Received: 15 November 2024 | Revised: 22 January 2025 | Accepted: 23 January 2025

DOI: 10.1002/alz.70007

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

RESEARCH ARTICLE

Physical activity changes during midlife link to brain integrity and amyloid burden

Muge Akinci[1,2,3,4] | **Pablo Aguilar-Domínguez**[1,3,4,5] | **Eleni Palpatzis**[1,2,3,4] | **Mahnaz Shekari**[2,3,6] | **Marina García-Prat**[2] | **Carme Deulofeu**[2] | **Karine Fauria**[2] | **Judith García-Aymerich**[1,3,4] | **Juan Domingo Gispert**[2,3,6,7] | **Marc Suárez-Calvet**[2,6,8,9] | **Oriol Grau-Rivera**[2,6,8,9] | **Gonzalo Sánchez-Benavides**[2,6,8] | **Eider M. Arenaza-Urquijo**[1,2,3,4,6,8] | **for the ALFA study**

[1]Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain

[2]Barcelonaβeta Brain Research Center - Pasqual Maragall Foundation, Barcelona, Spain

[3]Universitat Pompeu Fabra (UPF), Barcelona, Spain

[4]CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

[5]Sant Pau Memory Unit, Department of Neurology, Hospital de la Santa Creu i Sant Pau, Biomedical Research Institute Sant Pau (IIBSant Pau), Barcelona, Spain

[6]Hospital del Mar Medical Research Institute, Barcelona, Spain

[7]Centro de Investigación Biomédica en Red de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Madrid, Spain

[8]Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES), Madrid, Spain

[9]Servei de Neurologia, Hospital del Mar, Barcelona, Spain

Correspondence
Eider Arenaza-Urquijo, ISGlobal, C/ del Dr. Aiguader, 88, 08003 Barcelona, Spain.
Email: eider.arenza@isglobal.org

Karine Fauria, Barcelonaβeta Brain Research Center, C/ de Wellington, 30, 08005 Barcelona, Spain.
Email: kfauria@barcelonabeta.org

Collaborators of the ALFA Study can be found in the Acknowledgments section.

Funding information
'la Caixa' Foundation, Grant/Award Numbers: ID 100010434, LCF/PR/GN17/50300004; Alzheimer's Association, Grant/Award Numbers: AARG 2019-AARG-644641, AARG 2019-AARG-644641-RAPID; International Anonymous Charity; TriBEKa Imaging Platform project, Grant/Award Number: TriBEKa-17-519007; Universities and Research Secretariat, Ministry of Business and Knowledge of the Catalan Government,

Abstract

INTRODUCTION: Evidence suggests that midlife physical activity may reduce Alzheimer's disease (AD) risk. In at-risk individuals, we investigated midlife physical activity changes in relation to AD-related pathologies.

METHODS: We included 337 cognitively unimpaired adults with baseline and follow-up physical activity evaluations within 4.07 ± 0.84 years. We performed multiple regressions considering follow-up amyloid-PET burden and MRI-based medial temporal lobe cortical thickness as outcomes. Independent variables encompassed changes in adherence to World Health Organization (WHO)-recommended physical activity levels, activity amounts, and sedentary behavior (no activity reported).

RESULTS: Remaining sedentary was associated with lower cortical thickness compared to doing limited physical activity, maintaining adherence, or becoming adherent to WHO recommendations. Becoming adherent to recommendations was linked to lower amyloid burden compared to becoming non-adherent. Increased activity amounts showed a dose-dependent association with lower amyloid burden.

Grant/Award Number: 2021 SGR 00913; Ministry of Science and Innovation, Grant/Award Number: PID2019-111514RA-I00; European Social Fund (ESF); EU Joint Programme-Neurodegenerative Disease Research, Grant/Award Number: JPND2022-138; European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme, Grant/Award Number: No. 948677; Instituto de Salud Carlos III (ISCIII), Grant/Award Number: PI19/00155; European Union; European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement, Grant/Award Number: 847648; MCIN/AEI/10.13039/501100011033, Grant/Award Number: CEX2018000806-S; Generalitat de Catalunya CERCA Program; Spanish Ministry of Science and Innovation - State Research Agency, Grant/Award Number: RYC2018-026053-I; the Spanish Ministry of Science and Innovation, Grant/Award Number: PRE2020-095827

DISCUSSION: Increasing physical activity and new adherence to WHO recommendations could be key objectives for preventive strategies during midlife.

CLINICAL TRIAL REGISTRATION INFORMATION: Registered at Clinicaltrials.gov (identifier: NCT02485730).

KEYWORDS
Alzheimer's disease, amyloid-β, cortical thickness, midlife physical activity, physical activity change, prevention

Highlights

- Boosting physical activity in midlife may have beneficial effects in preclinical AD.
- Physical activity increases relate to lower Aβ burden in a dose-dependent manner.
- Remaining sedentary links to lower cortical thickness in AD-vulnerable structures.
- New adherence to WHO-recommended physical activity levels may enhance brain health.

1 | BACKGROUND

Alzheimer's disease (AD) starts with a preclinical phase, during which the earliest disease-related pathophysiological events begin to manifest.[1,2] These include abnormal accumulation of amyloid-β (Aβ) plaques, neurofibrillary tangles, and neurodegeneration, which can be monitored through biomarkers decades before the clinical symptom onset.[1–3] The preclinical stage of AD thus offers a valuable opportunity for interventions targeting earliest disease-related brain changes to prevent or delay the subsequent development of dementia.[1,4] With about one-third of AD cases attributable to modifiable risk factors,[5] there has been a growing interest in slowing down or halting AD pathologies through managing lifestyle behaviors.

