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Physical activity as a modifiable risk factor in preclinical Alzheimer's disease

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Physical inactivity is a recognized modifiable risk factor for Alzheimer's disease (AD), yet its relationship with progression of AD pathology in humans remains unclear, limiting the effective translation into prevention trials. Using pedometer-measured step counts in cognitively unimpaired older adults, we demonstrated an association between higher physical activity and slower cognitive and functional decline in individuals with elevated baseline amyloid. Importantly, this beneficial association was not related to lower amyloid burden at baseline or longitudinally. Instead, higher physical activity was associated with slower amyloid-related inferior temporal tau accumulation, which significantly mediated the association with slower cognitive decline. Dose–response analyses further revealed a curvilinear relationship, where the associations with slower tau accumulation and cognitive decline reached a plateau at a moderate level of physical activity (5,001–7,500 steps per day), potentially offering a more approachable goal for older sedentary individuals. Collectively, our findings support targeting physical inactivity as an intervention to modify the trajectory of preclinical AD in future prevention trials, and further suggest that preferentially enrolling sedentary individuals with elevated amyloid may maximize the likelihood of demonstrating a protective effect of physical activity on tau accumulation and cognitive and functional decline in early AD.

It is estimated that nearly half of AD cases worldwide are attributable to modifiable risk factors[1–3]. Physical inactivity, in particular, plays a prominent role in the USA and Europe[1,2]. Although animal studies support a benefit of physical activity on AD progression[4,5], important knowledge gaps remain in human literature, limiting the effective translation into AD prevention trials. Most existing observational studies rely on self-reported physical activity[6–12], which is prone to recall bias and misreporting, especially in populations with or at risk for cognitive impairment. In addition, most studies focused on the clinical syndrome of AD[7,9,12–14], with few directly examining core AD biomarkers[15–21], and even fewer have done so longitudinally[22,23]. A clearer understanding of how objectively measured physical activity is associated with the progression of AD neuropathology is essential, particularly during the preclinical period, when there is likely the greatest potential to modify disease trajectory.

With the increasing popularity of digital wearables, daily step count has become an easily accessible and understood measure of physical

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Table 1 | Participant characteristics

	All participants *n*=296	Longitudinal PiB subgroup *n*=241	Longitudinal tau subgroup *n*=172
Age at baseline, years, mean (s.d.)	72.3 (7.2)	72.0 (7.5)	70.9 (7.5)
Female, *n* (%)	175 (59)	143 (59)	100 (58)
Education, years, mean (s.d.)	15.8 (3.0)	16.0 (3.0)	16.1 (2.9)
APOE ε4 carriers, *n* (%)	81 (28)	66 (28)	48 (28)
Mean steps per day (s.d.)	5,719 (2,954)	5,762 (2,961)	5,888 (2,870)
Baseline PiB PET FLR DVR, PVC, mean (s.d.)	1.38 (0.4)	1.37 (0.4)	1.35 (0.4)
Baseline Aβ positive, *n* (%)	88 (30)	67 (28)	44 (26)
Baseline cortical gray matter volume, mm^3, mean (s.d.)	420,306 (42,135)	421,218 (42,783)	424,958 (44,209)
Baseline ICV-adjusted hippocampal volume, mm^3, mean (s.d.)	7,501 (739)	7,496 (748)	7,538 (756)
Baseline PACC5 *z*-score, mean (s.d.)	−0.6 (1.5)	−0.6 (1.6)	−0.5 (1.6)
No. of longitudinal PACC assessments, median (IQR; range)	9 (6–11; 2–14)	9 (7–11; 4–14)	10 (8–12; 4–14)
Duration of cognitive follow-up, years, median (IQR; range)	9.2 (5.3–11.8; 0.9–14.2)	10.4 (7.0–12.2; 2.8–14.2)	11.0 (8.1–12.7; 3.4–14.2)
No. of longitudinal PiB PET scans, median (IQR; range)	–	3 (2–4; 2–6)	–
Duration of PiB PET follow-up, years, median (IQR; range)	–	5.3 (3.3–8.0; 1.5–13.3)	–
Baseline ITC tau PET SUVR, PVC, mean (s.d.)	–	–	1.46 (0.2)
No. of longitudinal tau PET scans, median (IQR; range)	–	–	3 (2–3; 2–5)
Duration of tau PET follow-up, years, median (IQR; range)	–	–	5.0 (3.0–5.5; 1.3–10.5)
Time between baseline and first tau PET, years, mean (s.d.)	–	–	2.2 (1.5)

APOE ε4, apolipoprotein E ε4 allele; DVR, distribution volume ratio; FLR, frontal, lateral temporal and parietal, and retrosplenial regional uptake; ICV, intracranial volume; IQR, interquartile range; PiB, Pittsburgh compound-B; SUVR, standardized uptake value ratio.

activity. Emerging literature suggests that higher step counts are linked to lower all-cause mortality[24,25]. Our previous study demonstrated that higher step counts in cognitively unimpaired (CU) older adults with elevated baseline beta-amyloid (Aβ) burden were associated with slower prospective cognitive decline[26], supporting a potential protective role of physical activity in the preclinical stage of AD. However, it remains unknown whether this protective association with cognition is mediated by differences in AD neuropathology burden, or what levels of physical activity are associated with slower cognitive decline.

The current study addressed these questions by leveraging an expanded Harvard Aging Brain Study (HABS) cohort of CU older individuals with pedometer-measured physical activity, longitudinal Aβ and tau positron emission tomography (PET) data, and annual cognitive assessments up to 14 years. We examined whether physical activity is associated with slower cognitive and functional decline through different rates of Aβ and tau accumulation. We further examined the dose–response associations with physical activity levels to help inform future AD prevention trials and public health policies.

Results

Participant characteristics and longitudinal trajectories

The current study examined 296 participants from HABS who were CU at baseline and followed longitudinally[27]. Cognition and function were assessed annually using the Preclinical Alzheimer's Cognitive Composite-5 (PACC5) and Clinical Dementia Rating[28] Sum of Boxes (CDR-SOB) scores, respectively. Global Aβ and inferior temporal cortex (ITC) tau burdens were measured longitudinally in a subset of participants (Aβ $n = 241$; tau $n = 172$), with participants undergoing their first tau scan at 2.2 ± 1.5 years after baseline because the technique was introduced mid-study. Table 1 summarizes the participant characteristics and longitudinal follow-up. The unadjusted longitudinal trajectories for global Aβ, ITC tau, PACC5 and CDR-SOB are shown in Extended Data Fig. 1. For illustration purposes only, to more clearly visualize the individual trajectories, the data were plotted according to high versus low baseline Aβ burden in columns and physical activity (pedometer-measured mean steps per day) in rows, defined by above and below the median values.

Baseline associations with physical activity

We first examined the associations between physical activity and baseline demographics, imaging and cognitive variables. There was a negative association between physical activity and age (Spearman's $r = -0.27$, $P < 0.001$). Males had greater physical activity than females (Sex [males compared to females]: $\beta = 927$ [95% confidence intervals 247 to 1,607], $P = 0.008$). There were no significant associations between physical activity and education ($r_{partial} = 0.08$, $P = 0.16$), or baseline Aβ burden ($r_{partial} = -0.004$, $P = 0.95$), adjusting for age and sex. There was a significant interaction between lower baseline physical activity and elevated Aβ on greater initial ITC tau burden, adjusting for age, sex, years of education and time interval between study baseline and first tau scan (Physical activity × Aβ: $\beta = -0.19$ [−0.30 to −0.08], $P = 0.001$) (Extended Data Fig. 2). There was no additional independent association between baseline physical activity and initial ITC tau burden (Physical activity: $\beta = -0.06$ [−0.18 to 0.05], $P = 0.28$). Importantly, there were no interactive or independent associations of initial Aβ and tau burden with baseline physical activity, adjusting for the same covariates (Aβ × ITC tau: $\beta = -0.04$ [−0.15 to 0.07], $P = 0.44$; Aβ: $\beta = 0.10$ [−0.07 to 0.28], $P = 0.25$; ITC tau: $\beta = 0.01$ [−0.21 to 0.22], $P = 0.96$) (Extended Data Fig. 3). There were also no significant interactive (Physical activity × Aβ) or independent effects of physical activity on baseline PACC5 (Physical activity × Aβ: $\beta = 0.003$ [−0.07 to 0.08], $P = 0.93$; Physical activity: $\beta = 0.003$ [−0.07 to 0.08], $P = 0.92$). Baseline associations with CDR-SOB were not examined because participants were clinically unimpaired at baseline.

