Received: 26 July 2023 | Revised: 13 October 2023 | Accepted: 23 October 2023

DOI: 10.1002/alz.13556

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Physical activity and brain amyloid beta: A longitudinal analysis of cognitively unimpaired older adults

Michael G. Slee[1] | Stephanie R. Rainey-Smith[1,2,3,4] | Victor L. Villemagne[5,6,7] | James D. Doecke[8] | Hamid R. Sohrabi[1,2,3,9] | Kevin Taddei[2,3] | David Ames[10,11,12] | Vincent Dore[5] | Paul Maruff[10,13] | Simon M. Laws[7,14,15] | Colin L. Masters[10] | Christopher C. Rowe[5,10] | Ralph N. Martins[2,3,9] | Kirk I. Erickson[16] | Belinda M. Brown[1,2,3]

[1]Centre for Healthy Ageing, Healthy Futures Institute, Murdoch University, Murdoch, Western Australia, Australia

[2]School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia, Australia

[3]Australian Alzheimer's Research Foundation, Nedlands, Western Australia, Australia

[4]School of Psychological Science, University of Western Australia, Crawley, Western Australia, Australia

[5]Department of Molecular Imaging & Therapy, Austin Health, Heidelberg, Victoria, Australia

[6]Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[7]Centre for Precision Health, Edith Cowan University, Joondalup, Western Australia, Australia

[8]The Australian e-Health Research Centre, CSIRO, Herston, Queensland, Australia

[9]Department of Biomedical Sciences, Macquarie University, Sydney, New South Wales, Australia

[10]The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, Victoria, Australia

[11]National Ageing Research Institute, Parkville, Victoria, Australia

[12]Academic Unit for Psychiatry of Old Age, University of Melbourne, Carlton, Victoria, Australia

[13]Cogstate Ltd, Melbourne, Victoria, Australia

[14]Collaborative Genomics and Translation Group, School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia, Australia

[15]Curtin Medical School, Curtin University, Bentley, Western Australia, Australia

[16]Department of Psychology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Correspondence
Michael G. Slee, Centre for Healthy Ageing, Murdoch University, 90 South Street, Murdoch, Western Australia 6150, Australia.
Email: Michael.Slee@murdoch.edu.au

Funding information
Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Science and Industry Endowment Fund; Dementia Collaborative Research Centres; Victorian Government's Operational Infrastructure Support program; Australian Alzheimer's Research Foundation;

Abstract

INTRODUCTION: The current study evaluated the relationship between habitual physical activity (PA) levels and brain amyloid beta (Aβ) over 15 years in a cohort of cognitively unimpaired older adults.

METHODS: PA and Aβ measures were collected over multiple timepoints from 731 cognitively unimpaired older adults participating in the Australian Imaging, Biomarkers and Lifestyle (AIBL) Study of Aging. Regression modeling examined cross-sectional and longitudinal relationships between PA and brain Aβ. Moderation analyses examined apolipoprotein E (*APOE*) ε4 carriage impact on the PA-Aβ relationship.

National Health and Medical Research Council; Yulgilbar Foundation

RESULTS: PA was not associated with brain Aβ at baseline ($\beta = -0.001$, $p = 0.72$) or over time ($\beta = -0.26$, $p = 0.24$). *APOE* ε4 status did not moderate the PA-Aβ relationship over time ($\beta = 0.12$, $p = 0.73$). Brain Aβ levels did not predict PA trajectory ($\beta = -54.26$, $p = 0.59$).

DISCUSSION: Our study did not identify a relationship between habitual PA and brain Aβ levels.

KEYWORDS

Alzheimer's disease, amyloid beta, dementia, exercise, genetics, longitudinal, physical activity

Highlights

- Physical activity levels did not predict brain amyloid beta (Aβ) levels over time in cognitively unimpaired older adults (≥60 years of age).
- Apolipoprotein E (*APOE*) ε4 carrier status did not moderate the physical activity–brain Aβ relationship over time.
- Physical activity trajectories were not impacted by brain Aβ levels.

1 | BACKGROUND

The precise cause of Alzheimer's disease (AD) is not known; however, several biomarkers are indicative of AD brain pathology (i.e., amyloid beta [Aβ] plaques and neurofibrillary tangles of hyperphosphorylated tau). Brain Aβ burden quantified via positron emission tomography (PET) imaging, or cerebrospinal fluid sampling for measuring of Aβ and tau species, is considered the current gold-standard AD biomarkers.[1–4] Generally, patients with AD have higher brain Aβ burden when compared to cognitively unimpaired older adults, with high levels of brain Aβ associated with greater, and faster, cognitive decline.[5,6] Estimates from PET data indicate that Aβ may begin accumulating up to two decades before the onset of clinical AD symptoms,[5] thus highlighting a potential window of opportunity for intervention. Genetics is also thought to impact the risk for developing sporadic AD, with carriage of the apolipoprotein E (*APOE*) ε4 allele being the strongest known genetic risk factor.[7]

Physical activity (PA) plays a vital role in healthy brain functioning[8] and has been found to preserve cognition and slow cognitive decline.[9–12] Higher levels of habitual PA have also been associated with a 38% and 24% reduction in AD and all-cause dementia, respectively.[13] Nevertheless, a lack of evidence regarding the causal direction of the PA–dementia relationship has prompted research examining changes in PA prior to diagnosis, that is, do dementia-related brain changes lead to a decrease in PA participation, rather than PA contributing to reduced dementia risk. Indeed, Sabia et al.[14] observed a decline in PA up to 9 years prior to dementia diagnosis, suggesting that reduced PA levels may be a predictive factor for the preclinical phase of dementia.

To elucidate the PA–dementia relationship further, research has focused on understanding the links between PA and brain Aβ. Animal studies have shown convincingly that exercise reduces brain Aβ levels. In contrast, human studies of PA and AD-related brain biomarkers have produced inconsistent findings to date.[10] Numerous studies have found higher PA levels to be inversely associated with Aβ brain load measured using PET imaging,[15–21] whereas other studies have found no such relationship.[22,23] The impact of PA on Aβ accumulation is likely via action on multiple biological pathways. Ineffective insulin and insulin signaling pathways are believed to play a role in decreased Aβ clearance and aggregation.[24,25] Animal studies have also shown that exercise influences enzymes that regulate the amyloidogenic and non-amyloidogenic pathways including β-site APP cleaving enzyme 1 (BACE1)[26–28] and A disintegrin and metalloproteinase domain protein 10 (ADAM-10).[27,29] To date, most studies examining the relationship between PA and brain Aβ in humans have been cross-sectional in design. As brain Aβ is detectable decades prior to the onset of clinical symptoms, the examination of the relationship between PA and brain Aβ using longitudinal measurements is vital to establish temporal relationships and provide insight into how PA levels affect the progression of AD biomarkers.[5,11] Establishing these associations would help encourage the use of PA as part of a long-term strategy in AD prevention.