Sedentary behavior and physical inactivity are well-known risk factors for dementia.[6–8] Previous research reported that approximately 13% of AD cases worldwide could be attributable to physical inactivity.[7] Physical activity engagement, instead, has been associated with a decreased risk of developing cognitive decline and AD,[9–12] especially during midlife.[13,14] In particular, sustained physical activity in midlife can reduce AD risk[7,15] through improving cardiovascular[7,16] and mental health.[11] Midlife is also a critical period during which significant age-related and pathological brain changes may occur,[17] particularly in individuals at risk of developing AD.[18] Moreover, midlife exposures may contribute to the development of neuropathological events.[15,17,18]

Recent evidence suggests that physical activity may have a direct impact on AD-related brain changes.[7] Studies in cognitively unimpaired (CU) individuals reported association of physical activity with lower levels of Aβ pathology[19–22] and greater volume in AD-vulnerable brain regions,[23,24] whereas sedentary behavior has been linked to lower cortical thickness in medial temporal lobe structures.[25] Moreover, the amount of physical activity performed may play a role in reducing AD risk.[26,27] Indeed, the World Health Organization (WHO)[28] provides recommendations on physical activity amounts to prevent non-communicable diseases. Specifically, the WHO recommends 150–300 min/week of moderate-intensity activity or 75–150 min/week of vigorous-intensity activity, or an equivalent combination of moderate-intensity and vigorous-intensity activity for middle-aged and older individuals.[28] However, little is known on how adherence to WHO-recommended activity levels or changing activity amounts during midlife are linked to AD-related pathologies.

Here, we explored change in physical activity over a 4-year period in relation to brain Aβ burden and cortical thickness in AD-vulnerable structures in CU adults at increased risk of developing AD. We hypothesized that (1) maintained adherence and new adherence to the WHO-recommended activity levels and (2) increased activity amounts during midlife would be related to lower brain Aβ burden and preserved cortical thickness in medial temporal lobe structures.

2 | METHODS

2.1 | Participants

The study participants were recruited from the longitudinal ALFA+ study cohort nested to the ALFA (ALzheimer's and FAmilies) study. The ALFA study aims to evaluate early pathophysiological changes in preclinical AD and includes 2743 CU adults at risk of developing AD (86.3% have at least one parent with AD).[29] The participants of the ALFA+ study (n = 451) have been characterized at multiple levels including lifestyle questionnaires, lumbar puncture procedures and

neuroimaging acquisitions. Inclusion criteria of the ALFA+ study were: (1) having participated in the ALFA study; (2) age between 45 and 65 years at the moment of inclusion in the ALFA cohort; and (3) long-term commitment to the study. ALFA+ exclusion criteria were: (1) cognitive impairment; (2) any significant systemic illness or unstable medical condition that could result in difficulty complying with the study protocol; (3) contraindication to any test or procedure; and (4) having a family history of monogenic AD.

In the current study, the inclusion criteria were: (1) being an ALFA+ study participant, (2) having completed a self-reported physical activity assessment (see below) both at the baseline (2013–2014) and follow-up visits (2016–2019), and (3) having structural magnetic resonance imaging (sMRI) and/or positron emission tomography (PET) data available during the follow-up visit (see Figure 1 for details).

The ALFA+ study (ALFA-FPM-0311) was approved by the Independent Ethics Committee "Parc de Salut Mar," Barcelona, and registered at Clinicaltrials.gov (identifier: NCT02485730). All participants signed an informed consent form at the baseline visit, which had been approved by the Independent Ethics Committee "Parc de Salut Mar," Barcelona. All methods were carried out in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature using search engines such as PubMed. Previous studies reported cross-sectional associations of physical activity with Alzheimer's disease (AD) pathologies and brain integrity in middle-aged or older adults. However, no studies to date have examined how changes in physical activity or adherence to World Health Organization (WHO)-recommended activity levels during midlife are linked to AD-related pathologies in individuals at risk of AD.
2. **Interpretation**: Our findings suggest that increasing physical activity during midlife, including to the WHO-recommended levels, is related to lower amyloid-β (Aβ) pathology. Remaining sedentary, instead, is associated with lower cortical thickness in AD-vulnerable brain structures. These findings underscore the potential of increased physical activity in enhancing brain health in middle-aged individuals at the preclinical stage of AD.
3. **Future directions**: Investigating the effects of physical activity changes on the evolution of AD-related pathologies will be crucial to plan effective lifestyle-based interventions to prevent AD progression.

2.2 | Physical activity evaluation

We used the Minnesota Leisure Time Physical Activity Questionnaire (MLTPAQ)[30] to obtain the frequency, duration, and type of the physical activity performed by participants at baseline and follow-up visits. We determined activity intensities (moderate/vigorous) based on the type of activity performed (Figure S1). Then, we obtained the physical activity amounts as total minutes per week of activity of any intensity. We inspected the distributions of the physical activity amounts at both time points and removed the extreme values falling outside of three times the interquartile range below the first quartile or above the third quartile.

First, we examined theadherence to the WHO-recommended physical activity levels in our cohort. Participants meeting the recommended activity levels for middle-aged and older individuals[28] were considered adherent to the recommendations, whereas those who did not perform sufficient activity to meet the recommendations were considered non-adherent. Participants who did not perform any activity (0 min/week both at baseline and follow-up) were considered sedentary. Then, we classified our participants into the following groups considering their adherence status to WHO-recommended activity levels at both time points: (1) maintained sedentary behavior, (2) maintained non-adherence, (3) maintained adherence, (4) became non-adherent, and (5) became adherent (see Table 1 for details of the classification).