Physical activity associations with longitudinal Aβ

For primary analyses, we examined the effects of baseline physical activity on longitudinal imaging and cognitive measures. Using a

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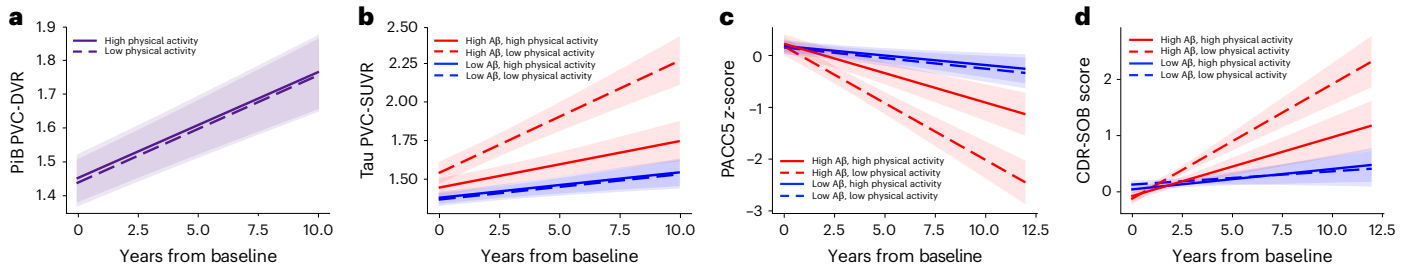

Fig. 1 | Associations of baseline physical activity with longitudinal Aβ, tau and cognition. a, Linear mixed effects model revealed no association between baseline physical activity and longitudinal Aβ burden ($\beta = -0.0006$ [−0.01 to 0.01], $P = 0.92$; $n = 241$). **b**–**d**, By contrast, there were significant interactions between baseline physical activity and Aβ burden on longitudinal ITC tau burden (**b**), longitudinal cognition measured with PACC5 (**c**) and longitudinal functional decline measured with CDR-SOB scores (**d**). Individuals with high baseline physical activity and elevated Aβ (solid red line) showed slower ITC tau accumulation ($\beta = -0.13$ [−0.19 to −0.06], $P < 0.001$; $n = 172$) (**b**), slower PACC5 decline ($\beta = 0.10$ [0.05 to 0.16], $P < 0.001$; $n = 296$) (**c**) and slower CDR-SOB progression ($\beta = -0.14$ [−0.22 to −0.05], $P = 0.001$; $n = 296$) (**d**). Statistical significance was assessed using two-tailed *t*-tests, with $P < 0.05$ considered statistically significant without adjustment for multiple comparisons. Baseline physical activity (mean steps per day) and Aβ burden were modeled as continuous variables. To visualize the model results, the estimated trajectories based on representative levels of low versus high baseline physical activity and (for tau, PACC5 and CDR-SOB models) low versus high baseline Aβ burden are presented, with error bands representing 95% confidence intervals for the estimated trajectories. Low and high physical activity are represented by −1 and +1 s.d. relative to the mean (low, 2,800 steps per day; high, 8,700 steps per day). Low and high Aβ are represented, for illustration purposes, by the mean Aβ burden of Aβ-negative (PiB PVC-DVR = 1.17) and Aβ-positive (PiB PVC-DVR = 1.85) participants, respectively. The numbers of participants contributing longitudinal data to each 2.5-year segment for the respective statistical models are summarized in Extended Data Table 5.

linear mixed effects model, we found no association between baseline physical activity and longitudinal Aβ burden (Physical activity × Time: $\beta = -0.0006$ [−0.01 to 0.01], $P = 0.92$) (Fig. 1a).

Physical activity–Aβ interactions on longitudinal tau, cognition

We then examined the interactive associations between baseline physical activity and Aβ burden on longitudinal cognition and function. Baseline Aβ was modeled as a continuous variable to leverage the full dynamic range of global Aβ burden[29]. Consistent with our earlier work[26], this larger HABS sample with extended follow-up showed a significant physical activity by Aβ interaction on longitudinal PACC5, whereby higher physical activity was associated with slower Aβ-related PACC5 decline (Physical activity × Aβ × Time: $\beta = 0.10$ [0.05 to 0.16], $P < 0.001$; Fig. 1c). In addition, there was an independent association between higher physical activity and slower PACC5 decline (Physical activity × Time: $\beta = 0.06$ [0.004 to 0.12], $P = 0.04$). We further extended our previous findings and identified a significant physical activity by Aβ interaction on longitudinal CDR-SOB, whereby higher physical activity was associated with slower Aβ-related functional decline (Physical activity × Aβ × Time: $\beta = -0.14$ [−0.22 to -0.05], $P = 0.001$) (Fig. 1d). There was no additional main effect of physical activity on CDR-SOB progression (Physical activity × Time: $\beta = -0.05$ [−0.13 to 0.04], $P = 0.29$).

We then addressed the question of whether the associations between physical activity and cognitive and functional decline were mediated by differences in tau pathology. We found a concordant interaction, whereby higher baseline physical activity was associated with attenuated Aβ-related ITC tau accumulation (Physical activity × Aβ × Time: $\beta = -0.13$ [−0.19 to −0.06], $P < 0.001$) (Fig. 1b). There was additionally an independent association between higher physical activity and slower tau accumulation (Physical activity × Time: $\beta = -0.07$ [−0.13 to −0.003], $P = 0.04$). Moderated mediation analysis demonstrated that slower ITC tau accumulation fully mediated the association between higher physical activity and slower PACC5 decline in individuals with elevated baseline Aβ (mediated effect: $\beta = 0.59$ [0.32 to 0.91], $P < 0.001$; direct effect: $\beta = 0.11$ [−0.30 to 0.52], $P = 0.61$; 84% mediated) (Fig. 2a). For CDR-SOB, slower ITC tau accumulation partially mediated the association between higher physical activity and slower CDR-SOB progression in individuals with elevated baseline Aβ ($\beta = -0.43$ [−0.71 to −0.20], $P < 0.001$; 40% mediated) (Fig. 2b). There remained a significant direct effect of physical activity on functional decline ($\beta = -0.64$ [−1.16 to −0.13], $P = 0.01$). In individuals with low baseline Aβ, there were no significant total or mediated effects of physical activity on PACC5 decline or CDR-SOB progression ($P > 0.75$).

Sensitivity analyses

The interaction between baseline physical activity and Aβ on longitudinal tau, PACC5 and CDR-SOB remained significant in sensitivity analyses assessing for possible confounds (Table 2): (1) using a more stringent physical activity cutoff excluding days that registered fewer than 1,000 steps; (2) using Aβ and tau PET data without partial volume correction (PVC); (3) including only participants age <70 years to minimize potential confounding effects of advanced age (the negative association between physical activity and age was absent in this age <70 subgroup; Spearman's $r = -0.01$, $P = 0.93$); (4) adjusting for the season of physical activity measurement, self-reported physical activity, systemic vascular risk and depressive symptoms; (5) excluding participants who developed mild cognitive impairment or dropped out of the study within the first 2 years of follow-up; and (6) adjusting for baseline tau, PACC or CDR-SOB in their respective models to account for physical activity effects on baseline outcome measures.

Physical activity levels on Aβ-related changes in tau, cognition

Lastly, we examined the dose–response associations between levels of physical activity and longitudinal tau accumulation, cognitive and functional decline. Ordinal levels of physical activity were defined using cutoffs adapted from ref. 30, which were modified to better suit the lower activity levels in older adults and to ensure an adequate number of participants in each subgroup (Extended Data Table 1): 'inactive' (≤3,000 per day), 'low activity' (3,001–5,000 steps per day), 'moderate activity' (5,001–7,500 steps per day) and 'active' (≥7,501 steps per day). Participant characteristics across physical activity levels are summarized in Extended Data Table 2. Higher physical activity levels were associated with younger age, but baseline demographics, imaging and cognitive variables were not significantly different across physical activity groups adjusting for age and sex. In linear mixed effects models using the inactive subgroup as reference, all higher levels of physical activity were associated with slower Aβ-related ITC tau accumulation, PACC5 decline and CDR-SOB progression, except that the slower CDR-SOB progression in the low activity group did not reach statistical significance (Table 3). To better visualize the dose–response relationships, we modeled the physical activity level by Aβ interaction on extracted

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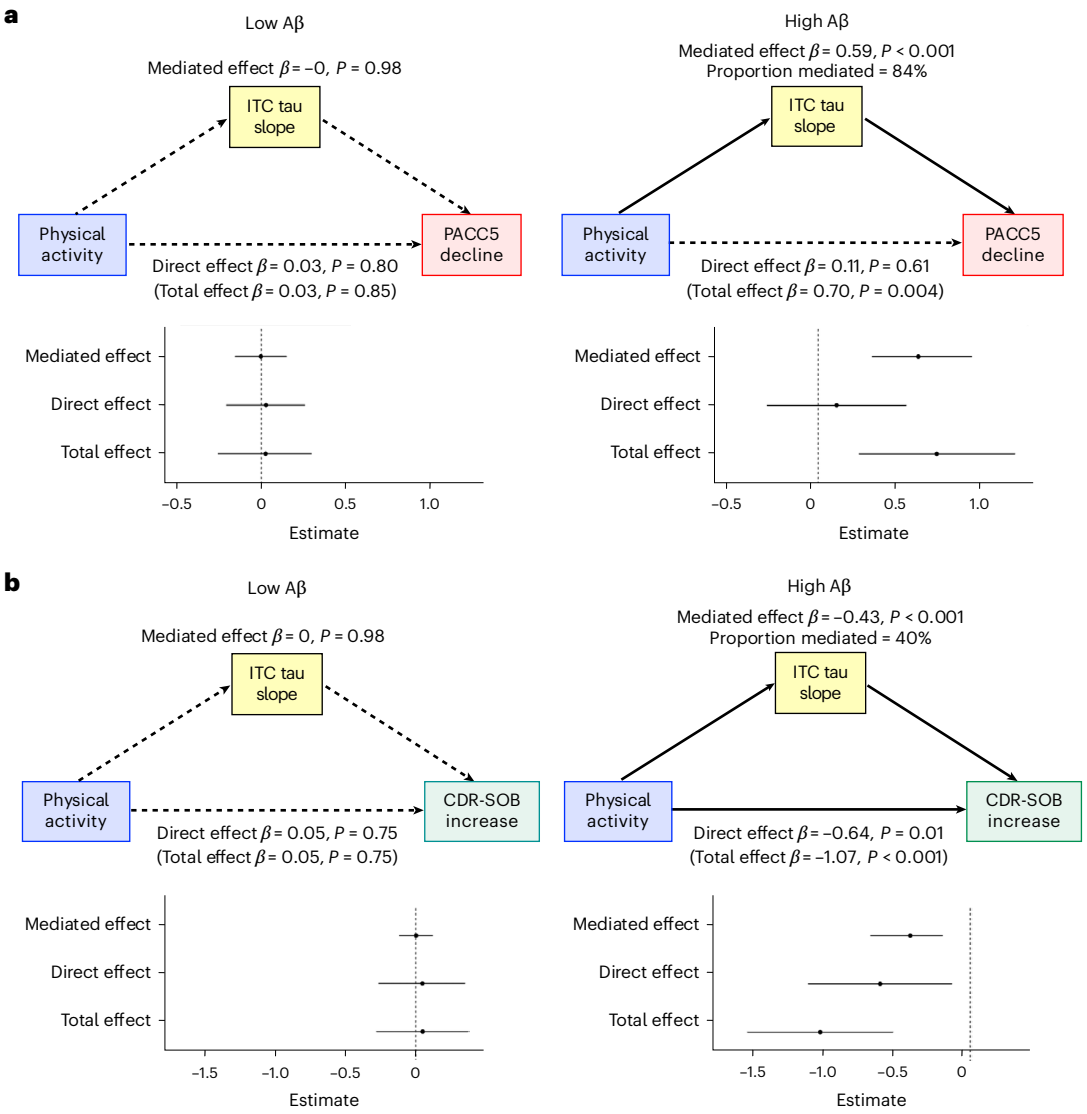