Several studies examining PA and brain health have also assessed the moderating effect of *APOE* ε4 carriage with mixed results.[30] Most of these studies reported reduced dementia risk at greater levels of PA, regardless of *APOE* ε4 allele status. Nevertheless, although *APOE* ε4 carriage was found to moderate the PA and brain Aβ relationship in some studies,[15,17,18] both carriers and non-carriers have been shown to benefit from higher PA levels.[30] Understanding the moderating effect of *APOE* ε4 status is helpful in determining whether PA will be more effective in reducing AD risk for some individuals compared with others.

The current study uses both cross-sectional and longitudinal observational data to better understand how PA is associated with brain Aβ burden. More specifically, we examined how self-reported PA is

associated with brain Aβ at a single timepoint, and over multiple assessments, in a cohort of cognitively unimpaired older adults. We also examined the potential for *APOE* ε4 carriage to moderate the PA–brain Aβ relationship cross-sectionally and longitudinally. Furthermore, building on findings that suggest that PA levels may decline prior to dementia diagnosis,[14] the relationship between PA trajectory and brain Aβ status was also investigated. We anticipate that our findings will address gaps in our current knowledge of the relationship between PA and brain Aβ burden.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors searched traditional databases and previous literature to determine current knowledge regarding physical activity and brain amyloid beta (Aβ). Several small observational studies, and few intervention studies, have examined the relationship among physical activity, exercise, and brain Aβ, with inconsistent findings reported. Few studies have examined physical activity and Aβ longitudinally.
2. **Interpretation**: Our findings demonstrate that baseline self-reported habitual physical activity levels in cognitively unimpaired older adults did not predict the accumulation of brain Aβ over time. In addition, brain Aβ levels did not predict the trajectory of physical activity. Apolipoprotein E (*APOE*) ε4 status did not moderate the physical activity and brain Aβ relationship.
3. **Future directions**: Our findings suggest that this type of investigation should be conducted from mid-life when brain Aβ has been shown to start accumulating.

2 | METHODS

Data from 731 cognitively unimpaired older adults participating in the Australian Imaging, Biomarkers and Lifestyle (AIBL) Study of Ageing were used to achieve the study objectives. AIBL is a longitudinal, multidisciplinary study of aging and AD, established in 2006, with participants repeatedly assessed at 18-month intervals at two scanning sites (Perth and Melbourne) following established protocols to ensure consistency between the sites. The AIBL study's recruitment screening process involved volunteers answering a series of questions before their initial assessment. Exclusion criteria included non-AD dementia, bipolar disorder, Parkinson's disease, schizophrenia, cancer other than basal cell skin carcinoma (within prior 2 years), uncontrolled diabetes, symptomatic stroke, excessive daily alcohol consumption, or current significant depression (defined by a Geriatric Depression Scale score above 5/15). AIBL is approved by the human research ethics committees of Austin Health, St Vincent's Health, Hollywood Private Hospital and Edith Cowan University. Written informed consent was obtained from all participants prior to undergoing any assessments.

2.1 | Participants

A subset of the AIBL cohort who were cognitively unimpaired at baseline, underwent Aβ brain PET imaging at a minimum of one assessment point, and who had PA assessed with the International Physical Activity Questionnaire (IPAQ) at baseline, were included in the current study (Figure 1). Of this subset, 105 participants were excluded due to incomplete IPAQ responses. Furthermore, those participants who only had data for one collection point were excluded for longitudinal analysis (see Figure 1 for full detail). Five of the baseline sample transitioned to an AD clinical status during the timeline of their collection period.

2.2 | Brain Aβ imaging

At all imaging time points, brain Aβ burden was measured with PET imaging using the Aβ binding tracers: 11C-Pittsburgh Compound-B (PiB), 18F-NAV4694, 18F-Florbetaben, 18F-Flutemetamol, or 18F-Florbetapir. Image processing software (CapAIBL) was used to analyse PET images,[31] and standard methods were used to convert tracer uptake values to the Centiloid scale to allow harmonization of PET data across tracers.[31,32] According to the Centiloid scale, a score of 100 is typically associated with brain the amyloid levels seen in individuals with mild AD.[33]

Centiloid values were used to categorize individuals at any single time point as either Aβ high ($A\beta^{high}$) for Centiloid scores of 20 or above, or Aβ low ($A\beta^{low}$) for scores less than 20, as described previously.[34]

2.3 | Physical activity measure

At all time points participants were required to complete the IPAQ to determine habitual PA levels. The long-form IPAQ is a subjective self-report questionnaire that collects information on PA completed over the prior 7 days in the domains of work, housework, leisure time, and transportation activities. PA levels were determined by allocating a Metabolic Equivalent of Task (MET) score to each of the questions, based on the intensity of the activity (e.g., walking = 3.3, moderate activities = 4, vigorous activities = 8), and then multiplying by duration and frequency during that 7-day period. The individual scores for each question were totaled to calculate a final score (MET minutes/week). The IPAQ has both good reliability and validity[35] and has been found to be an acceptable measure of PA in large observational studies comprising older (mean 72 years) adults.[36] IPAQ data were further evaluated to ensure completeness and accuracy, with incomplete questionnaires excluded from subsequent analysis.