Second, we derived a continuous measure reflecting the change in activity amounts for all participants as follows: (follow-up activity amount of any intensity) – (baseline activity amount of any intensity).

2.3 | Clinical evaluations

2.3.1 | CAIDE-I score

The CAIDE (Cardiovascular Risk Factors, Aging and Incidence of Dementia)[31] score is a validated tool for predicting the risk of late-life dementia among middle-aged individuals. At baseline, we calculated the CAIDE-I score for each participant, which estimates dementia risk within 20 years[31] considering the following variables (see details in[32]): age, sex, years of education, systolic blood pressure, body mass index, total cholesterol, physical activity status.[32,33]

2.3.2 | Mental health

During the follow-up visit, we evaluated the mental health symptoms using the Hospital Anxiety and Depression Scale (HADS).[34] Higher HADS-total scores indicate greater levels of anxious-depressive symptoms.

2.3.3 | Apolipoprotein E genotyping

The sample was genotyped for the rs429358 and rs7412 polymorphisms to define the apolipoprotein E (*APOE*) allelic variants.

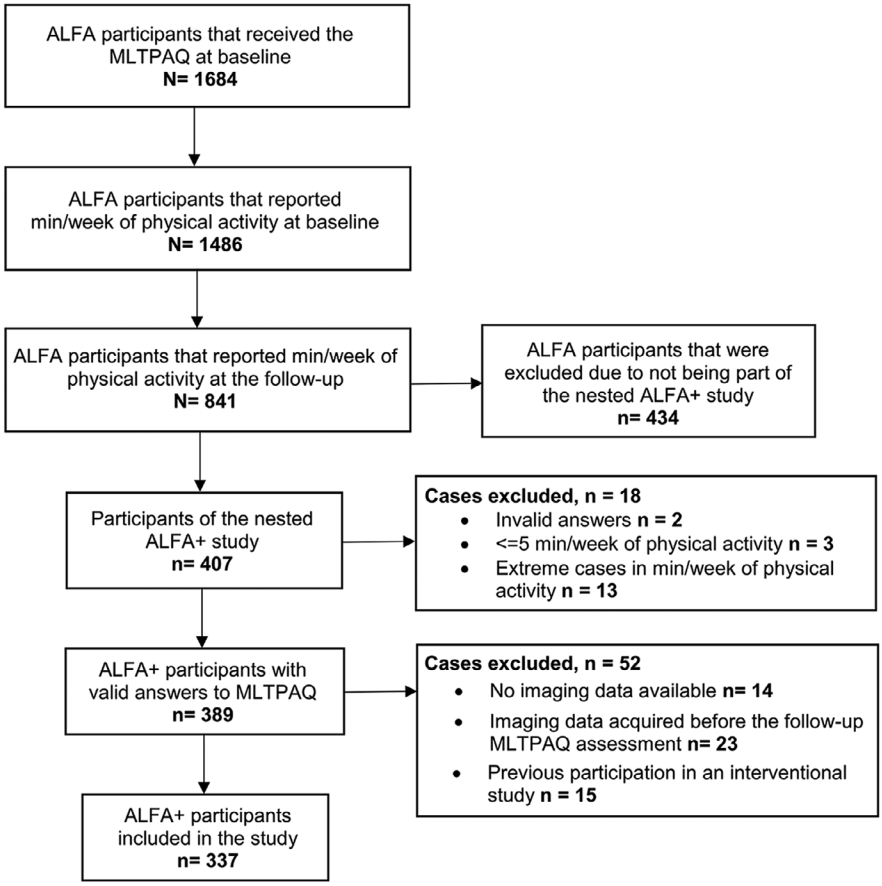

FIGURE 1 Flow diagram showing the selection of study participants. ALFA, ALzheimer's and FAmilies; MLTPAQ, Minnesota Leisure Time Physical Activity Questionnaire; MRI, magnetic resonance imaging; PA, physical activity; PET, positron emission tomography.

Participants were classified as *APOE*-ε4 carriers (carriers of one or two ε4 alleles) or non-carriers.

2.4 | PET acquisition and processing

Acquisition of [^{18}F]flutemetamol PET images were performed in a Siemens Biograph mCT scanner following a cranial computed tomography scan for attenuation correction. Participants were injected with 185 MBq (range 166.5–203.5 MBq) of [^{18}F]flutemetamol. Ninety minutes post-injection, the acquisition of PET data was carried out for 20 min (four frames of 5 min each). The images were reconstructed using an OSEM3D algorithm with point spread function and time-of-flight corrections.

PET images were preprocessed following a validated Centiloid pipeline[35] using SPM12.[36] The images were averaged and co-registered to corresponding MRI scans. The MRIs were segmented and normalized to the Montreal Neurological Institute (MNI) space along with the PET images. Then, standard uptake value ratios (SUVRs) were computed in MNI space using the standard target region (www.gaain.org) and the whole cerebellum as the reference region. The SUVR values were transformed to Centiloid scale.[35,36]

2.5 | MRI acquisition and processing

Anatomical 3D T1-weighted fast field echo sequence MRI scans were obtained in a 3T scanner (Ingenia CX, Philips, Amsterdam, Netherlands) with the following parameters: voxel size = 0.75 × 0.75 × 0.75 mm^3 isotropic, field of view = 240 × 240 × 180 mm^3, flip angle = 8°, repetition time = 9.9 ms, echo time = 4.6 ms, and inversion time = 900 ms in sagittal acquisition.