Fig. 2 | Tau accumulation mediated the associations between physical activity and cognitive/functional decline in preclinical AD. a,**b**, Individual slopes for ITC tau, PACC5 (**a**) and CDR-SOB (**b**) were extracted from linear mixed effects models for moderated mediation analyses ($n = 172$; in participants who have both longitudinal tau and cognitive data). We modeled physical activity (mean steps per day) as predictor, ITC tau slope as mediator and PACC5 or CDR-SOB slopes as outcome. Both physical activity and Aβ burden were modeled as continuous variables in the mediation models. For the moderation analyses, low and high levels of Aβ burden were represented by the mean Aβ burden of Aβ-negative (PiB PVC-DVR = 1.17) and Aβ-positive (PiB PVC-DVR = 1.85) participants, respectively. Statistical testing was performed using a quasi-Bayesian Monte Carlo method based on 10,000 simulations to generate the estimates and 95% confidence intervals, with two-tailed $P < 0.05$ considered statistically significant without adjustment for multiple comparisons. Results demonstrated that at an elevated level of baseline Aβ burden, slower ITC tau accumulation fully mediated the association between higher physical activity and slower PACC5 decline ($\beta = 0.59$ [0.32 to 0.91], $P < 0.001$, 84% mediated) (**a**) and partially mediated the association between higher physical activity and slower CDR-SOB progression ($\beta = -0.43$ [−0.71 to −0.20], $P < 0.001$, 40% mediated) (**b**). In individuals with low baseline Aβ burden, there were no significant total or mediated effects of physical activity on PACC5 decline (total effect: $\beta = 0.03$ [−0.27 to 0.31], $P = 0.85$; mediated effect: $\beta = -0.002$ [−0.16 to 0.15], $P = 0.98$) or CDR-SOB progression (total effect: $\beta = 0.05$ [−0.28 to 0.37], $P = 0.75$; mediated effect: $\beta = 0.001$ [−0.11 to 0.12], $P = 0.98$). The error bars represent the 95% confidence intervals for the estimated mediated, direct and total effects.

ITC tau, PACC5 and CDR-SOB slopes (Fig. 3). In individuals with elevated baseline Aβ, even low levels of physical activity (3,001–5,000 steps per day) were associated with substantially slower rates of tau accumulation, cognitive and functional decline. There were further attenuations of tau accumulation and cognitive and functional decline at moderate activity (5,001–7,500 steps per day), with similar rates in the active group (≥7,501 steps per day), suggesting a plateauing of effects.

To help contextualize the associations between physical activity levels and cognitive and functional decline, we used the linear mixed effects models from Table 3 to estimate the longitudinal PACC5 and CDR-SOB trajectories at representative levels of low versus high baseline Aβ burden (represented by the mean global Aβ burden of Aβ-negative and Aβ-positive participants, respectively) across physical activity levels (Extended Data Fig. 4). For individuals with elevated Aβ, from baseline to the median cognitive follow-up of 9 years, estimated PACC5 z-scores declined by 2.5 (inactive), 1.5 (low activity), 1.1 (moderate activity) and 1.2 (active) points, respectively. Compared to inactive individuals, cognitive decline was lower by 40%, 54% and 51% across increasing physical activity levels. Over the same period, estimated CDR-SOB scores increased by 2.2 (inactive), 1.4 (low activity), 1.2 (moderate activity) and 1.1 (active) points in individuals with elevated Aβ. Compared to inactivity, there were 34%, 45% and 51%

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Table 2 | Sensitivity analyses for the baseline physical activity and Aβ interaction on longitudinal tau and cognitive decline

	ITC tau			PACC5			CDR-SOB		
	n	Estimate	*P* value	*n*	Estimate	*P* value	*n*	Estimate	*P* value
Primary analyses	172	−0.13 [−0.19 to −0.06]	<0.001	296	0.10 [0.05 to 0.16]	<0.001	296	−0.14 [−0.22 to −0.05]	0.001
Sensitivity analyses									
Excluding days under 1,000 steps	161	−0.10 [−0.16 to −0.04]	<0.001	280	0.10 [0.04 to 0.15]	<0.001	280	−0.13 [−0.21 to −0.05]	0.002
Using non-PVC PET data	172	−0.09 [−0.15 to −0.03]	0.006	296	0.10 [0.04 to 0.16]	<0.001	296	−0.14 [−0.22 to −0.06]	<0.001
Including only age <70	87	−0.27 [−0.36 to −0.18]	<0.001	124	0.24 [0.16 to 0.32]	<0.001	124	−0.36 [−0.45 to −0.27]	<0.001
Adjusting for season, self-reported physical activity, FHS-CVD, and GDS	130	−0.10 [−0.17 to −0.04]	0.003	244	0.10 [0.04 to 0.16]	<0.001	244	−0.13 [−0.22 to −0.04]	0.003
Excluding mild cognitive impairment within 2 years	171	−0.12 [−0.18 to −0.05]	<0.001	280	0.10 [0.04 to 0.16]	<0.001	280	−0.11 [−0.19 to −0.02]	0.01
Adjusting for baseline outcome measure	172	−0.08 [−0.13 to −0.02]	0.007	296	0.10 [0.04 to 0.16]	<0.001	296	−0.14 [−0.22 to −0.06]	<0.001

Sensitivity analyses were conducted using linear mixed effects models to examine the robustness of our primary findings of significant interactions between baseline physical activity (continuous) and Aβ (continuous) on longitudinal ITC tau, PACC5 and CDR-SOB. All models adjusted for age, sex, education, their interactions with time and any additional covariates specified for the respective sensitivity analysis. All models included random intercepts and slopes. Statistical significance of the Physical activity × Aβ × Time interaction was assessed using two-tailed *t*-tests, with $P < 0.05$ considered statistically significant without adjustment for multiple comparisons. FHS-CVD, office-based Framingham Heart Study cardiovascular disease risk; GDS, Geriatric Depression Scale.

slower functional decline across increasing physical activity levels. Using −1.5 PACC5 *z*-score as a threshold for impaired cognition[31], CU individuals with elevated Aβ were estimated to reach this threshold for cognitive worsening at 6.5 (inactive), 9.6 (low activity), 13.6 (moderate activity) and 12.7 (active) years from baseline, respectively. Similarly, using a CDR-SOB increase of 1.5 as a threshold for clinically meaningful functional decline in early AD[32], individuals with elevated Aβ were estimated to reach this threshold at 7.1 (inactive), 10.2 (low activity), 11.9 (moderate activity) and 13.6 (active) years from baseline, respectively.

Discussion

In an expanded cohort of 296 CU older adults with pedometer-measured physical activity, baseline Aβ PET and up to 14 years of annual cognitive follow-up, we replicated our previous finding of a protective association between higher physical activity and slower Aβ-related cognitive decline, and further demonstrated a similar relationship with functional decline. Importantly, we demonstrated that these associations with cognition and function were not related to differences in cross-sectional or longitudinal Aβ pathology. Instead, in a subset of 172 individuals with longitudinal tau PET, we found a new and concordant association between higher physical activity and slower Aβ-related early neocortical tau accumulation, which significantly mediated the relationships with slower cognitive and functional decline. Our dose–response analyses further suggest that the largest incremental differences between increasing physical activity levels were observed in the most sedentary individuals, with plateauing associations with both tau and cognition at a moderate level of activity (5,001–7,500 steps per day), potentially offering a more approachable physical activity goal for older sedentary individuals. Collectively, our results support targeting physical inactivity, either alone or in combination with anti-Aβ therapy, as an intervention in future prevention trials to slow the progression of tau pathology and delay the onset of cognitive and functional decline in preclinical AD.

Many observational studies have demonstrated associations between physical activity and reduced risks of cognitive impairment and AD. However, most existing literature relied on self-reported physical activity, which is susceptible to recall bias or misreporting, especially among populations with or at risk for cognitive impairment. A few longitudinal studies have examined the effects of objectively measured physical activity (by pedometer or accelerometer) in older adults without dementia and found associations with reduced risks of cognitive decline, AD or all-cause dementia[13,33–35]. Our previous study[26] extended these findings to CU individuals and demonstrated an association between higher step counts and slower prospective cognitive decline in preclinical AD. The current study replicated this finding using a considerably larger cohort, including younger individuals in late midlife, and over a substantially longer duration of follow-up (median of 9.3 years instead of 6 years). The latter is notable given that some observational studies found diminished benefits of physical activity with longer follow-up time[36–38]. We further expanded our cognitive findings and demonstrated a similar association with slower Aβ-related functional decline measured by CDR-SOB, which has been frequently used as an outcome measure in AD clinical trials[39,40].

