18 (0.10 to 0.26)	4.452	<.001
APOE ε4 carrier	0.09 (−0.10 to 0.28)	0.938	.35
Time	−0.03 (−0.06 to −0.002)	−2.146	.03
Model 2[b]			
Aβ × PA × time	482.07 (189.40 to 774.74)	3.185	.002
PA × time	131.12 (−207.07 to 469.31)	0.750	.45
Aβ × time	−714.67 (−1058.11 to −371.22)	−4.023	<.001
Age × time	−354.27 (−693.53 to −15.02)	−2.019	.04
Male sex × time	28.78 (−859.38 to 916.95)	0.063	.95
Education × time	−110.92 (−441.44 to 219.60)	−0.649	.52
APOE ε4 status × time	401.21 (−354.24 to 1156.67)	1.027	.31
ICV × time	−77.19 (−523.26 to 368.87)	−0.335	.74
PA × Aβ	−39.88 (−3359.28 to 3279.53)	−0.023	.98
PA	1289.69 (−2303.75 to 4883.13)	0.696	.49
Aβ	−2368.67 (−6259.74 to 1522.40)	−1.181	.24
Age	−11 409.96 (−15 082.23 to −7737.69)	−6.028	<.001
Male sex	11 338.78 (1681.01 to 20 996.55)	2.278	.02
Education	1351.84 (−2256.06 to 4959.73)	0.727	.47
APOE ε4 carrier	2922.86 (−5429.52 to 11 275.24)	0.679	.50
ICV	44 211.94 (39 336.91 to 49 086.96)	17.595	<.001
Time	−2789.53 (−3318.31 to −2260.76)	-10.199	<.001

Abbreviations: *APOE ε4*, apolipoprotein E ε4; ICV, intracranial volume; PA, physical activity.

[a] The following equation was used for model 1: Preclinical Alzheimer Cognitive Composite ~ PA × Aβ × Time + Covariates × Time.

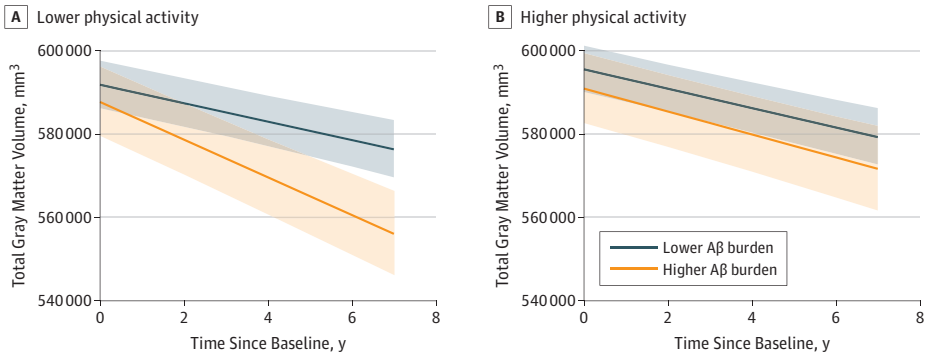
[b] The following equation was used for model 2: Gray Matter Volume ~ PA × Aβ × Time + Covariates × Time.

Figure 1. Interactive Associations of Physical Activity and β-Amyloid (Aβ) Burden on Cognitive Decline



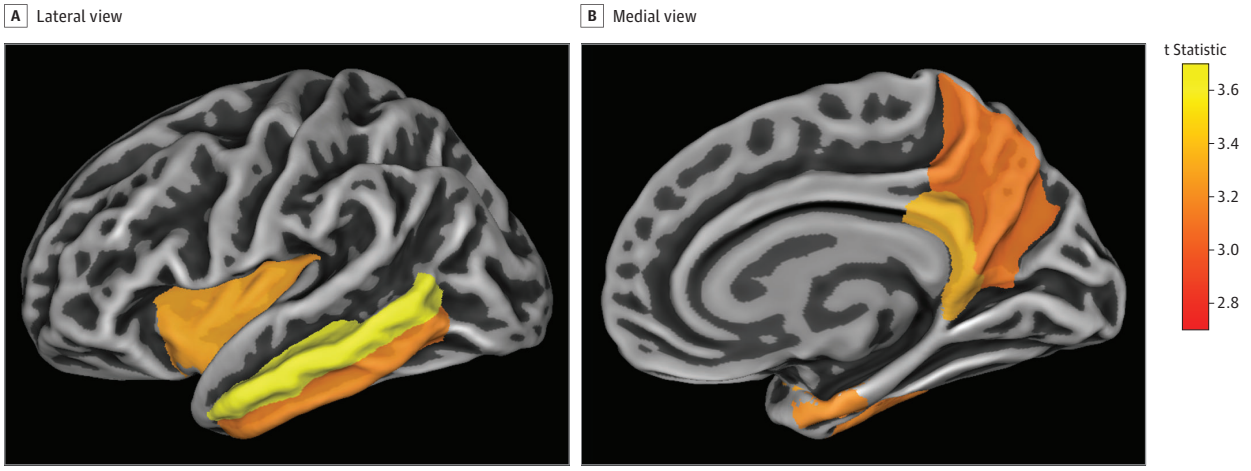
For visualization purposes, modeled longitudinal change in a cognitive composite (Preclinical Alzheimer Cognitive Composite [PACC]) is depicted in individuals with lower (A) and higher (B) levels of physical activity. To create the 2 groups, we used the values that correspond to 1 SD below and above the group mean (2900 steps per day and 8300 steps per day, respectively). Lower and higher Aβ burden groups were created using the median Aβ levels in Aβ-negative and Aβ-positive groups, which correspond to a distribution volume ratio value of 1.1 and 1.9, respectively. The plots demonstrate that greater physical activity protects against Aβ-related cognitive decline (physical activity × Aβ × time; $P < .001$). Shaded regions represent the 95% CIs.