We used FreeSurfer 7.0 to segment and parcellate the brain tissue into different anatomical regions of interest (ROIs) using the Desikan Killiany cortical atlas and subcortical labeling pipelines of the software.[37,38] We derived a composite-ROI, known as the AD-signature, by calculating the surface-area weighted average of the mean cortical thickness values of entorhinal, middle temporal, inferior temporal, and fusiform cortices,[39] which undergo subtle atrophy early in AD.[40]

2.6 | Statistical analyses

Differences between the WHO-based physical activity groups in sociodemographic and clinical variables were examined performing chi-squared analyses or F-tests when appropriate.

TABLE 1 Physical activity status definitions.

Parameter	Physical activity groups based on the change in adherence to World Health Organization recommendations
Maintained sedentary behavior	0 min/week of activity at both time points
Maintained non-adherence	<150 min/week of light/moderate-intensity or <75 min/week of vigorous-intensity activity at both time points, or 0 min/week of activity at one time point and <150 min/week of light/moderate-intensity or <75 min/week of vigorous-intensity activity at the other time point
Maintained adherence	≥150 min/week of moderate-intensity or ≥75 vigorous-intensity activity at both time points
Became non-adherent	≥150 min/week of moderate-intensity or ≥75 vigorous-intensity activity at baseline and <150 min/week of light/moderate-intensity activity or <75 min/week of vigorous-intensity or 0 min/week of activity at follow-up
Became adherent	<150 min/week of light/moderate-intensity or <75 min/week of vigorous-intensity activity or 0 min/week of activity at baseline and ≥150 min/week of moderate-intensity or ≥75 min/week of vigorous-intensity activity at follow-up

Note: Participants who did not specify the type of the activity they performed were considered as "adherent" to the recommendations only if they engaged in ≥150 min/week of physical activity.

In our main analyses, we performed different sets of multiple regression models considering the (1) WHO-based physical activity groups, and (2) the continuous measure of change in activity amounts as the independent variable. In all models, outcomes were brain Aβ burden and AD signature thickness at the follow-up visit.

In the first set of analyses, we explored the association of WHO-based physical activity status with brain outcomes considering the group with maintained sedentary behavior as the reference category.

In the second and third set of analyses, we evaluated the association of maintained or new adherence to WHO-recommended activity levels with brain health comparing the (1) maintained adherence group and (2) became adherent group with the other WHO-based physical activity groups in relation to brain outcomes.

Finally, we investigated Aβ burden and AD signature thickness as a function of change in physical activity amounts from baseline to follow-up. Participants who did not perform any physical activity (i.e., maintained sedentary behavior) and who showed < 10 min/week of change in physical activity were excluded from these analyses.

All models were adjusted by age, sex, education (years), and *APOE*-ε4 status. Additionally, we controlled the models for inter-individual variability in the time between baseline and follow-up physical activity assessments. As sensitivity analyses, we performed further adjustments for mental and cardiovascular health-related variables as potential confounders.[7,11]

We carried out statistical analyses using RStudio v1.4.1103–4. Results with a $p < 0.05$ were considered statistically significant. We performed false discovery rate (FDR) correction[41] for multiple comparisons.

3 | RESULTS

The final sample included 337 ALFA+ participants (Figure 1), who were middle-aged men and women from different educational backgrounds across Catalonia, Spain. The majority of the participants (99.4%) were identified as White Caucasian ($n = 335$), while 0.6% ($n = 2$) were identified as Latino.

All participants had data available on the physical activity measured with the MLTPAQ at baseline and follow-up (average time lapse between the two assessments = 4.07 ± 0.84 years, range = 2.16–6.00 years). During the follow-up, participants had sMRI ($n = 299$) and Aβ PET ($n = 277$) data acquired with an average of 0.003 ± 0.02 and 0.37 ± 0.23 years after the follow-up MLTPAQ assessment, respectively. Of all participants, 29.4% ($n = 99$) maintained sedentary behavior. Twenty-four percent ($n = 82$) maintained non-adherence, 16.9% ($n = 57$) maintained adherence, 13.6% ($n = 46$) became non-adherent, and 15.7% ($n = 53$) became adherent to WHO-recommended activity levels. The variability in time between the physical activity assessments did not influence the group classification. Thus, there was no statistically significant difference between the groups that changed (i.e., became non-adherent and became adherent) or maintained (i.e., maintained sedentary behavior, maintained non-adherence, and maintained adherence) their physical activity status in the time interval from baseline to follow-up MLTPAQ assessments ($t_{175.9} = 0.085$; $p = 0.466$).

Table 2 summarizes the sociodemographic, clinical, imaging, and physical activity-related sample characteristics.

3.1 | Physical activity status during midlife: associations with sociodemographic and clinical variables

There were significant differences between the WHO-based physical activity groups in change in minutes of activity from baseline to follow-up ($F[4, 332] = 91.6$; $p < 0.001$), became adherent > all groups). The groups also showed significant differences in CAIDE-I scores ($F[4, 322] = 4.78$; $p < 0.001$), maintained sedentary behavior > maintained non-adherence and maintained adherence and became non-adherent), and HADS-total scores ($F[4, 331] = 2.65$; $p = 0.033$), became adherent < maintained non-adherence). No significant group differences were found in age ($F[4, 332] = 0.37$; $p = 0.827$), education ($F[4, 332] = 2.29$; $p = 0.059$), sex ($X^2 = 9.43$; $p = 0.051$), or *APOE*-ε4 status ($X^2 = 6.14$; $p = 0.189$) (Table 3).

TABLE 2 Characteristics of the sample.