There is growing interest in understanding whether physical activity associations with reduced cognitive decline are mediated by differences in AD neuropathology, with most studies focusing on Aβ. Although animal models suggest that physical exercise may reduce Aβ burden[4,41], evidence in human studies has been mixed. A few cross-sectional studies found associations between higher self-reported physical activity and lower Aβ pathology[15–20]. Other large CU cohort studies have found no associations between self-reported physical activity and cross-sectional or longitudinal Aβ PET burden[21–23]. Consistent with the latter, our study found no associations between pedometer-measured physical activity and baseline or longitudinal Aβ burden, suggesting that our findings were unlikely to be driven by different rates of Aβ accumulation.

By contrast, we demonstrated a new relationship between physical activity and longitudinal tau burden, where higher step counts were associated with slower early neocortical tau accumulation in individuals with elevated baseline Aβ. We further demonstrated that reduced tau accumulation significantly mediated the associations between higher physical activity and slower cognitive decline in preclinical AD. These observational findings support a potential role for physical activity in modifying the AD pathological cascade, which remains to be confirmed in future randomized clinical trials. Interestingly, although tau change fully mediated the effects of PACC5 decline (84% mediated), it only partially mediated (40%) the effects on CDR-SOB progression, with a significant remaining direct effect. This suggests that a substantial portion of the physical activity association with slower functional decline was mediated by mechanisms besides tau-related injury, which should be further examined in future studies (for example, physical frailty and functional reserve).

A small number of prior studies have investigated the cross-sectional associations between physical activity and tau. A few have found associations between higher physical activity and lower cerebrospinal fluid phosphorylated tau or phosphorylated tau to Aβ42 ratios[19,20,42,43]. Others have examined the cross-sectional relationships

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Table 3 | Dose–response associations between physical activity levels and Aβ-associated longitudinal ITC tau accumulation, PACC5 decline and CDR-SOB progression

Reference: Inactive (≤3,000 steps per day)	ITC tau		PACC5		CDR-SOB	
	Estimate	*P* value	Estimate	*P* value	Estimate	*P* value
Low activity (3,001–5,000 steps per day)	−0.21 [−0.41 to −0.02]	0.03	0.20 [0.04 to 0.36]	0.02	−0.16 [−0.36 to 0.04]	0.11
Moderate activity (5,001–7,500 steps per day)	−0.30 [−0.52 to −0.08]	0.007	0.26 [0.09 to 0.43]	0.003	−0.23 [−0.44 to −0.03]	0.03
Active (≥7,501 steps per day)	−0.39 [−0.58 to −0.21]	<0.001	0.28 [0.12 to 0.44]	<0.001	−0.29 [−0.49 to −0.10]	0.004

We used linear mixed effects models to examine the interactive effects of baseline physical activity levels (ordinal) and Aβ (continuous) on longitudinal ITC tau, PACC5 and CDR-SOB, adjusting for age, sex, education, their interactions with time, and included random intercepts and slopes. Statistical significance for the Activity level×Aβ×Time interaction was assessed using two-tailed *t*-tests, using the inactive subgroup (≤3,000 steps per day) as reference. $P < 0.05$ was considered statistically significant without adjustment for multiple comparisons.

between self-reported physical activity and tau PET with mixed results. Two studies found that higher self-reported physical activity was associated with lower cross-sectional tau burden[44,45]. However, a larger study of CU individuals found no cross-sectional associations between self-reported physical activity and regional tau burden and no significant mediation of physical activity effects on cross-sectional cognition by tau[21]. It is likely that our use of objectively measured physical activity and, more importantly, our longitudinal design increased our sensitivity to detect a relationship between physical activity and early aggregated tau pathology in preclinical AD.

Although our rich longitudinal PET and cognitive data are a substantial strength, this study remains observational, and we are unable to rule out potential reverse causality (that is, individuals with prodromal AD may have reduced physical activity from their underlying disease). However, several factors reduce this likelihood. First, there were no associations between physical activity (independently or interactively with Aβ) and baseline cognition. Although there was a physical activity and Aβ interaction on baseline tau burden, a reversed relationship was not observed—higher cross-sectional Aβ or tau burden (individually or interactively) was not associated with lower baseline physical activity. In addition, the association between higher physical activity and slower longitudinal ITC tau accumulation remained significant after adjusting for the effects of lower initial tau burden. Our findings were further unchanged in sensitivity analyses that excluded participants who developed mild cognitive impairment (or dropped out) within the first 2 years of follow-up, reducing the likelihood that our findings were driven by individuals with impending cognitive and/or clinical changes. Although these observations are reassuring, it is important to emphasize that randomized clinical trials are ultimately needed to establish causal relationships between physical activity and preclinical AD progression.

There is substantial public interest in understanding how much physical activity is needed to improve health. Although this question cannot be directly answered by observational studies, we examined the dose–response associations between physical activity levels and progression of tau and cognitive decline, which may help inform the design of future AD prevention trials. Our results suggest that even a modest increase in physical activity may be associated with attenuated tau accumulation and cognitive decline in sedentary individuals on a preclinical AD trajectory: compared to inactive individuals, low levels of physical activity were associated with 34% to 40% slower cognitive and functional decline over 9 years (the median duration of cognitive follow-up). Notably, the associations with more favorable tau and cognitive trajectories reached a plateau by moderate levels of physical activity (5,001–7,500 steps per day), which may be a less daunting goal for sedentary older adults than the popular goal of 10,000 steps per day commonly referenced in lay media. Several studies have demonstrated a similar curvilinear relationship between step count and all-cause mortality or dementia[24,25,34], with benefits plateauing around 6,000–8,000 steps per day for older adults and around 8,000–10,000 steps per day for younger populations, suggesting a ceiling effect. Specifically for the current study, our findings suggest that there may be a limit to how much increasing physical activity may dampen the detrimental effects of Aβ on tau and cognitive and functional decline, and support designing clinical trials that combine lifestyle interventions with anti-Aβ therapy to more effectively modify the trajectory of preclinical AD.

Future studies are needed to understand the mechanisms underlying the protective effects of physical activity on Aβ-related tau pathology and cognitive decline. Although adjusting for composite vascular risk did not impact our findings, better vascular fitness remains a likely potential mechanism. Greater physical activity has been linked to better cardiopulmonary fitness[46,47], which has, in turn, been shown to dampen the negative association between Aβ and cognition[48]. In addition, greater accelerometer physical activity in CU older adults has been associated with greater cerebral blood flow[49], which has been shown to be impaired early in the AD cascade[50]. Lastly, greater physical activity and/or exercise have also been shown in animal models and humans to decrease inflammation and upregulate VEGF-A, BDNF and Irisin[51–55], which are candidate pathways with the potential to modulate Aβ effects on tau and cognition[56–60].

The current study has several limitations. As discussed above in greater detail, this is an observational study and we are unable to fully rule out the potential influence of reverse causality. Future randomized clinical trials are required to establish causal relationships. Although our pedometer-measured physical activity is a strength, it was only assessed at baseline and did not classify the duration, intensity or history of physical activity, nor capture nonstep-related physical activity (for example, swimming, resistance training). Future studies with longitudinal physical activity measurements (for example, with actigraphy) and life course physical activity data are needed to better delineate temporal trends. The HABS cohort consists of highly educated, predominantly non-Hispanic white individuals and excluded those with symptomatic cerebrovascular disease and poorly controlled vascular risk factors at baseline, which may limit the generalizability of our findings to other populations.

In summary, leveraging a deeply phenotyped CU cohort with objectively measured physical activity and longitudinal neuroimaging and cognitive assessments, we demonstrated an association between higher physical activity and attenuated accumulation of early neocortical tau pathology, which significantly mediated the relationship with slower cognitive and functional decline in preclinical AD. Our dose–response analyses further suggest that the incremental differences in associations between higher physical activity levels and slower tau and cognitive changes were greatest for the most sedentary individuals, and appeared to reach a plateau by moderate levels of physical activity (5,001–7,500 steps per day). Taken together, our findings support targeting physical inactivity as a strategy in future randomized clinical trials to modify the trajectory of tau and cognition in preclinical AD, and potentially provide an easily understood and more attainable physical activity goal for older sedentary individuals at high risk of cognitive decline. Our results further suggest that AD prevention trials using activity-based interventions may benefit from preferentially enrolling

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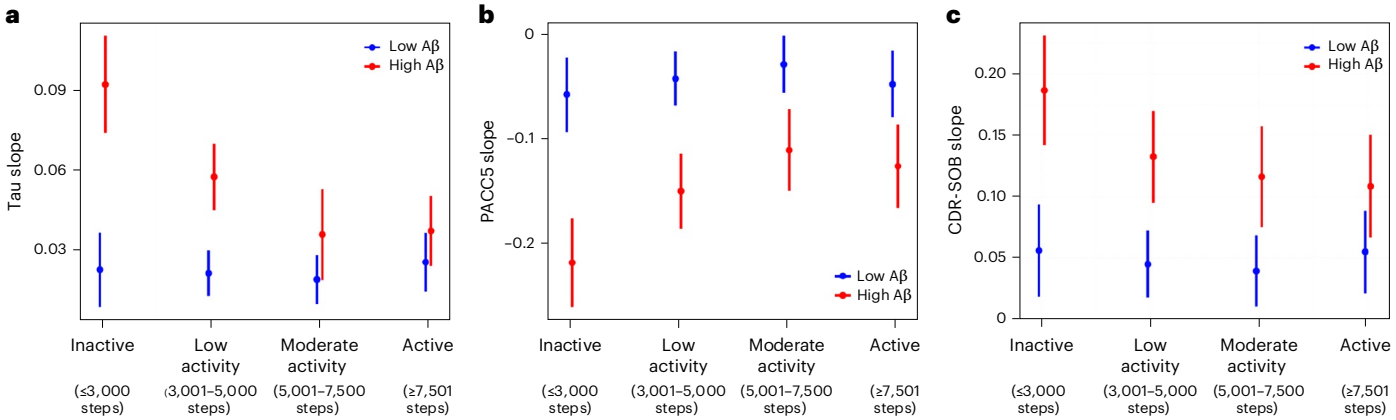