2.4 | Covariates

Age and sex data were recorded via a questionnaire completed at screening. *APOE* ε4 allele carriage status was determined from a

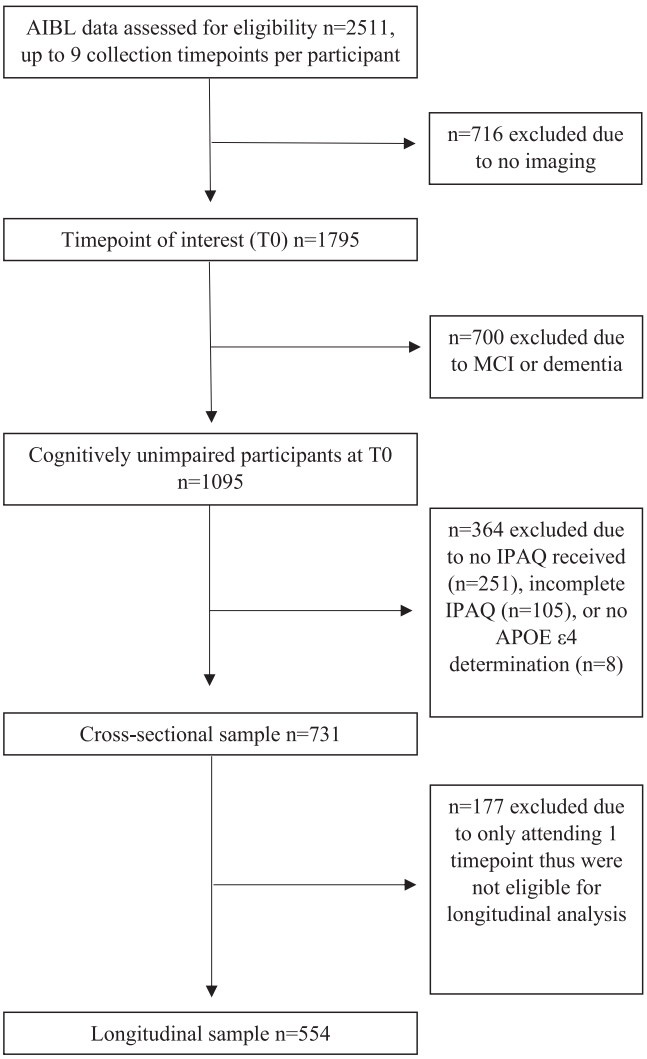

FIGURE 1 **Flow diagram outlining the process of defining data sample**. AIBL, Australian Imaging, Biomarkers and Lifestyle Study of Ageing; *APOE*, apolipoprotein E gene; IPAQ, International Physical Activity Questionnaire; MCI, mild cognitive impairment; T0, first imaging assessment timepoint.

whole-blood sample collected at baseline. Briefly, DNA extracted from blood samples was analysed using *APOE*-specific genotyping assays and polymerase chain reaction (PCR) systems as per manufacturer's instructions and detailed previously.[34] Based on genotype, participants were categorized as either an *APOE* ε4 carrier or non-carrier. A cardiovascular disease risk score based on diagnosis of hypertension, angina, heart attack, and diabetes was considered and calculated for each participant for use in all models.

2.5 | Data analysis

All analyses were conducted in R version 4.1.1[37] and significance was determined by $p < 0.05$. Visual inspection of the IPAQ data histogram revealed that data were not normally distributed; therefore, interquartile range transformation was performed to address outliers. In all instances of IPAQ data use, the interquartile range transformation variable was used. The cardiovascular disease risk score was removed from all models for goodness of fit as it was found not to be a predictor of the independent variables assessed.

2.5.1 | Cross-sectional relationship between physical activity and brain Aβ

Linear regression was used to examine the cross-sectional relationship between habitual PA and brain Aβ. Data collected at the first imaging time point "T0" were used, as this timepoint had the greatest number of data points (i.e., no attrition). IPAQ score was entered as the independent variable, and brain Aβ load (Centiloid) as the dependent variable. Modeling using age, sex, and *APOE* ε4 allele carriage status as covariates was performed, based on associations of these variables with PA and/or brain Aβ in our cohort.

2.5.2 | Longitudinal relationship between physical activity and brain Aβ

Linear mixed modeling (LMM) was used to examine the relationship between baseline habitual PA and longitudinal measures of brain Aβ. Baseline IPAQ levels were entered as the independent variable to examine whether habitual PA at one time point predicts repeated future measures of brain Aβ. Due to the scale of difference between the IPAQ and the brain Aβ data, the IPAQ data were rescaled by normalizing the data through a scale function in R before use. We also examined whether *APOE* ε4 carriage status moderated the PA and brain Aβ relationship. Time (in years) from baseline was entered into all LMMs, and the IPAQ**APOE* ε4 carriage*Time interaction was modeled. Covariates included in the model were age and sex.

2.5.3 | Evaluation of brain Aβ and physical activity trajectory

We examined whether there were differences in PA between individuals who were classified as Aβ^{high} (Centiloid score of 20 or above) at any timepoint in the study, versus those who remained Aβ^{low} (under 20 Centiloid score level) for the entirety of the study. PA trajectory was calculated using a backwards timeline,[38] with year 0 being either the first scan date a participant was classified as Aβ^{high} or the last scanning date for those who remained Aβ^{low} for the study duration. Only data in the period prior to their year 0 determination was used in this analysis. Exploratory analyses were conducted using a regression spline by plotting Time to year 0 on the x-axis (i.e., only values under 0) and brain Aβ on the y-axis. Aβ status (high or low) was plotted separately to allow for visual comparison between the two groups. LMM was used to examine the differences between Aβ^{high} and Aβ^{low} in terms of the relationship between IPAQ score and Time from year 0 (i.e., did PA levels change a certain number of years before an Aβ^{high} brain scan result was observed). All covariates remained the same as prior analyses.

TABLE 1 Baseline demographic characteristics stratified by brain Aβ status.

	Aβ Status			
	$A\beta^{low}$ ($n = 521$)	$A\beta^{high}$ ($n = 210$)	Total ($n = 731$)	*p*-value
Age, years				
Mean (SD)	71.5 (6.23)	74.2 (5.86)	72.3 (6.24)	<**0.001**
Sex, *n* (%)				
Female	302 (58.0)	107 (51.0)	409 (56.0)	0.1
Male	219 (42.0)	103 (49.0)	322 (44.0)	
***APOE* ε4 status, *n* (%)**				
No	407 (78.1)	100 (47.6)	507 (69.4)	<**0.001**
Yes	114 (21.9)	110 (52.4)	224 (30.6)	
MMSE				
Mean (SD)	28.6 (1.19)	28.2 (1.48)	28.5 (1.29)	<**0.001**
Aβ Score, Centiloid				
Mean (SD)	−0.197 (10.2)	61.6 (30.7)	17.6 (33.6)	<**0.001**
Median [Min, Max]	−0.400 [−40.6, 19.9]	56.9 [20.1, 179]	4.20 [−40.6, 179]	
IPAQ Score, MET minutes/week				
Mean (SD)	4970 (4900)	4220 (3790)	4750 (4620)	0.048
Median [Min, Max]	3440 [0, 44,500]	3150 [0, 23,300]	3340 [0, 44,500]	

Abbreviations: Aβ, amyloid beta; $A\beta^{low}$, <20 Centiloid score: $A\beta^{high}$, ≥20 Centiloid score; *APOE*, apolipoprotein E gene; IPAQ, international physical activity questionnaire; MET, Metabolic Equivalent of Task; MMSE, Mini-Mental State Examination; SD, standard deviation.