Variable	Full sample (*N* = 337)
Baseline age, mean (SD), years	60.5 (4.78)
Education, mean (SD), years	13.5 (3.55)
White Caucasians, no. (%)	99.4 (335)
Women, no. (%)	209 (62)
APOE-ε4 carriers, no. (%)	171 (50.7)
Baseline CAIDE score, mean (SD)[a]	6.31 (2.08)
Follow-up HADS total scores, mean (SD)[b]	6.99 (5.11)
Change in minutes of physical activity, mean (SD)	21.1 (139.6)
Maintained sedentary behavior, no. (%)	99 (29.4)
Maintained non-adherence, no. (%)	82 (24.3)
Maintained adherence, no. (%)	57 (16.9)
Became non-adherent, no. (%)	46 (13.6)
Became adherent, no. (%)	53 (15.7)
Brain Aβ burden (*CL*), mean (SD)[c]	2.57 (16.3)
AD Signature cortical thickness (mm^3)[d]	2.49 (0.08)
Time from baseline to follow-up evaluations, mean (SD), years	4.07 (0.84)

Abbreviations: Aβ, amyloid–β, AD, Alzheimer's disease; APOE, apolipoprotein E; CAIDE, cardiovascular risk factors, aging, and incidence of dementia; CL, Centiloid; HADS, Hospital Anxiety and Depression Scale; PET, positron emission tomography.
[a] $n = 327$.
[b] $n = 336$.
[c] $n = 277$.
[d] $n = 299$.

3.2 | Adherence to the WHO-recommended activity levels versus maintaining sedentary behavior in relation to brain outcomes

Participants with maintained sedentary behavior had lower cortical thickness in AD signature regions compared to those who maintained non-adherence, maintained adherence, or became adherent to the WHO-recommended activity levels. They also showed higher brain Aβ burden compared to those who became adherent to the WHO-recommended activity levels. Only the latter finding did not survive the FDR correction (Table 4/A).

3.3 | Maintained or new adherence to WHO-recommended activity levels versus other activity status in relation to brain outcomes

Participants who maintained adherence to the WHO-recommended levels did not show significant differences in brain Aβ burden or AD signature cortical thickness when compared to those who maintained non-adherence, became non-adherent, or became adherent to the recommendations (Table 4/B).

Participants who became adherent to WHO recommendations showed lower Aβ burden compared to those who became non-adherent to the recommendations. This finding survived the FDR correction. On the other hand, they did not show any significant AD signature cortical thickness differences compared to those who maintained non-adherence or became non-adherent to the recommended activity levels (Table 4/C).

3.4 | Association between change in physical activity amounts and brain outcomes

Increased physical activity amounts from baseline to follow-up were associated with lower levels of Aβ burden (B = −0.015; 95% CI −0.027 to −0.003; $p = 0.012$, Figure 2), which survived the FDR correction. No association was found between change in activity amounts and AD signature cortical thickness ($p = 0.652$).

3.5 | Sensitivity analysis

3.5.1 | Adjustments by cardiovascular and mental health variables

Following the adjustment of the models by CAIDE-I and HADS scores, previously observed results remained significant except for the difference in AD signature cortical thickness between the maintained sedentary behavior and maintained adherence groups, which reduced to a non-significant trend ($p = 0.066$, Table S1).

4 | DISCUSSION

In middle-aged adults at increased risk of AD, our findings showed that maintaining sedentary behavior over time was related to lower cortical thickness in AD-vulnerable brain structures. New adherence to the WHO-recommended activity levels during midlife, instead, was related to lower brain Aβ burden as compared to becoming non-adherent, and to a lesser extent, as compared to maintaining sedentary behavior. Additionally, our findings suggest a dose-dependent relationship between increased physical activity amounts and lower levels of brain Aβ burden, but not cortical thickness of AD-vulnerable brain structures. Overall, these findings suggest a beneficial effect of increased physical activity in preclinical AD.

In the current study, participants who maintained adherence, became adherent, and maintained non-adherence to the WHO-recommended activity levels demonstrated greater cortical thickness in AD-vulnerable brain structures as compared to those who maintained sedentary behavior. In line with these findings, previous research reported lower cortical thickness in medial temporal lobe structures in sedentary individuals.[25] A possible explanation is that sedentary behavior may be an indicator of brain atrophy, and individuals may engage more in sedentary behavior as a result of brain

TABLE 3 Sociodemographic and clinical characteristics of the physical activity groups.

Parameter	Age	Education (years)	Minutes of change in physical activity	CAIDE	HADS	Sex (women)	*APOE ε4* carriers
Maintained sedentary behavior ($n = 99$)	60.6 (4.65)	12.8 (3.56)	0	7.04 (1.99)	7.57 (5.41)	63 (63.6%)	55 (55.6%)
Maintained non-adherence ($n = 82$)	59.9 (4.90)	13.3 (3.64)	4.50 (64.8)	6.17 (2.14)	7.72 (5.44)	59 (72%)	37 (45.1%)
Maintained adherence ($n = 57$)	60.6 (4.49)	14.2 (3.70)	79.7 (149.6)	5.70 (1.78)	6.28 (4.57)	27 (47.7%)	27 (47.4%)
Became non-adherent ($n = 46$)	60.7 (4.90)	13.6 (3.34)	−169.8 (117.5)	5.93 (2.40)	7.33 (5.60)	26 (56.5%)	29 (63%)
Became adherent ($n = 53$)	60.7 (5.16)	14.4 (3.25)	189.1 (131.4)	6.17 (1.85)	5.25 (3.56)	34 (64.2%)	23 (43.4%)

Note: CAIDE is available at the baseline visit for a total of 95 participants with maintained sedentary behavior, 81 participants who maintained non-adherence, 54 participants who maintained adherence, and 45 participants who became non-adherent to World Health Organization physical activity recommendations. HADS is available at the follow-up visit for a total of 98 participants with maintained sedentary behavior.
Abbreviations: CAIDE, cardiovascular risk factors, aging, and incidence of dementia; HADS, Hospital Anxiety and Depression Scale.