Fig. 3 | Physical activity levels and changes in tau and cognition in preclinical AD. a–**c**, Using extracted slopes for ITC tau ($n = 172$) (**a**), PACC5 (**b**) and CDR-SOB (**c**) (PACC5 and CDR-SOB, $n = 296$), we examined the interactive effects of baseline physical activity level (ordinal) and Aβ burden (continuous) using linear regression models. Levels of physical activity (ordinal) were defined as inactive (≤3,000 steps), low activity (3,001–5,000 steps), moderate activity (5,001–7,500 steps) and active (≥7,501 steps). The number of individuals in each physical activity subgroup included in the tau, PACC5 and CDR-SOB analyses are summarized in Extended Data Table 1. Aβ burden was modeled as a continuous variable. For illustration purposes, low and high Aβ are represented by the mean Aβ burden of Aβ-negative (PiB PVC-DVR = 1.17) and Aβ-positive (PiB PVC-DVR = 1.85) participants, respectively. The error bars represent the 95% confidence intervals for the estimated effects of physical activity levels on tau and cognitive slopes at representative levels of low and high Aβ burden. Results demonstrate that in individuals with elevated baseline Aβ, even low levels of physical activity (3,001–5,000 steps) were associated with substantially slower rates of tau accumulation and cognitive decline compared to inactive individuals. There were further attenuations of tau accumulation and cognitive and functional decline at moderate activity (5,001–7,500 steps per day), with similar rates in the active group (≥7,501 steps per day).

sedentary individuals with elevated Aβ levels, longer trial durations, and consideration of examining biomarker endpoint with tau PET, because these approaches may maximize the likelihood of demonstrating a protective effect of physical activity on early AD progression.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-025-03955-6.

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Methods

Participants

The current study included 296 participants from HABS[27], a community cohort of individuals aged 50 to 90 who were CU at baseline (global CDR[28] of 0, education-adjusted Mini-Mental State Examination[61] score of 27 or greater, and Logical Memory IIa Delayed Recall performance in the normal range[62]). Inclusion and exclusion criteria and study protocol have been detailed previously[27] and published online (https://www.synapse.org/Synapse:syn53910452/wiki/631007). We examined all eligible participants with baseline physical activity measurement, Aβ PET imaging and at least two longitudinal cognitive assessments. Extended Data Fig. 5 illustrates that of 348 eligible HABS participants at baseline, 50 were excluded from the current study because of missing data. Importantly, the included group did not differ in demographics or baseline cognition (Extended Data Table 3). Baseline characteristics by self-reported sex are summarized in Extended Data Table 4. Additional subsets of participants were used in the longitudinal Aβ PET ($n = 241$) and tau PET ($n = 172$) analyses (Table 1). Data were collected from April 2010 to February 2025. The Mass General Brigham Institutional Review Board approved the HABS protocol and procedures, and all participants signed a written informed consent before the completion of any study procedures.

Physical activity

Baseline physical activity was measured using a waistband-mounted pedometer (HJ-720ITC; Omron Healthcare), which has been shown to accurately measure step counts[63]. Participants were asked to wear the pedometer for seven consecutive days during waking hours. Using previously published cutoffs for pedometer data quality, days that registered <100 or >30,000 steps were excluded[26,64]. We included participants with at least 4 days of recorded activity within these cutoffs[64]. Mean steps per day were used as the primary measure of physical activity, which was square-root transformed to account for skewness.

PET imaging

Detailed methods have been published previously[65]. Briefly, global Aβ burden was measured using PiB PET as a DVR across a composite of frontal, lateral temporal and parietal, and retrosplenial regional uptake defined using FreeSurfer (v.6.0). ^{18}F-Flortaucipir PET was introduced mid-study to measure tau, with participants undergoing their first ^{18}F-flortaucipir PET at 2.2 ± 1.5 years after baseline. Tau was measured as standardized uptake value ratio in the ITC, a prominent site of early neocortical tau accumulation in preclinical AD associated with emerging cognitive impairment[65]. Both Aβ and tau PET used cerebellar gray matter as reference and the geometric transfer matrix method for PVC[66]. Sensitivity analyses were performed using PET data without PVC.

Cognitive assessment

Cognition was assessed using the PACC5 (ref. 67), a composite *z*-score that includes the Mini-Mental State Examination[61], Wechsler Adult Intelligence Scale-Revised Digit Symbol Coding[68], Wechsler Memory Scale-Revised Logical Memory delayed recall[62], Free and Cued Selective Reminding Test (free recall plus total recall)[69] and Category Fluency Test[70]. Functional decline was assessed using the CDR-SOB score.

Statistical analyses

We used R v.4.3.1. Continuous variables were *z*-transformed before analysis to obtain standardized effect sizes, with the exception of PACC5 (already a *z*-score). For illustrative purposes, nonstandardized variables were used when plotting model results to enhance interpretability ('ggplot2' and 'plot_model' packages). A two-tailed $P < 0.05$ was considered statistically significant.

We first examined the associations between baseline physical activity with age and sex. We also examined the associations between physical activity and baseline imaging and cognitive variables, adjusting for age and sex.

For primary analyses, we used linear mixed effects model ('nlme' package) to examine: (1) the effects of physical activity on longitudinal Aβ; and (2) the interactive effects of physical activity and baseline Aβ on longitudinal ITC tau, PACC5 and CDR-SOB, respectively. Baseline Aβ was modeled as a continuous variable to leverage the full dynamic range of Aβ burden, which has been shown to capture additional information on preclinical AD progression over a dichotomous approach and avoids variability introduced by positivity threshold selection, which remains an evolving area of research[29]. Time was operationalized as years from baseline assessment. We adjusted for age, sex, *APOE* ε4 carrier status, education, their interactions with time, and included random intercepts and slopes. There were no significant *APOE* ε4 effects on longitudinal tau, PACC5 or CDR-SOB; therefore, *APOE* was removed from these models to include three participants with missing genotype data.

We conducted the following sensitivity analyses to examine the robustness of our primary findings: (1) using a more stringent physical activity cutoff excluding days that registered <1,000 steps; (2) using PET data without PVC; (3) including only participants age <70 years to minimize potential confounding effects of advanced age; (4) adjusting for additional potential confounders and their interactions with time—season of physical activity measurement, total self-reported physical activity (CHAMPS questionnaire[71]), systemic vascular risk (office-based Framingham Heart Study cardiovascular disease risk score[72]) and depressive symptoms (geriatric depression scale); (5) excluding participants who developed mild cognitive impairment ($n = 5$) or dropped out ($n = 11$) within the first 2 years of follow-up to reduce the potential for reverse causality; and (6) adjusting for baseline tau, PACC or CDR-SOB in their respective models to account for physical activity effects on baseline outcome measures.

We further used moderated mediation analysis ('mediation' package[73]) to examine whether tau accumulation mediated the interactive effects of physical activity and Aβ on PACC5 decline or CDR-SOB progression. Individual slopes of ITC tau, PACC5 and CDR-SOB change were extracted from unadjusted linear mixed models with time as the only predictor, including both random slopes and intercepts. We conducted moderated mediation analysis with PACC5 or CDR-SOB slope as outcome, ITC tau slope as mediator, baseline Aβ (continuous) as moderator, and adjusted for age, sex, education and time interval between baseline Aβ and first tau scan. To examine for moderation effects by baseline Aβ, mediation models were run at both low and high levels of baseline Aβ, which were represented by the mean Aβ burden of Aβ-negative (PiB PVC-DVR = 1.17) and Aβ-positive (PiB PVC-DVR = 1.85) participants respectively, defined using the conventional Aβ-positivity threshold (PiB PVC-DVR = 1.324). Statistical testing was performed using a quasi-Bayesian Monte Carlo method based on 10,000 simulations to generate the estimates and 95% confidence intervals.

Lastly, we examined the dose–response relationships between the levels of physical activity and associations with Aβ-related tau accumulation and cognitive decline. Ordinal levels of physical activity were defined using cutoffs adapted from ref. 30: inactive (≤3,000 steps per day), low activity (3,001 to 5,000 steps per day), moderate activity (5,001 to 7,500 steps per day) and active (≥7,501 steps per day). Using linear mixed effects models, we examined the interactive effects of baseline physical activity levels (ordinal) and Aβ (continuous) on longitudinal ITC tau, PACC5 and CDR-SOB, adjusting for the same covariates. To contextualize the effects of physical activity on cognitive decline, we used the model results to estimate predicted PACC5 and CDR-SOB trajectories across physical activity levels at representative levels of low versus high baseline Aβ burden, which were represented by the mean global Aβ burden of Aβ-negative (PiB PVC-DVR = 1.17) and Aβ-positive participants (PiB PVC-DVR = 1.85) respectively as described above. We calculated the predicted changes in PACC5 and CDR-SOB scores from baseline to

year 9 (median duration of cognitive follow-up) and calculated the percent difference in decline across higher activity levels compared to inactive individuals. Lastly, we used literature-derived thresholds for cognitive impairment (lower than −1.5 PACC5 *z*-score[31]) and clinically meaningful functional decline in early AD (increase of 1.5 points on CDR-SOB[32]) to estimate the time from baseline to these thresholds of cognitive and functional worsening for individuals with elevated Aβ across physical activity levels.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Deidentified data from HABS can be requested online (https://www.synapse.org/habs). Details of the request process have been published previously[27] and include the completion of an online data request form and acceptance of the terms of a data use agreement. The approval process is primarily designed to ensure that the proposed purpose of the data request is consistent with the data use agreement and would not pose a risk to the HABS participants. The most important restriction of use is to not attempt to re-identify the participants in any way. Other requirements include agreement to abide by human subject research policies, only using the data for the project detailed in the data request (separate requests can be made for additional projects), no commercialization of the data, and no marketing or fundraising with the data.