3 | RESULTS

3.1 | Descriptive statistics

Data from 731 cognitively unimpaired older adults were used for the current analysis (Table 1). The mean age of the cohort was 72.3 (SD = 6.2) years with 56.4% of participants being female. About a third (30.6%) of the cohort were identified as *APOE* ε4 allele carriers. The average time between completion of the IPAQ and undertaking a brain Aβ scan was 96.4 days. Demographic and medical history data from individuals excluded due to incomplete IPAQ forms were compared with included individuals: no differences were detected (Table SA).

3.2 | Cross-sectional relationship between physical activity and brain Aβ

Older age ($\beta = 1.22$, $SE = 0.19$, $p < 0.001$), sex ($\beta = 4.98$, $SE = 2.30$, $p = 0.03$) and *APOE* ε4 allele carriage ($\beta = 29.18$, $SE = 3.90$, $p < 0.001$) were associated with greater levels of brain Aβ. However, habitual PA measured by IPAQ was not associated with brain Aβ after controlling for covariates (Table 2). The *APOE* ε4*IPAQ interaction was also not significant, indicating that genetic risk does not moderate the Aβ relationship with PA.

TABLE 2 Linear regression of habitual physical activity as a predictor of brain Aβ levels at baseline.

	Brain Aβ (Centiloid)		
Predictors	**Estimate**	**Std. Error**	***p*-value**
(Intercept)	−79.68	13.90	<**0.001**
IPAQ Score, MET minutes/week	−0.0002	0.0004	0.63
Age	1.23	0.19	<**0.001**
Sex	4.98	2.30	**0.03**
APOE ε4 allele carriage	29.18	3.88	<**0.001**
IPAQ * *APOE* ε4 allele carriage	−0.001	0.001	0.23

Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E gene; IPAQ, International Physical Activity Questionnaire; MET, Metabolic Equivalent of Task.

3.3 | Longitudinal relationship between physical activity and brain Aβ

Baseline IPAQ levels did not predict change in brain Aβ over time (IPAQ*Time; $\beta = -0.26$, standard error (SE) = 0.23, $p = 0.241$; Table 3). However, the main effects time ($\beta = 1.66$, $SE = 0.20$, $p < 0.001$) and higher baseline age ($\beta = 0.89$, $SE = 0.19$, $p < 0.001$) were associated with greater accumulation of brain Aβ. *APOE* ε4 allele carriage was also associated with higher levels of brain Aβ ($\beta = 17.48$, $SE = 2.70$, $p < 0.001$),

TABLE 3 Linear mixed model of baseline habitual physical activity as a predictor of brain Aβ levels over time.

	Brain Aβ (Centiloid)		
Predictors	**Estimates**	**Std. Error**	***p*-value**
(Intercept)	−57.50	13.87	<**0.001**
IPAQ Score, MET minutes/week	−2.52	1.52	0.10
APOE ε4 allele carriage	17.48	2.70	<**0.001**
Time	1.66	0.20	<**0.001**
Age	0.88	0.19	<**0.001**
Sex	4.38	2.31	0.06
IPAQ * *APOE* ε4 allele carriage	−0.37	2.50	0.88
IPAQ * Time	−0.26	0.22	0.24
APOE ε4 allele carriage * Time	2.17	0.38	<**0.001**
IPAQ * *APOE* ε4 allele carriage * Time	0.12	0.35	0.73

Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E; IPAQ, International Physical Activity Questionnaire; MET, Metabolic Equivalent of Task.

TABLE 4 Linear mixed model of time before high brain Aβ levels is reached as a predictor of habitual physical activity levels.

	IPAQ Score (MET minutes/week)		
Predictor	**Estimate**	**Std. Error**	***p*-value**
(Intercept)	8676.73	1512.61	<**0.001**
Time from Year 0^	−67.03	42.23	0.11
Brain $A\beta^{high}$ status reached	−516.44	369.62	0.16
Age	−64.86	20.88	**0.002**
Sex	−81.50	256.67	0.75
APOE ε4 allele carriage	712.06	308.32	**0.02**
Time from Year 0 * Brain $A\beta^{high}$ status reached	−42.26	100.82	0.68

Abbreviations: Aβ, amyloid beta; $A\beta^{high}$, ≥20 Centiloid score; *APOE*, apolipoprotein E gene; IPAQ, International Physical Activity Questionnaire, MET, Metabolic Equivalent of Task.
^Year 0 refers to either the first scan date a participant was classified as $A\beta^{high}$ or the last scanning date for those that remained $A\beta^{low}$ for the study duration.

and the *APOE* ε4*Time ($\beta = 2.17$, $SE = 0.38$, $p < 0.001$) interaction indicated that those carrying an *APOE* ε4 had the greatest increase in Aβ burden over time compared to non- carriers. The *APOE* ε4*IPAQ interaction was not significant, indicating that *APOE*-attributable genetic risk does not moderate the Aβ relationship with PA.

3.4 | Evaluation of brain Aβ and physical activity trajectory

Classification of brain Aβ status (i.e., $A\beta^{high}$ or $A\beta^{low}$) was unrelated to PA trajectory over time, with no differences observed between PA levels of $A\beta^{high}$ and $A\beta^{low}$ participants at any time before year 0 (Table 4). Greater age ($\beta = -64.86$, $SE = 20.88$, $p = 0.002$) and *APOE* ε4 allele carriage ($\beta = 712.06$, $SE = 308.32$, $p = 0.021$) were associated with PA trajectory.

A plot of IPAQ scores (Figure 2) by brain Aβ status shows that PA levels are decreased for individuals who were $A\beta^{high}$ compared to those who were $A\beta^{low}$ approximately 3 years prior to year 0. However, an exploratory two-way analysis of variance (ANOVA) between mean IPAQ scores of $A\beta^{high}$ and $A\beta^{low}$ groups at 6-month intervals from −4 to year 0 indicated that the PA trajectories of the two brain Aβ status groups were not different ($F(7,780) = 1.385$, $p < 0.208$). The earlier separation slopes observed at −12 to −8 years from year 0 can be attributed to uncertainty around the mean IPAQ scores in the $A\beta^{high}$ group, due to only a small number of scores being available in that time frame.