TABLE 4 Results from the analyses comparing WHO-based physical activity groups in relation to brain outcomes.

	Outcomes			
	AD signature cortical thickness		Brain Aβ burden	
A. Reference category: Maintained sedentary behavior	**B (95% CI)**	***p***	**B (95% CI)**	***p***
Maintained non-adherence	0.027 (0.002 to 0.052)	**0.036***	−2.06 (−7.17 to 3.05)	0.428
Maintained adherence	0.036 (0.007 to 0.063)	**0.014***	−2.11 (−7.73 to 3.51)	0.461
Became non-adherent	0.029 (−0.001 to 0.059)	0.059	0.87 (−5.27 to 7.02)	0.780
Became adherent	0.039 (0.01 to 0.068)	**0.008***	−7.20 (−12.9 to −1.47)	**0.014**
B. Reference category: Maintained adherence	**B (95% CI)**	***p***	**B (95% CI)**	***p***
Maintained non-adherence	−0.006 (−0.036 to 0.025)	0.705	0.126 (−5.09 to 5.34)	0.962
Became non-adherent	−0.007 (−0.042 to 0.028)	0.691	2.90 (−3.09 to 8.88)	0.341
Became adherent	0.006 (−0.028 to 0.04)	0.730	−5.04 (−10.6 to 0.574)	0.078
C. Reference category: Became adherent	**B (95% CI)**	***p***	**B (95% CI)**	***p***
Maintained non-adherence	−0.012 (−0.044 to 0.021)	0.476	3.94 (−1.70 to 9.57)	0.169
Became non-adherent	−0.015 (−0.052 to 0.023)	0.434	7.90 (1.66 to 14.1)	**0.014***

Note: Models were controlled for age, sex, years of education, *APOE ε4* status, and the inter-individual variability in time between the two physical activity assessments. Statistically significant *p* values are highlighted in bold.
Abbreviations: Aβ, amyloid-β; AD, Alzheimer's disease; APOE, apolipoprotein E; CI, confidence interval; WHO, World Health Organization.
**p*-value survived the false discovery rate correction.

atrophy.[42] Alternatively, our findings suggest a favorable effect of physical activity in preserving structural integrity in age- or AD-related brain regions. This is further supported by previous studies observing greater gray matter volumes in AD-vulnerable structures[43,44] and a decreased risk of dementia[45] in individuals who replaced sedentary behavior with physical activity. Finally, greater cortical thickness observed in participants with insufficient activity levels (i.e., maintained non-adherence group) as compared to those who maintained sedentary behavior aligns with the current WHO guidelines, which suggests that doing some activity is better than none for achieving health benefits.[28]

Regarding Aβ pathology, our findings showed lower brain Aβ burden in participants who became adherent to the WHO-recommended physical activity levels as compared to those who became non-adherent or maintained sedentary behavior, although the evidence for the latter finding was weaker. Nonetheless, these findings are consistent with previous studies reporting greater Aβ pathology in individuals with lower activity levels,[19] or with sedentary behavior.[21,46]

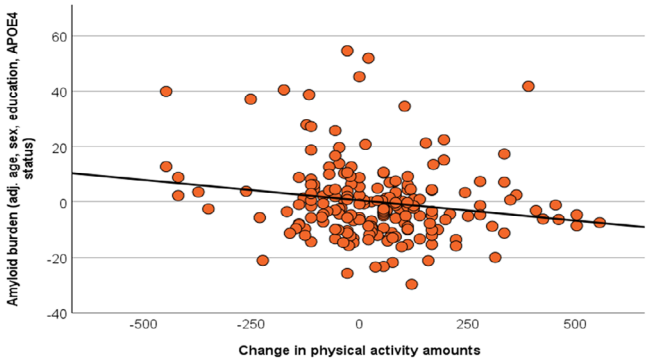

FIGURE 2 Change in physical activity amounts in relation to brain Aβ burden. Scatter plot illustrating brain amyloid-β burden (Centiloids) as a function of change in physical activity amounts from baseline to follow-up. Age, sex, years of education, *APOE*-ε4 status, and inter-individual variability in time between the two physical activity assessments were regressed out from the Centiloid values. Aβ, amyloid-beta; APOE, apolipoprotein E.

Notably, there were no differences in Aβ levels between the participants with new or maintained adherence to the recommended activity levels. Furthermore, we observed lower Aβ levels as a function of increased physical activity amounts, suggesting a dose-dependent effect of physical activity on Aβ levels. Altogether, these findings suggest that increased physical activity during midlife may play a role in enhancing the brain's resistance against Aβ accumulation in individuals at risk of developing AD. Importantly, these findings were independent of cardiovascular and mental health factors, suggesting a potential link between physical activity and the production and/or clearance of Aβ.[11,47] Nevertheless, these associations may be mediated by other factors that were not investigated in our study, such as enhanced sleep[11] or neurogenesis.[15]

Maintained adherence to the WHO-recommended activity levels during midlife was related to greater cortical thickness in AD signature only when compared to maintained sedentary behavior, which dissipated following the adjustments by cardiovascular and mental health factors. Contrary to our hypothesis, maintained adherence to the recommendations was also not related to lower brain Aβ burden compared to engaging in insufficient activity levels or maintaining sedentary behavior. A possible explanation is that additional activity may have little[48] or no benefit[27] after passing a certain threshold.[49] Alternatively, the beneficial effects of physical activity on Aβ levels may depend on the increase in the amount of activity, rather than surpassing a specific activity threshold.