Code availability

All statistical analyses and raw figures were generated using R (v.4.3.1), with the following open source packages: car (v.3.1-2), dplyr (v.1.1.2), ggplot2 (v.3.5.1), mediation (v.4.5.0), nlme (v.3.1-162), ppcor (v.1.1), sjPlot (v.2.8.15). No custom code or packages were used in the statistical analyses.

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Author contributions

W.-Y.W.Y., J.S.R., D.M.R., K.A.J., R.A.S. and J.P.C. conceived and/or designed the project. D.R.K., K.P., P.M., C.M., D.M.R., K.A.J., R.A.S. and J.P.C. contributed to the acquisition of data. W.-Y.W.Y., D.R.K., J.S.R., M.J.P., A.P.S., J.J.P., R.A.S. and J.P.C. contributed to data analysis. W.-Y.W.Y., J.S.R., Z.S., J.J.P., S.A.S., R.A.S., D.M.R., K.A.J., R.A.S. and J.P.C. contributed to interpretation of data. W.-Y.W.Y. drafted the initial manuscript. All authors provided substantive contributions to the revisions and approve the final version of the submitted manuscript.

Competing interests

The authors declare no competing interests relevant to the current study. Potential conflicts of interest outside the submitted work are included below. J.J.P. has served as a consultant for Eisai. K.A.J. has served as a consultant for Novartis, Merck and Janssen. R.A.S. has served as a consultant for AbbVie, AC Immune, Acumen, Alector, Apellis, Biohaven, Bristol Myers Squibb, Genentech, Ionis, Janssen, Oligomerix, Prothena, Roche and Vaxxinity over the past 3 years. K.A.J. and R.A.S. have received research funding from Eisai and Eli Lilly for public–private partnership clinical trials but do not have any personal financial relationship with the companies. J.P.C. has served as a consultant for ExpertConnect.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-025-03955-6.

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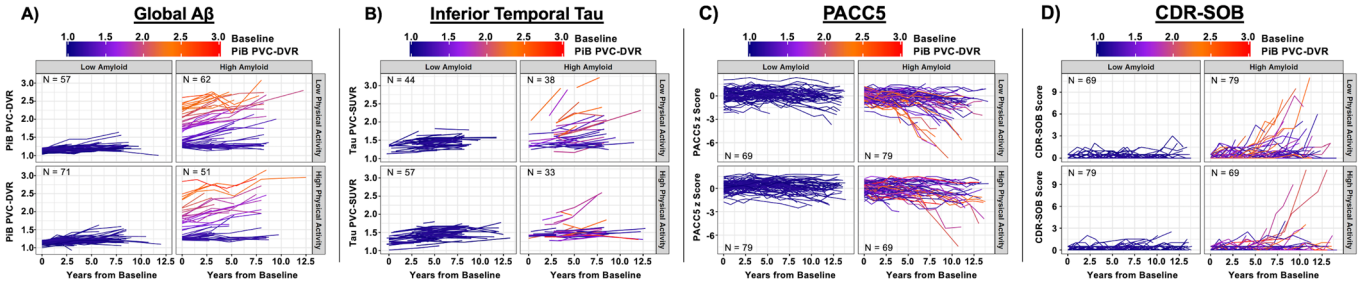

Extended Data Fig. 1 | Individual longitudinal Aβ, tau, PACC5 and CDR-SOB trajectories. Individual trajectories of (**a**) global Aβ, (**b**) inferior temporal cortex (ITC) tau, (**c**) Preclinical Alzheimer's Cognitive Composite-5 (PACC5) scores, and **d**) Clinical Dementia Rating Sum of Boxes (CDR-SOB) scores from all participants are shown without adjustment for any covariates. To allow clear visualization of the individual trajectories, participants were plotted according to high versus low baseline Aβ burden in columns and physical activity (mean steps per day) in rows, defined by above and below the median values. The trajectories are color coded by baseline Aβ burden according to the color bar, with each line representing one participant. The number of participants represented in each facet is provided for reference. The time of baseline PiB PET was used as the study baseline (time = 0). Timing of the first tau PET scan varied across participants (2.2 ± 1.5 years), as tau PET was introduced mid-study when it became available. Aβ = beta-amyloid; DVR = distribution volume ratio; PVC = partial volume correction; PiB = Pittsburgh compound-B; SUVR = standardized uptake value ratio.

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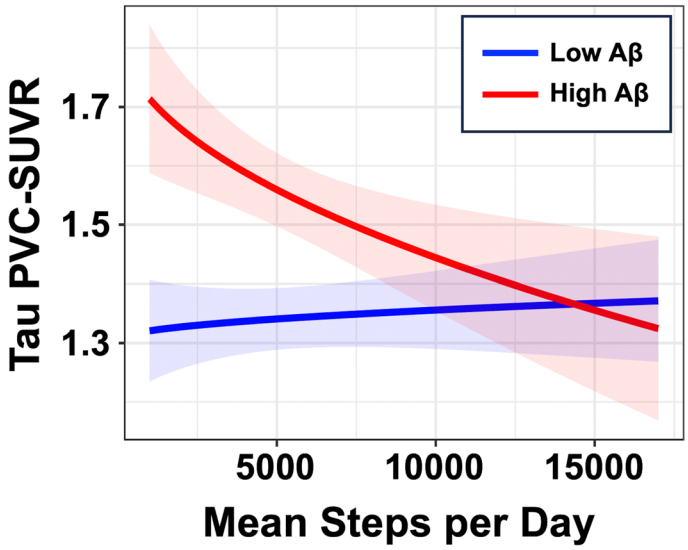

Extended Data Fig. 2 | Interactive association between baseline physical activity and Aβ burden on initial ITC tau burden. Linear regression model revealed a significant interaction between baseline physical activity and Aβ burden on initial inferior temporal cortex (ITC) tau burden (Physical activity*Aβ: β = -0.19 [-0.30 to -0.08], p = 0.001), adjusting for age, sex, years of education, and time interval between study baseline and first tau scan. There was no significant independent effect of physical activity on tau (Physical activity: β = -0.06 [-0.18 to 0.05], p = 0.28). Statistical significance was assessed using two-tailed t-tests, with $p < 0.05$ considered statistically significant without adjustment for multiple comparisons. Physical activity (mean steps per day) was square-root transformed prior to model entry to account for skewness with improvement in model fit (reduced BIC by 2.2). Non-transformed mean steps per day was used to plot the model result to enhance interpretability. Baseline Aβ burden was modeled as a continuous variable. To visualize the model results, the estimated ITC tau burden across the range of baseline physical activity at representative levels of low versus high baseline Aβ burden are presented. Error bands represent the 95% confidence intervals for the estimated tau burden. Low and high Aβ are represented, for illustration purposes, by the mean Aβ burden of Aβ-negative (PiB PVC-DVR 1.17) and Aβ-positive (PiB PVC-DVR 1.85) participants respectively. Aβ = beta-amyloid; DVR = distribution volume ratio; ITC = inferior temporal cortex; PVC = partial volume correction; SUVR = standardized uptake value ratio.

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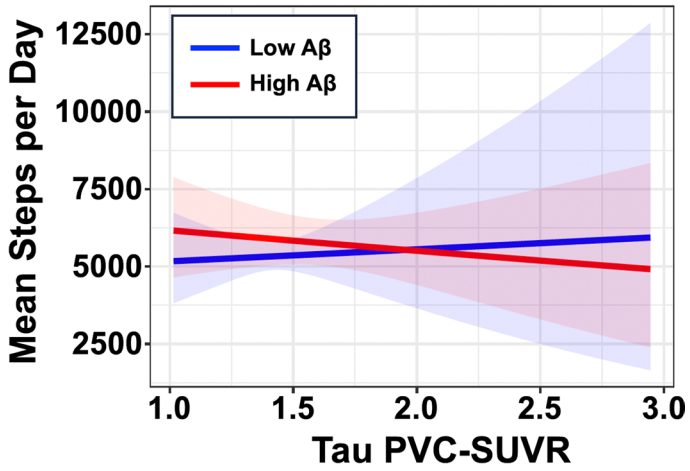

Extended Data Fig. 3 | Interactive association between cross-sectional Aβ and initial ITC tau burdens on baseline physical activity. Linear regression model revealed no significant interaction between cross-sectional Aβ and ITC tau burdens on baseline physical activity (Aβ*ITC tau: β = -0.04 [-0.15 to -0.07], p = 0.44), adjusting for age, sex, years of education, and time interval between study baseline and first tau scan. There were further no significant independent effects of Aβ or ITC tau on baseline physical activity (Aβ: β = 0.10 [-0.07 to 0.28], t = 1.16, p = 0.25; ITC tau: β = 0.01 [-0.21 to 0.22], p = 0.96). Statistical significance was assessed using two-tailed t-tests, with $p < 0.05$ considered statistically significant without adjustment for multiple comparisons. Physical activity (mean steps per day) was square-root transformed prior to model entry, but non-transformed mean steps per day was used to plot the model result to enhance interpretability. Baseline Aβ burden was modeled as a continuous variable. To visualize the model results, the estimated means steps per day across the range of initial ITC tau burden at representative levels of low versus high baseline Aβ burden are presented. Error bands represent the 95% confidence intervals for the estimated mean steps per day. Low and high Aβ are represented, for illustration purposes, by the mean Aβ burden of Aβ-negative (PiB PVC-DVR 1.17) and Aβ-positive (PiB PVC-DVR 1.85) participants respectively. Aβ = beta-amyloid; DVR = distribution volume ratio; ITC = inferior temporal cortex; PVC = partial volume correction; SUVR = standardized uptake value ratio.