4 | DISCUSSION

Previous research evaluating the brain Aβ levels and PA relationship has produced mixed findings. Undertaking one of the largest studies of brain Aβ and self-reported PA, we found that: (1) cross-sectional habitual PA levels were not associated with brain Aβ in cognitively unimpaired older adults, (2) baseline habitual PA levels were not associated with the accumulation of brain Aβ over time in cognitively unimpaired older adults, (3) the PA–brain Aβ relationship in the current study was not moderated by *APOE* ε4 allele status, and (4) brain Aβ levels were not associated with the trajectory of habitual pre $A\beta^{high}$ PA.

We found that cross-sectional levels of self-reported PA were not associated with brain Aβ. This result is consistent with findings using a PET-derived measurement of brain Aβ and a self-reported 2-week MET score measurement of PA[22] and corroborate findings using an earlier version of the AIBL data set ($n = 116$) utilizing IPAQ for PA measures and PET brain Aβ.[15] Both of these studies noted that due to the long-term nature of brain Aβ accumulation, cross-sectional designs might not be optimal, due to a lack of ability to establish temporal relationships. Although overall higher brain Aβ levels assessed by PET have been found previously to be useful in predicting progression to AD,[39] the large range of Centiloid scores measured in the current study illustrates that individual variability exists within cognitively unimpaired older adults, such that high brain Aβ levels do not necessarily indicate cognitive impairment. For this reason, evaluating change in brain Aβ burden over time, rather than levels at a single timepoint, could be a more useful strategy to understand the impact of PA on brain Aβ load deposition.

The current study is the first to use longitudinal data to evaluate the PA–brain Aβ relationship over more than two timepoints. We found that baseline PA levels did not predict brain Aβ accumulation over time. This lack of association between PA and longitudinal brain Aβ is in line with the few longitudinal studies published in this field utilizing only two timepoints.[40–42] Notably, two of the prior studies were exercise interventions[40,41] and not evaluations of habitual PA levels. Neither a 16-week exercise program of 180 min/week high to moderate intensity exercise[40] nor 52 weeks of 150 min/week of

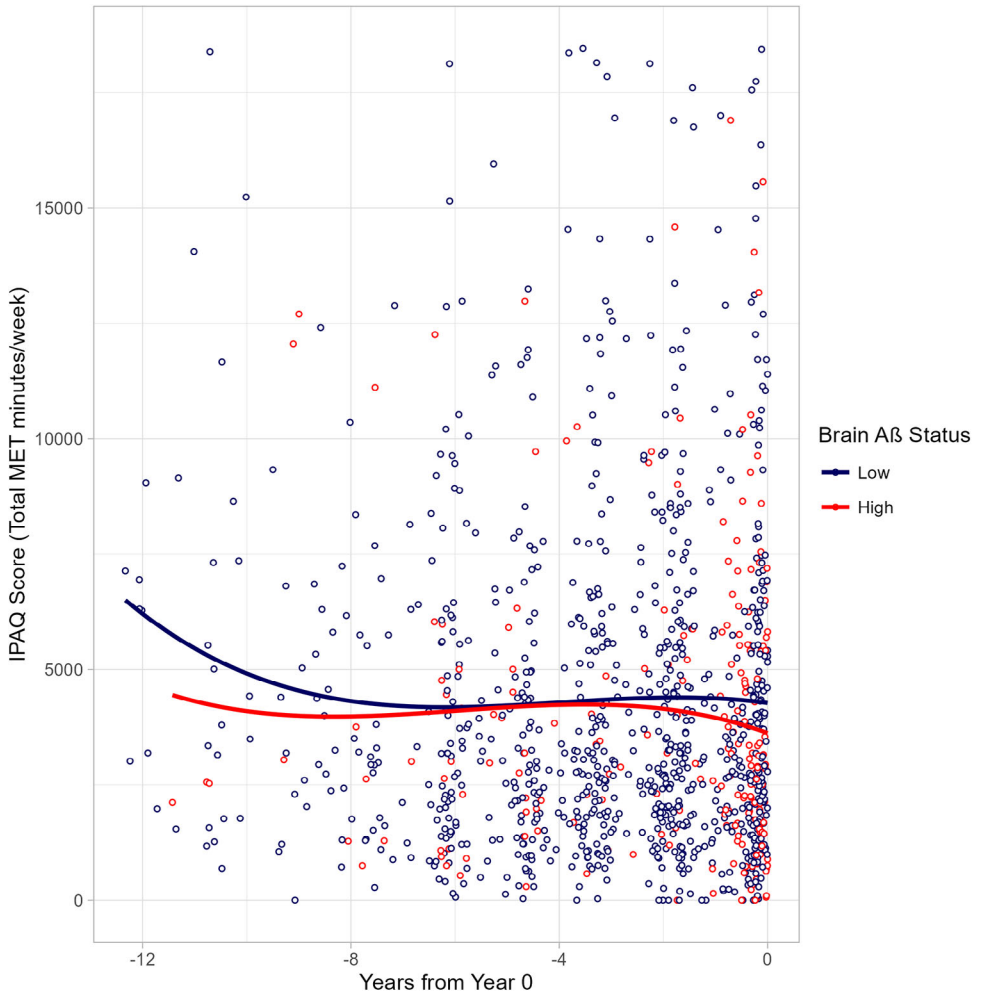

FIGURE 2 Trajectory of physical activity levels for participants with low and high brain Aβ up to year 0. The red line shows the trajectory of IPAQ-measured PA levels for those participants who recorded a brain Aβ burden of greater than or equal to 20 Centiloid (Aβ^{high}) at any point in this study. Conversely, the blue line shows IPAQ-measured PA levels up until the last brain scan date for those participants whose brain Aβ levels were less than 20 Centiloid (Aβ^{low}) for the study duration. Year 0 refers to either the first scan date a participant was classified as Aβ^{high} or the last scanning date for participants who remained Aβ^{low} for the study duration. Aβ, amyloid beta; IPAQ, International Physical Activity Questionnaire; MET, Metabolic Equivalent of Task (score).

moderate intensity exercise[41] contributed to differences in PET brain Aβ from pre- to post-intervention compared to the control groups. Furthermore, a previous observational study did not detect a relationship between self-reported PA and longitudinal Aβ deposition with a 2-year follow-up.[42] These findings suggest that there is insufficient evidence to indicate a relationship between habitual PA levels at a single timepoint and accumulation of Aβ over time.