The current study has some limitations. Although we evaluated physical activity longitudinally, brain outcomes were measured at one time point, raising the possibility of a reverse causation in interpreting the results (i.e., increases in sedentary behavior or inactivity due to pathological changes in preclinical AD). Indeed, ALFA+ participants are CU and the potential effects of lifestyle changes on AD pathology could be more evident in the symptomatic stages. Nevertheless, imaging measures are being acquired longitudinally as part of the ALFA+ study, which will enable future work to clarify the directionality of potential causal relationships between physical activity and AD-related pathologies. Further, we used a self-reported questionnaire to assess physical activity, and determined the activity intensities in a subjective manner (e.g., activities can be moderate- or vigorous-intensity depending on the effort),[50] which may have resulted in a bias while creating the WHO-based physical activity groups. Future studies with objective measures are warranted as they may better evaluate the possible AD-related brain benefits of the WHO recommendations. Another limitation is the 4.07 ± 0.84 years' time interval between the two physical activity assessments, given that the MLTPAQ measures the activity performed over the course of 1 year.[30] However, investigating activity patterns over a longer time frame may be useful to evaluate lifestyle-related behavior patterns instead of short-term habits. Finally, our sample consisted of individuals at an increased risk of AD, which limits the generalizability of our findings to the general population of middle-aged individuals.

Overall, our findings suggest that increasing physical activity during midlife, including to the levels recommended by the WHO, may have beneficial effects on Aβ pathology. Remaining sedentary during midlife, instead, may have detrimental effects on cortical thickness of brain structures vulnerable to AD. These results support the beneficial effect of physical activity and new adherence to the WHO recommendations from the standpoint of AD prevention, and call for interventions to promote physical activity increases in middle-aged adults in preclinical AD.

ACKNOWLEDGMENTS

This publication is part of the ALFA study (ALzheimer and FAmilies). The authors express their sincerest gratitude to the participants of the ALFA project. Collaborators of the ALFA study are: Ricardo Aquite Aguilar, Annabella Beteta Gorriti, Anna Brugulat-Serrat, Raffaele Cacciaglia, Lidia Canals Gispert, Alba Cañas Martinez, Marta del Campo Milan, Ruth Dominguez Iglesias, Sherezade Fuentes Julian, Patricia Genius Serra, Armand González-Escalante, Laura Hernández Penas, Gema Huesa Rodriguez, Jordi Huguet Ninou, Laura Iglesias Gamaz, Iva Knezevic, Paula Marne Alvarez, Tania Menchón Diaz, Eva Palacios, Maria Pascual, Albina Polo Ballester, Sandra Pradas Mendez, Blanca Rodríguez-Fernandez, Laura Ros Freixedes, Aleix Sala Vila, Lluis Solsona Harster, Anna Soteras Prat, Marc Vilanova Jaramillo, and Natalia Vilor-Tejedor. This work was supported by 'la Caixa' Foundation (ID 100010434), under agreement LCF/PR/GN17/50300004, the Alzheimer's Association, and an international anonymous charity foundation through the TriBEKa Imaging Platform project (TriBEKa-17-519007). Support has also been received from the Universities and Research Secretariat, Ministry of Business and Knowledge of the Catalan Government under grant no. 2021 SGR 00913. EMA-U has received funding by the Ministry of Science and Innovation (PID2019-111514RA-I00) and the Alzheimer's Association research grants (AARG 2019-AARG-644641, AARG 2019-AARG-644641-RAPID). EMA-U is supported by the Spanish Ministry of Science and Innovation—State Research Agency (RYC2018-026053-I), co-funded by the European Social Fund (ESF) and EU Joint Programme-Neurodegenerative Disease Research (JPND2022-138). EP is funded

by the Spanish Ministry of Science and Innovation (PRE2020-095827). MSC receives funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (Grant agreement No. 948677), Project "PI19/00155", funded by Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union, and from a fellowship from "la Caixa" Foundation (ID 100010434) and from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 847648 (LCF/BQ/PR21/11840004). We acknowledge support from the grant CEX2018-000806-S funded by MCIN/AEI/10.13039/501100011033, and support from the Generalitat de Catalunya through the CERCA Program.

CONFLICT OF INTEREST STATEMENT

O.G-R. has given lectures in symposia sponsored by Roche Diagnostics, and receives support for research (to the institution) from F- Hoffmann La Roche. MSC has given lectures in symposia sponsored by Roche Diagnostics, S.L.U, Roche Farma, S.A and Amirall. He has served as a consultant and at advisory boards for Roche Diagnostics International Ltd and Grifols S.L. He was granted with a project funded by Roche Diagnostics International Ltd; payments were made to the institution (BBRC). He received in-kind support for research (to the institution) from Roche Diagnostics International Ltd, Avid Radiopharmaceuticals, Inc., Eli Lilly and Janssen Research & Development. J.G.-A. reports speaking and lecture fees from Chiesi España and AstraZeneca Pharmaceuticals LP, not related to the topic of this publication. M.A., P.A.-D., E.P., M.G.-P., M.S., C.D., K.F., J.D.G., G.S.-B., and E.M.A.-U. declare that they have no competing interests. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All human subjects provided informed consent.