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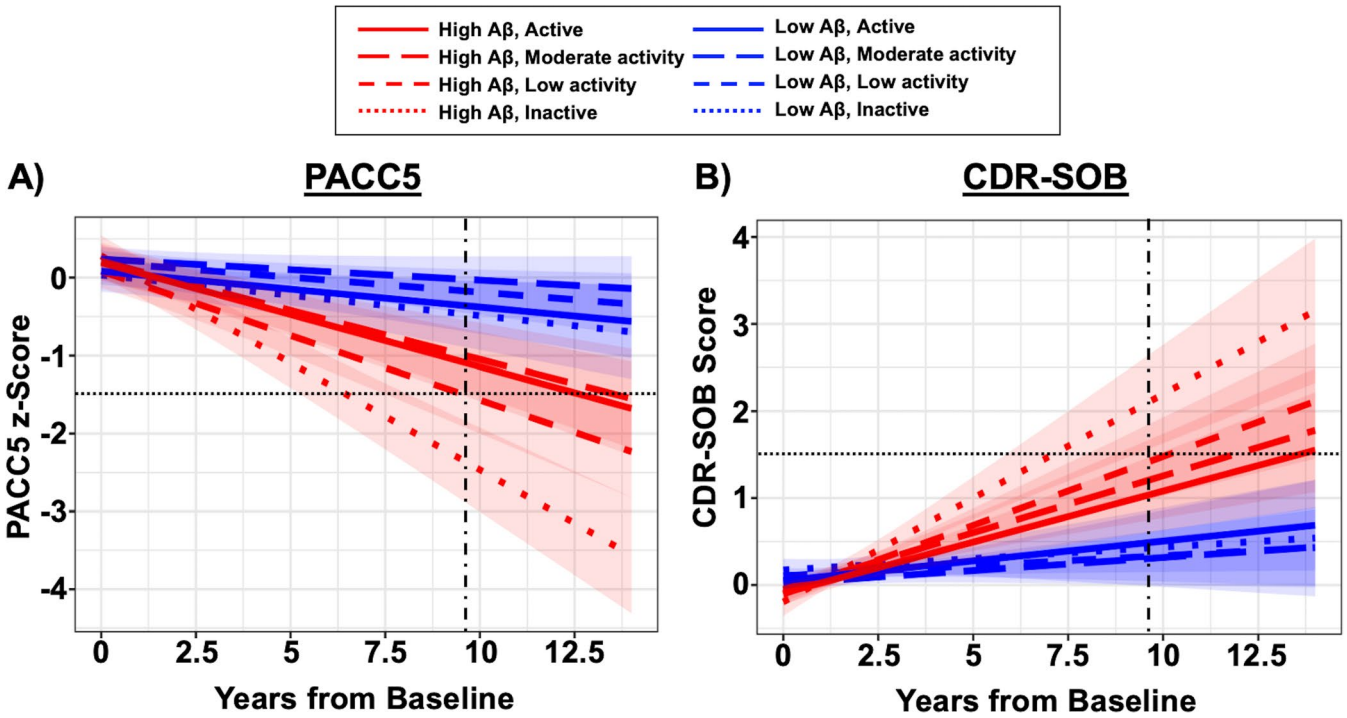

Extended Data Fig. 4 | Association between physical activity levels and baseline Aβ burden on longitudinal (a) PACC5 decline and (b) CDR-SOB progression. Linear mixed effects models revealed interaction between baseline physical activity levels (ordinal) and Aβ burden (continuous) on longitudinal PACC5 decline and CDR-SOB progression. Using the inactive subgroup as reference, all higher levels of physical activity were associated with slower Aβ-related PACC5 decline and CDR-SOB progression, except the slower CDR-SOB progression in the low activity group did not reach statistical significance (Table 3). To visualize the model results, the estimated trajectories based on representative levels of low versus high baseline Aβ burden across physical activity levels are presented, with error bands representing 95% confidence intervals for the estimated trajectories. Low and high Aβ are represented, for illustration purposes, by the mean Aβ burden of Aβ-negative (PiB PVC-DVR 1.17) and Aβ-positive (PiB PVC-DVR 1.85) participants respectively, defined using the conventional Aβ-positivity threshold (PiB PVC-DVR of 1.324). The horizontal dotted line represents thresholds for cognitive impairment (-1.5 PACC5 z-score) and functional decline (1.5 points on CDR-SOB). The vertical dot-dash line represents median duration of cognitive follow-up (9 years). Aβ = β-amyloid; DVR = distribution volume ratio; PiB = Pittsburgh compound-B; PVC = partial volume corrected; SUVR = standardized uptake value ratio.

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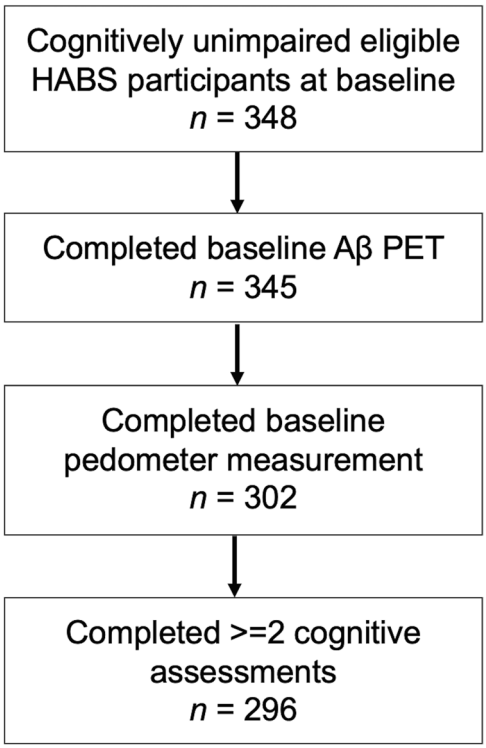

Extended Data Fig. 5 | Participant flow chart.

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Extended Data Table 1 | Number of participants by physical activity levels

Activity Level	Inactive	Low activity	Moderate activity	Active
Steps/day	<=3000	3001-5000	5001-7500	>=7501
N (PACC5; CDR-SOB)	53	90	85	68
N (Tau)	22	57	53	40

The number of participants in each physical activity level included in the tau, PACC5 and CDR-SOB analyses were summarized. CDR-SOB = Clinical Dementia Rating Sum of Boxes; PACC5 = Preclinical Alzheimer's Cognitive Composite-5.

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Extended Data Table 2 | Participant characteristics by baseline physical activity levels

Activity Level Steps/day	Inactive <=3000	Low activity 3001-5000	Moderate activity 5001-7500	Active >7500	*p*	*p* (adjusted for age, sex)
Age at baseline, yr, mean (SD)	76.5 (7.7)	72.63 (6.27)	71.5 (7.5)	69.9 (6.5)	<0.001	-
Females, n (%)	34 (64)	56 (62)	53 (62)	32 (47)	0.15	-
Education, yr, mean (SD)	14.9 (3.3)	16.1 (2.8)	15.9 (3.0)	16.2 (2.8)	0.07	0.14
APOE ε4 carriers, n (%)	20 (38)	22 (25)	22 / 84 (26)	17 (25)	0.34	0.55
Baseline PiB PET FLR DVR, PVC, mean (SD)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	0.79	0.81
Baseline Aβ positive, n (%)	21 (40)	26 (29)	23 (27)	18 (26)	0.37	0.76
Baseline cortical gray matter volume, mm^3, mean (SD)	412769 (44537)	414207 (382450)	425539 (44122)	427930 (41383)	0.07	0.26
Baseline ICV-adjusted hippocampal volume, mm3, mean (SD)	7260 (750)	7541 (688)	7541 (718)	7588 (796)	0.07	0.80
Baseline PACC5 z-score, mean (SD)	-0.1 (0.7)	0.1 (0.7)	0.2 (0.7)	0.0 (0.6)	0.08	0.35

Baseline participant characteristics were compared across levels of physical activity. For continuous variables, statistical comparisons were performed using one-way ANOVA in unadjusted analyses and using linear regression with Type II ANOVA (F-tests) in analyses adjusted for age and sex. For binary variables, statistical comparisons were performed using Pearson's Chi-squared tests in unadjusted analyses and using logistic regression with Type II ANOVA (likelihood ratio chi-squared tests) in analyses adjusted for age and sex. Two-tailed $p<0.05$ was considered statistically significant without adjustment for multiple comparisons. Aβ=β-amyloid; APOE ε4 = apolipoprotein E ε4 allele; DVR = distribution volume ratio; FLR = frontal, lateral temporal and parietal, and retrosplenial regional uptake; ICV = intracranial volume; PACC5 = Preclinical Alzheimer's Cognitive Composite-5; PET = positron emission tomography; PiB = Pittsburgh compound-B; PVC = partial volume corrected; SD = standard deviation.