In the current study, 58.6% of individuals reported, through their IPAQ, moderate or vigorous PA minutes of at least 150 min per week (M = 248.2 min per week) as recommended for general health.[43,44] Thus this cohort is highly active when compared to average levels reported in the Australian National Health Surveys (26.1% in 2017 to 2018 and 41.8% in 2020 to 2021 for individuals 65 years or older[45,46]). Conceivably the activity levels seen in the current group are such that there is diminished impact of PA on brain Aβ and the smaller sample of individuals reporting lower rates of activity is reducing the predictive ability of PA in the current sample. In addition, we know that PA levels can alter within an individual over time, and therefore it will be vital for future studies to examine concurrent changes in PA and brain Aβ over a 5- to 10-year period. The Aβ^{high} group also had a lower IPAQ score compared to the Aβ^{low} group when our analyses were unadjusted for covariates (Table 1). This difference is likely due to the Aβ^{high} group being older (3 years), explaining why the result did not survive correction for covariates (including age).

APOE ε4 status, along with age and sex, have been found to be direct predictors of Aβ burden.[47] The current study found that possession of an *APOE* ε4 allele did not moderate the association of self-reported habitual PA with brain Aβ accumulation. Previous studies have investigated the moderating impact of *APOE* ε4 allele status on the relationship between PA and Aβ, with mixed results.[30] The current findings are, however, in line with a recent meta-analysis of eight studies that also used PET Aβ measures and MET score as a PA measurement.[48] Of interest, the current study findings did not align with prior work from the AIBL study where the PA and Aβ association

was noted in *APOE* ε4 carriers. To put the current findings into context, the data used by Brown et al.[15] was smaller in number ($n = 116$) due to the study's duration to that point. The current study has the benefit of further recruitment to increase the sample size substantially and allow more power for the statistical analysis. The addition of the new participants has also seen an increase in the mean age between the samples in the two studies of 2 years (70.3 vs 72.3 years). It is possible that increased age may reduce the relationship between PA and Aβ, and this mitigates any benefits noted for *APOE* ε4 carriers by Brown et al.[15] The current study results do suggest, however, that the lack of moderation by *APOE* ε4 status previously seen in cross-sectional studies extends over the time course of the PA and Aβ relationship.

When assessing PA trajectory over time, we found no differences between those with $A\beta^{high}$ and $A\beta^{low}$ brain levels. However, a downward trend in PA levels was noted for the $A\beta^{high}$ group, compared to the $A\beta^{low}$ group, in the 3 years immediately preceding year 0 (where year 0 represented either the first scan date a participant was classified as $A\beta^{high}$ or the last scan date for those individuals that remained $A\beta^{low}$ for the study duration). Although this result may appear inconsistent with findings that PA levels begin to decrease up to 9 years before dementia diagnosis,[14] our findings must be considered in the context of disease stage. Specifically, published work from the AIBL study has shown that ~17 to 23 years elapse between the commencement of the preclinical stage of AD (when $A\beta^{high}$ status is reached) and dementia diagnosis.[5] Thus, even with the long period of follow-up in the current study, it is possible that individuals were not followed for long enough to observe the significant decrease in PA levels that Sabia et al.[14] noted as occurring later in the disease continuum. The ongoing collection of data from AIBL study participants may in the future provide additional information on PA trajectories across the AD continuum.

It is possible that the age of our sample ($M = 72$ years) may have influenced the PA–brain Aβ relationships reported in the current study. Villemagne et al.[5] showed that brain Aβ accumulation assessed by PET can occur over several decades prior to AD-related dementia onset, suggesting that Aβ accumulation could start in midlife. Based on these findings we hypothesise that PA may only be potent enough to impact Aβ accumulation when Aβ is at low levels, which is generally 20 to 30 years before symptom onset (i.e., mid-life). It is conceivable that by age 72 years (at baseline in the current sample), the capacity for PA to mitigate Aβ accumulation has diminished. Future longitudinal studies should consider recruiting middle-aged participants to investigate whether lifetime PA influences brain Aβ accumulation at earlier ages.

There are various mechanisms through which PA may slow cognitive decline, including alterations to brain structure, such as enhanced brain volume.[49] One key mechanism underlying the PA and brain volume relationship is believed to be increases in brain-derived neurotropic factor, which promotes neurogenesis and synaptic plasticity.[50] Although this study did not observe an association between higher PA and lower Aβ accumulation, it is possible that PA may contribute to reduced AD risk via other mechanisms within our cohort.

The results of the current study should be considered in the context of several limitations. First, the study utilized self-reported PA measured using the IPAQ. Although self-report tools have advantages such as low cost of administration, the IPAQ is a subjective evaluation of PA levels over a 7-day period. Self-reported PA questionnaire in general have several barriers in determining "representative" activity levels, including the use of vague wording, activity variability via seasonal/situational limitations, and inter-individual variability in reporting of performed PA.[51] Future studies of the PA–brain Aβ relationship may wish to use an objective or device-monitored PA measure, such as actigraphy, as utilized by Law et al.,[52] when evaluating PA and cerebrospinal fluid AD biomarker levels. Finally, the AIBL cohort comprises a relatively homogenous high-functioning sample of older adults. Thus, our findings may not be generalizable to the wider population. Nevertheless, there are aspects of the current study that provide confidence in its findings. The internal validity of the results is increased by the utilization of a highly characterized cohort and gold-standard neuroimaging AD biomarkers. The IPAQ is well-validated and has been associated previously with objective measures of PA (actigraphy) in the AIBL cohort. Moreover, a conservative approach to analysis was undertaken by controlling for demographic variables.

In conclusion, our results show that self-reported habitual PA is not related to brain Aβ load in cognitively unimpaired older adults in either cross-sectional or longitudinal assessments, and that the PA–brain Aβ relationship is not moderated by *APOE* ε4 carrier status in our cohort. PA trajectories were also shown to not differ between cognitively unimpaired older adults with either high or low levels of brain Aβ. These results suggest that observing the PA–brain Aβ relationship in older adults is potentially problematic because the ability to significantly impact Aβ accumulation may have passed. Future research should consider assessing the PA–brain Aβ relationship in mid-life, when Aβ accumulation is first detectable, and potentially more modifiable.