Figure 2. Interactive Associations of Physical Activity and β-Amyloid (Aβ) Burden on Gray Matter Volume Loss



For visualization purposes, modeled longitudinal gray matter volume loss is depicted in individuals with lower (A) and higher (B) levels of physical activity. To create the 2 groups, we used the values that correspond to 1 SD below and above the group mean (2900 steps per day and 8300 steps per day, respectively). Lower and higher Aβ burden groups were created using the median Aβ levels in Aβ-negative and Aβ-positive groups, which correspond to a distribution volume ratio value of 1.1 and 1.9, respectively. The plots demonstrate that greater physical activity protects against Aβ-related neurodegeneration (physical activity × Aβ × time; *P* = .002). Shaded regions represent the 95% CIs.

Figure 3. Physical Activity Moderates the Association of β-Amyloid (Aβ) Burden on Regional Cortical Thinning



FreeSurfer-defined regions were averaged across left and right hemispheres. Greater physical activity was associated with slower rates of Aβ-related cortical thinning in medial and lateral temporal regions, medial parietal regions, and the insula. Color bars indicate the *t* statistic for the interaction of physical activity, Aβ, and time on longitudinal cortical thickness. The models are adjusted for age, sex, years of education, apolipoprotein E ε4 status, and their interactions with time. Regions shown have a *P* value less than .005 after familywise error correction for multiple comparisons.

The mechanism(s) underlying the protective effect of physical activity on Aβ-related longitudinal cognition and regional cortical thinning remains unclear. Possibilities include increased cerebral blood flow,[46] reduced inflammation,[47] increased fibronectin type III domain-containing protein 5/irisin,[48] and the upregulation of neuroprotective signaling molecules, such as brain-derived neurotrophic factor[41,47] and vascular endothelial growth factor.[41,46] Several recent human and animal studies have suggested that physical activity may modify AD pathology directly.[8,10-13] However, we did not observe a cross-sectional association of physical activity with Aβ burden in our cohort, which is consistent with several other findings,[49,50] including a previous study from our group that used a self-report measure of physical activity.[51] It is possible that an association may emerge when examining longitudinal measures of physical activity and Aβ burden.

Strengths and Limitations

Our study has several strengths. Physical activity was measured objectively with a pedometer, thereby alleviating concerns related to recall bias. In addition, our participants are well-characterized clinically and with multimodal imaging. However, consideration of the study sample is critical to the interpretation and generalizability of the findings. The Harvard Aging Brain Study excludes participants with cortical infarcts, symptomatic stroke, uncontrolled diabetes, and unstable hypertension, and therefore, our study sample likely underrepresents those with very high levels of cerebrovascular disease. In addition, most participants in HABS

have at least some advanced education and therefore likely have high cognitive reserve. Other limitations include that physical activity was only assessed at baseline and for a limited period (up to 7 days), leaving open the question of whether participants with higher levels of physical activity also had a history of greater physical activity over the course of their lifetime. In addition, the pedometers used in this study did not classify the duration, intensity, or type of physical activity in which participants engaged (ie, aerobic vs anaerobic). Therefore, it remains unknown whether participants with higher levels of physical activity met the recently released physical activity guidelines of at least 150 minutes of moderate to vigorous physical activity per week.[52] Future studies are needed to address the duration, intensity, and type of physical activity that is necessary to mitigate Aβ-related cognitive decline and neurodegeneration.

Conclusions

The present findings suggest that greater engagement in physical activity is protective against Aβ-related cognitive decline and neurodegeneration in asymptomatic older adults. Importantly, these associations were distinct from the associations of lower vascular risk with slower Aβ-related cognitive decline and neurodegeneration. Together, these findings support interventions that target both physical activity and management of vascular risk factors as a means of delaying cognitive decline and neurodegeneration in preclinical AD. These lifestyle interventions could be coupled with anti-Aβ or anti-tau treatments when they become available.

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