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Extended Data Table 3 | Participant characteristics of all eligible HABS participants at baseline and those included in the current study

	Eligible HABS Participants at Baseline *n* = 348	Participants Included in Current Study *n* = 296	*p*
Age at baseline, yr, mean (SD)	71.5 (8.0)	72.0 (7.3)	0.42
Females, n (%)	207 (59)	175 (59)	0.93
Education, yr, mean (SD)	15.9 (2.9)	15.8 (3.0)	0.91
APOE ε4 carriers, n (%)	98 (28)	81 (28)	0.83
Baseline PiB PET FLR DVR, PVC, mean (SD)	1.4 (0.4)	1.4 (0.4)	0.74
Baseline Aβ positive, n (%)	98 (28)	88 (30)	0.73
Baseline PACC5 z-score, mean (SD)	0.1 (0.7)	0.1 (0.7)	0.93

For continuous variables, statistical comparisons were performed using two-sample t-tests. For binary variables, statistical comparisons were performed using Pearson's Chi-squared tests. Two-tailed $p < 0.05$ was considered statistically significant without adjustment for multiple comparisons. Aβ=β-amyloid; APOE ε4 = apolipoprotein E ε4 allele; DVR = distribution volume ratio; FLR = frontal, lateral temporal and parietal, and retrosplenial regional uptake; PACC5 = Preclinical Alzheimer's Cognitive Composite-5; PET = positron emission tomography; PiB = Pittsburgh compound-B; PVC = partial volume corrected; SD = standard deviation.

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Extended Data Table 4 | Participant characteristics by sex

	Female *n*=175	Male *n*=121
Age at baseline, yr, mean (SD)	70.8 (7.5)	73.7 (6.7)
Education, yr, mean (SD)	15.7 (2.8)	16.1 (3.2)
APOE ε4 carriers, n (%)	54 (31)	27 (23)
Mean steps per day (SD)	5340 (2597)	6267 (3342)
Baseline PiB PET FLR DVR, PVC, mean (SD)	1.4 (0.4)	1.3 (0.3)
Baseline Aβ positive, n (%)	53 (30)	35 (29)
Baseline PACC5 z-score, mean (SD)	0.2 (0.7)	-0.1 (0.7)

Baseline participant characteristics were summarized by sex. Aβ=β-amyloid; APOE ε4 = apolipoprotein E ε4 allele; DVR = distribution volume ratio; FLR = frontal, lateral temporal and parietal, and retrosplenial regional uptake; PACC5 = Preclinical Alzheimer's Cognitive Composite-5; PET = positron emission tomography; PiB = Pittsburgh compound-B; PVC = partial volume corrected; SD = standard deviation.

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Extended Data Table 5 | Number of participants contributing data to longitudinal analyses across major time segments

		N in Longitudinal Time Segements (Years from Baseline)				
	Overall N	**0 to 2.5**	**2.5 to 5**	**5 to 7.5**	**7.5 to 10**	**10 to 12.5**
Aβ	**241**	241	230	138	102	-
ITC Tau	**172**	69	157	134	102	-
PACC5	**296**	296	280	228	183	136
CDR-SOB	**296**	296	280	226	180	131

The number of participants contributing data to each 2.5-year time segments in the longitudinal Aβ, ITC tau, PACC5, and CDR-SOB analyses were summarized. Aβ=β-amyloid; CDR-SOB = Clinical Dementia Rating Sum of Boxes; PACC5 = Preclinical Alzheimer's Cognitive Composite-5; PET = positron emission tomography; PiB = Pittsburgh compound-B; PVC = partial volume corrected; SD = standard deviation.

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Corresponding author(s): Wai-Ying Wendy Yau and Jasmeer Chhatwal

Last updated by author(s): 07/24/2025

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For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

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☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No custom software was used in data collection.
Data analysis	All statistical analyses and raw figures were generated using R (version 4.3.1), with the following open source packages: car (version 3.1-2), dplyr (version 1.1.2), ggplot2 (version 3.5.1), mediation (version 4.5.0), nlme (version 3.1-162), ppcor (version 1.1), sjPlot (version 2.8.15). No custom code or packages were used in the statistical analyses.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Deidentified data from HABS can be requested online (https://habs.mgh.harvard.edu/researchers/request-data/). Details of the request process have been published previously (Dagley et al., Neuroimage 2017) and include the completion of an online data request form and acceptance of the terms of a data use

agreement. The approval process is primarily designed to ensure that the proposed purpose of the data request is consistent with the data use agreement and would not pose a risk to the HABS participants. The most important restriction of use is to not attempt to re-identify the participants in any way. Other requirements include agreement to abide by human subject research policies, only using the data for the project detailed in the data request (separate requests can be made for additional projects), no commercialization of the data, and no marketing or fundraising with the data.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Harvard Aging Brain Study (HABS) aimed to have a balanced representation of both biological sex (self-report). In the aging population, the proportion of women compared to men is increased. The recruited cohort is comprised of 59% female participants. Sex was adjusted for in all statistical models. Baseline participant characteristic by sex were summarized in Extended Data Table 4. Sex-based analysis will be pursued in a future project.
Reporting on race, ethnicity, or other socially relevant groupings	HABS cohort consists of highly educated and predominantly (83%) non-Hispanic white individuals. We acknowledged in the manuscript and that future studies in more diverse cohorts (including race/ethnicity and education) are needed to improve generalizability of our findings.
Population characteristics	HABS is a community cohort of individuals aged 50 to 90 who were cognitively unimpaired at baseline and followed longitudinally. At study entry, all participants had a global Clinical Dementia Rating (CDR) of 0, education-adjusted Mini-Mental State Examination (MMSE) score of 27 or greater, and Logical Memory IIa Delayed Recall performance within the normal range. Exclusion criteria included a modified Hachinski ischemic score greater than 4, and a history of stroke with persistent neurological deficits.
Recruitment	Participants were recruited from several sources in order to maximize the ethnic, socio-economical and educational diversity of our cohort: 1. Advertisements posted in local community senior centers. 2. The Harvard Cooperative Program on Aging Newsletter, which is distributed to 8,000 older individuals of diverse ethnic backgrounds and the Harvard Medical School Division on Aging Volunteer Roster, which has over 1,500 local older individuals who are interested in participating in research. 3. Print advertisements in "Over Fifty" a local newspaper for older individuals, which highlights research opportunities, and the "Banner", a local newspaper that is focused on the African American population in the suburbs of Boston. 4. The Massachusetts Alzheimer's Disease Research Center (MADRC) database includes a large number of older subjects who have previously participated in cognitive studies and who have indicated the desire to be contacted for future studies. 5. The Alzheimer's Association's TrialMatch Website and Massachusetts Alzheimer's Association's Support Group Network for Research Opportunities.
Ethics oversight	The Mass General Brigham Institutional Review Board (IRB) approved HABS protocol and procedures, and all participants signed a written informed consent prior to the completion of any study procedures. Participants received compensation of between $50 to $200 per study visit, commensurate to the time and potential risks/discomfort involved, as approved by the IRB.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	We included all participants (N=296) with baseline physical activity measurement, amyloid PET imaging, and at least 2 longitudinal cognitive assessments. Extended Data Figure 5 illustrates that out of 348 eligible HABS participants at baseline, 50 were excluded from the current study due to missing data. Importantly, the included group did not differ in demographics or baseline cognition (Extended Data Table 3). Subsets of participants were used in the longitudinal amyloid PET (N=241) and tau PET (N=172) analyses. Data collected from April 2010 through February 2025 were included in the analyses.
Data exclusions	For pedometer data, we used previously published cutoffs for pedometer data quality, and excluded days that registered less than 100 or greater than 30000 steps. We included participants with at least 4 days of recorded activity within these cutoffs to calculate mean steps per day as the primary measure of physical activity.
Replication	We conducted sensitivity analyses to examine the robustness of our primary findings, as described in the manuscript. Direct replication was not pursued as we are not aware of other available data in cognitively unimpaired older adults that included pedometer-measured physical activity and longitudinal amyloid/tau PET imaging and cognitive assessments.
Randomization	Participants were not randomized due to the nature of HABS as an observational cohort study. In our statistical models, we adjusted for age,

Randomization	sex, education, and (in longitudinal amyloid models only) APOE ε4 carrier status. There were no significant APOE ε4 effects on longitudinal tau or cognition; therefore, APOE was removed from these models to include 3 participants with missing genotype data.
Blinding	Study investigators were blinded to the Alzheimer's disease biomarkers, genotype and cognitive status of participants during data collection.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☐	☒ MRI-based neuroimaging

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*

Magnetic resonance imaging

Experimental design

Design type	Structural T1 MRI was used in this study primarily for the purpose of processing and analysis of amyloid and tau PET data. Baseline total cortical grey matter volume and intracranial volume-adjusted hippocampal volume were included in Extended Data Table 2 to illustrate that there were no significant differences across physical activity groups.
Design specifications	*Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.*
Behavioral performance measures	*State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).*

Acquisition

Imaging type(s)	Structural T1 MRI
Field strength	3T
Sequence & imaging parameters	Structural T1-weighted volumetric magnetization-prepared, rapid acquisition gradient echo (MPRAGE) scans were collected using the following parameters: repetition time = 2300ms, echo time = 2.98ms, inversion time = 900ms, flip angle = 9°, 1x1x1.2mm resolution, 0 acceleration
Area of acquisition	Whole brain

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software

To use the structural T1 MRI for PET data processing, region of interest (ROI) labeling was implemented using FreeSurfer v6.0 (http://surfer.nmr.mgh.harvard.edu/). Cortical region of interest measurements were made using the Desikan-Killiany atlas (https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation). Subcortical region of interest measurements were made using the Freesurfer aseg atlas (https://surfer.nmr.mgh.harvard.edu/ftp/articles/fischl02-labeling.pdf)

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If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.

Normalization template

Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.

Noise and artifact removal

Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).

Volume censoring

Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.

Statistical modeling & inference

Model type and settings

Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).

Effect(s) tested

Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference

Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.

(See Eklund et al. 2016)

Correction

Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).

Models & analysis

n/a	Involved in the study
☐	☐ Functional and/or effective connectivity
☐	☐ Graph analysis
☐	☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).

Graph analysis

Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).

Multivariate modeling and predictive analysis

Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.