ACKNOWLEDGMENTS

Data used for this study were collected and supplied by the AIBL study (www.aibl.csiro.au), which is a collaboration between the Commonwealth Scientific and Industrial Research Organisation (CSIRO), Austin Health, Edith Cowan University, National Ageing Research Institute, and the Florey Institute (The University of Melbourne). The authors acknowledge and thank the participants of the AIBL study and their families for their ongoing support. Initial funding for the AIBL study was facilitated by CSIRO. The study has received partial financial support from the Alzheimer's Association (USA), the Alzheimer's Drug Discovery Foundation, an anonymous foundation, the Science and Industry Endowment Fund, the Dementia Collaborative Research Centres, the Victorian Government's Operational Infrastructure Support program, the Australian Alzheimer's Research Foundation, the National Health and Medical Research Council (NHMRC), and The Yulgilbar Foundation. Numerous commercial interactions have supported data collection and analyses. In-kind support has also been provided by Sir Charles Gairdner Hospital, Cogstate Ltd., Hollywood Private Hospital, The University of Melbourne, and St. Vincent's Hospital. M.G.S is supported by a Research Training Program (RTP) scholarship. S.R.R.S. is supported by an NHMRC Investigator Grant (GNT1197315). This

research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

M.G.S., S.R.R.S., H.R.S., K.T., D.A., K.I.E., and B.M.B. report no disclosures. P.M. is a full-time employee of Cogstate Ltd. C.L.M. is an advisor to Prana Biotechnology Ltd and a consultant to Eli Lilly. C.C.R. has served on scientific advisory boards for Bayer Pharma, Elan Corporation, GE Healthcare, and AstraZeneca, has received speaker honoraria from Bayer Pharma and GE Healthcare, and has received research support from Bayer Pharma, GE Healthcare, Piramal Lifesciences, and Avid Radiopharmaceuticals. R.N.M. is founder of, and owns stock in, Alzhyme, and is a co-founder of the KaRa Institute of Neurological Diseases. V.L.V. is a consultant for IXICO and Life Molecular Imaging, and has received speaker honoraria from GE Healthcare, Piramal Lifesciences and Avid Radiopharmaceuticals. S.M.L. has previously been a paid consultant to Alzhyme and is a scientific advisor/partner for Cytox Ltd. Author disclosures are available in the supporting information.

CONSENT STATEMENT

AIBL is approved by the human research ethics committees of Austin Health, St Vincent's Health, Hollywood Private Hospital and Edith Cowan University. Written informed consent was obtained from all participants prior to undergoing any assessments.

REFERENCES

1. Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol*. 2014;13:614-629.
2. Ikonomovic MD, Klunk WE, Abrahamson EE, et al. Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. *Brain*. 2008;131:1630-1645.
3. Masters CL, Beyreuther K. Neuronal origin of cerebral amyloidogenic proteins: their role in Alzheimer's disease and unconventional virus diseases of the nervous system. *Ciba Found Symp*. 1987;126:49-64.
4. Masters CL, Beyreuther K. Molecular neuropathology of Alzheimer's disease. *Arzneimittelforschung*. 1995;45:410-412.
5. Villemagne VL, Burnham S, Bourgeat P, et al. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *The Lancet Neurology*. 2013;12:357-367.
6. Lim YY, Maruff P, Kaneko N, et al. Plasma amyloid-β biomarker associated with cognitive decline in preclinical Alzheimer's disease. *J Alzheimers Dis*. 2020;77:1057-1065.
7. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993;261:921-923.
8. Di Liegro CM, Schiera G, Proia P, Di Liegro I. Physical activity and brain health. *Genes*. 2019;10:720.
9. Blondell SJ, Hammersley-Mather R, Veerman JL. Does physical activity prevent cognitive decline and dementia?: a systematic review and meta-analysis of longitudinal studies. *BMC Public Health*. 2014;14:510.
10. Brown BM, Peiffer J, SR Rainey-Smith. Exploring the relationship between physical activity, beta-amyloid and tau: a narrative review. *Ageing Research Reviews*. 2019;50:9-18.
11. Frederiksen KS, Gjerum L, Waldemar G, Hasselbalch SG. Physical activity as a moderator of alzheimer pathology: a systematic review of observational studies. *Curr Alzheimer Res*. 2019a;16:362-378.
12. Haan MN, Wallace R. Can dementia be prevented? Brain aging in a population-based context. *Annual Review of Public Health*. 2004;25:1-24.
13. Guure CB, Ibrahim NA, Adam MB, Said SM. Impact of physical activity on cognitive decline, dementia, and its subtypes: meta-analysis of prospective studies. *BioMed Research International*. 2017;2017:1-13.
14. Sabia S, Dugravot A, Dartigues J-F, et al. Physical activity, cognitive decline, and risk of dementia: 28 year follow-up of Whitehall II cohort study. *BMJ*. 2017:j2709.
15. Brown BM, Peiffer JJ, Taddei K, et al. Physical activity and amyloid-β plasma and brain levels: results from the Australian Imaging. *Biomarkers and Lifestyle Study of Ageing Molecular Psychiatry*. 2013b;18:875-881.
16. Brown BM, Rainey-Smith SR, Dore V, et al. Self-reported physical activity is associated with tau burden measured by positron emission tomography. *J Alzheimers Dis*. 2018;63:1299-1305.
17. Head D, Bugg JM, Goate AM, et al. Exercise engagement as a moderator of the effects of APOE genotype on amyloid deposition. *Arch Neurol*. 2012;69:636-643.
18. Liang KY, Mintun MA, Fagan AM, et al. Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. *Annals of Neurology*. 2010;68:311-318.
19. Okonkwo OC, Schultz SA, Oh JM, et al. Physical activity attenuates age-related biomarker alterations in preclinical AD. *Neurology*. 2014;83:1753-1760.
20. Rabin JS, Klein H, Kirn DR, et al. Associations of Physical activity and β-Amyloid with longitudinal cognition and neurodegeneration in clinically normal older adults. *JAMA Neurology*. 2019;76:1203.
21. Treyer V, Meyer RS, Buchmann A, et al. Physical activity is associated with lower cerebral beta-amyloid and cognitive function benefits from lifetime experience–a study in exceptional aging. *PLOS ONE*. 2021;16:e0247225.
22. de Souto Barreto P, Andrieu S, Payoux P, Demougeot L, Rolland Y, Vellas B. Physical activity and amyloid-β brain levels in elderly adults with intact cognition and mild cognitive impairment. *Journal of the American Geriatrics Society*. 2015;63:1634-1639.
23. Pedrero-Chamizo R, Szoeke C, Dennerstein L, Campbell S. Influence of physical activity levels and functional capacity on brain β-amyloid deposition in older women. *Front Aging Neurosci*. 2021;13:697528.
24. Craft S, Cholerton B, Baker LD. Insulin and Alzheimer's disease: untangling the web. *J Alzheimers Dis*. 2013;33(1):S263-S275. Suppl.
25. Gasparini L, Gouras GK, Wang R, et al. Stimulation of beta-amyloid precursor protein trafficking by insulin reduces intraneuronal beta-amyloid and requires mitogen-activated protein kinase signaling. *J Neurosci*. 2001;21:2561-2570.
26. Alkadhi KA, Dao AT. Exercise decreases BACE and APP levels in the hippocampus of a rat model of Alzheimer's disease. *Molecular and Cellular Neuroscience*. 2018;86:25-29.
27. Koo JH, Kang EB, Oh YS, Yang DS, Cho JY. Treadmill exercise decreases amyloid-β burden possibly via activation of SIRT-1 signaling in a mouse model of Alzheimer's disease. *Experimental Neurology*. 2017;288:142-152.
28. Zhang J, Guo Y, Wang Y, Song L, Zhang R, Du Y. Long-term treadmill exercise attenuates Aβ burdens and astrocyte activation in APP/PS1 mouse model of Alzheimer's disease. *Neurosci Lett*. 2018;666:70-77.
29. Nigam SM, Xu S, Kritikou JS, Marosi K, Brodin L, Mattson MP. Exercise and BDNF reduce Aβ production by enhancing α-secretase processing of APP. *Journal of Neurochemistry*. 2017;142:286-296.
30. de Frutos-Lucas J, Frost N, Erickson KI, et al. Does APOE genotype moderate the relationship between physical activity, brain health and dementia risk? A systematic review. *Ageing Res Rev*. 2020;64:101173.
31. Doré V, Bullich S, Rowe CC, et al. Comparison of 18 F-florbetaben quantification results using the standard Centiloid, MR-based, and MR-less CapAIBL ® approaches: validation against histopathology. *Alzheimer's & Dementia*. 2019;15:807-816.

32. Bourgeat P, Doré V, Fripp J, et al. Implementing the centiloid transformation for 11C-PiB and β-amyloid 18F-PET tracers using CapAIBL. *NeuroImage*. 2018;183:387-393.
33. Klunk WE, Koeppe RA, Price JC, et al. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimer's & Dementia*. 2015;11:1-15.
34. Fowler C, Rainey-Smith SR, Bird S, et al. Fifteen Years of the australian imaging, biomarkers and lifestyle (AIBL) Study: progress and Observations from 2,359 older adults spanning the spectrum from cognitive normality to Alzheimer's disease. *J Alzheimers Dis Rep*. 2021;5:443-468.
35. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-Country reliability and validity. *Medicine & Science in Sports & Exercise*. 2003;35:1381-1395.
36. Cleland C, Ferguson S, Ellis G, Hunter RF. Validity of the International Physical Activity Questionnaire (IPAQ) for assessing moderate-to-vigorous physical activity and sedentary behaviour of older adults in the United Kingdom. *BMC Medical Research Methodology*. 2018;18.
37. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2021
38. Amieva H, Le Goff M, Millet X, et al. Prodromal Alzheimer's disease: successive emergence of the clinical symptoms. *Annals of Neurology*. 2008;64:492-498.
39. Rowe CC, Bourgeat P, Ellis KA, et al. Predicting Alzheimer disease with β-amyloid imaging: results from the Australian imaging, biomarkers, and lifestyle study of ageing. *Annals of Neurology*. 2013;74:905-913.
40. Frederiksen KS, Madsen K, Andersen BB, et al. Moderate- to high-intensity exercise does not modify cortical β-amyloid in Alzheimer's disease. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*. 2019b;5:208-215.
41. Vidoni ED, Morris JK, Watts A, et al. Effect of aerobic exercise on amyloid accumulation in preclinical Alzheimer's: a 1-year randomized controlled trial. *PLOS ONE*. 2021;16:e0244893.
42. Walters MJ, Sterling J, Quinn C, et al. Associations of lifestyle and vascular risk factors with Alzheimer's brain biomarker changes during middle age: a 3-year longitudinal study in the broader New York City area. *BMJ Open*. 2018;8:e023664.
43. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*. 2011;43:1334-1359.
44. World Health Organisation. Global Recommendations on Physical Activity for Health. 2010
45. Australian Bureau of Statistics. Physical activity. In: ABS, editor. 2017-18
46. Australian Bureau of Statistics. Physical activity. In: ABS, editor. 2020-21
47. Bachmann D, Roman ZJ, Buchmann A, et al. Lifestyle affects amyloid burden and cognition differently in men and women. *Annals of Neurology*. 2022;92:451-463.
48. Pearce AM, Marr C, Dewar M, Gow AJ. Apolipoprotein E genotype moderation of the association between physical activity and brain health. A systematic review and meta-analysis. *Front Aging Neurosci*. 2021;13:815439.
49. Brown BM, Peiffer JJ, Martins RN. Multiple effects of physical activity on molecular and cognitive signs of brain aging: can exercise slow neurodegeneration and delay Alzheimer's disease? *Molecular Psychiatry*. 2013a;18:864-874.
50. Cotman CW, Engesser-Cesar C. Exercise enhances and protects brain function. *Exercise and Sport Sciences Reviews*. 2002;30:75-79.
51. Silsbury Z, Goldsmith R, Rushton A. Systematic review of the measurement properties of self-report physical activity questionnaires in healthy adult populations: figure 1. *BMJ Open*. 2015;5:e008430.
52. Law LL, Rol RN, Schultz SA, et al. Moderate intensity physical activity associates with CSF biomarkers in a cohort at risk for Alzheimer's disease. Alzheimer's & Dementia: diagnosis. *Assessment & Disease Monitoring*. 2018;10:188-195.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Slee MG, Rainey-Smith SR, Villemagne VL, et al. Physical activity and brain amyloid beta: A longitudinal analysis of cognitively unimpaired older adults. *Alzheimer's Dement*. 2024;20:1350–1359. https://doi.org/10.1002/alz.13556