REFERENCES

1. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement J Alzheimers Assoc*. 2011;7(3):280-292. doi:10.1016/j.jalz.2011.03.003
2. Dubois B, Hampel H, Feldman HH, et al. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimers Dement J Alzheimers Assoc*. 2016;12(3):292-323. doi:10.1016/j.jalz.2016.02.002
3. 2023 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2023;19(4):1598-1695. doi:10.1002/alz.13016
4. Crous-Bou M, Minguillón C, Gramunt N, Molinuevo JL. Alzheimer's disease prevention: from risk factors to early intervention. *Alzheimers Res Ther*. 2017;9:71. doi:10.1186/s13195-017-0297-z
5. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol*. 2014;13(8):788-794. doi:10.1016/S1474-4422(14)70136-X
6. Nianogo RA, Rosenwohl-Mack A, Yaffe K, Carrasco A, Hoffmann CM, Barnes DE. Risk factors associated with Alzheimer disease and related dementias by sex and race and ethnicity in the US. *JAMA Neurol*. 2022;79(6):584-591. doi:10.1001/jamaneurol.2022.0976
7. Barnes DE, Yaffe K. The projected impact of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol*. 2011;10(9):819. doi:10.1016/S1474-4422(11)70072-2
8. Yan S, Fu W, Wang C, et al. Association between sedentary behavior and the risk of dementia: a systematic review and meta-analysis. *Transl Psychiatry*. 2020;10:112. doi:10.1038/s41398-020-0799-5
9. Buchman AS, Boyle PA, Yu L, Shah RC, Wilson RS, Bennett DA. Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology*. 2012;78(17):1323-1329. doi:10.1212/WNL.0b013e3182535d35
10. 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(1):510. doi:10.1186/1471-2458-14-510
11. Iso-Markku P, Kujala UM, Knittle K, Polet J, Vuoksimaa E, Waller K. Physical activity as a protective factor for dementia and Alzheimer's disease: systematic review, meta-analysis and quality assessment of cohort and case-control studies. *Br J Sports Med*. 2022;56(12):701-709. doi:10.1136/bjsports-2021-104981
12. Gallaway PJ, Miyake H, Buchowski MS, et al. Physical activity: a viable way to reduce the risks of mild cognitive impairment, alzheimer's disease, and vascular dementia in older adults. *Brain Sci*. 2017;7(2):22. doi:10.3390/brainsci7020022
13. Zotcheva E, Bergh S, Selbæk G, et al. Midlife physical activity, psychological distress, and dementia risk: the hunt study. *J Alzheimers Dis JAD*. 2018;66(2):825-833. doi:10.3233/JAD-180768
14. Tin A, Bressler J, Simino J, et al. Genetic risk, midlife life's simple 7, and incident dementia in the atherosclerosis risk in communities study. *Neurology*. 2022;99(2):e154-e163. doi:10.1212/WNL.0000000000200520
15. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*. 2020;396(10248):413-446. doi:10.1016/S0140-6736(20)30367-6
16. Profenno LA, Porsteinsson AP, Faraone SV. Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. *Biol Psychiatry*. 2010;67(6):505-512. doi:10.1016/j.biopsych.2009.02.013
17. Vemuri P. "Exceptional brain aging" without Alzheimer's disease: triggers, accelerators, and the net sum game. *Alzheimers Res Ther*. 2018;10(1):53. doi:10.1186/s13195-018-0373-z
18. Ritchie K, Ritchie CW, Yaffe K, Skoog I, Scarmeas N. Is late-onset Alzheimer's disease really a disease of midlife? *Alzheimers Dement Transl Res Clin Interv*. 2015;1(2):122-130. doi:10.1016/j.trci.2015.06.004
19. Liang KY, Mintun MA, Fagan AM, et al. Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. *Ann Neurol*. 2010;68(3):311-318. doi:10.1002/ana.22096
20. 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. *Mol Psychiatry*. 2013;18(8):875-881. doi:10.1038/mp.2012.107
21. 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. *Alzheimers Dement Amst Neth*. 2018;10:188-195. doi:10.1016/j.dadm.2018.01.001
22. 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(2):e0247225. doi:10.1371/journal.pone.0247225
23. Okonkwo OC, Schultz SA, Oh JM, et al. Physical activity attenuates age-related biomarker alterations in preclinical AD. *Neurology*. 2014;83(19):1753-1760. doi:10.1212/WNL.0000000000000964

24. Bugg JM, Head D. Exercise moderates age-related atrophy of the medial temporal lobe. *Neurobiol Aging*. 2011;32(3):506-514. doi:10.1016/j.neurobiolaging.2009.03.008
25. Siddarth P, Burggren AC, Eyre HA, Small GW, Merrill DA. Sedentary behavior associated with reduced medial temporal lobe thickness in middle-aged and older adults. *PLoS ONE*. 2018;13(4):e0195549. doi:10.1371/journal.pone.0195549
26. Xu W, Wang HF, Wan Y, Tan CC, Yu JT, Tan L. Leisure time physical activity and dementia risk: a dose-response meta-analysis of prospective studies. *BMJ Open*. 2017;7(10):e014706. doi:10.1136/bmjopen-2016-014706
27. Wu W, Ding D, Zhao Q, et al. Dose-response relationship between late-life physical activity and incident dementia: a pooled analysis of 10 cohort studies of memory in an international consortium. *Alzheimers Dement J Alzheimers Assoc*. 2023;19(1):107-122. doi:10.1002/alz.12628
28. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med*. 2020;54(24):1451-1462. doi:10.1136/bjsports-2020-102955
29. Molinuevo JL, Gramunt N, Gispert JD, et al. The ALFA project: a research platform to identify early pathophysiological features of Alzheimer's disease. *Alzheimers Dement N Y N*. 2016;2(2):82-92. doi:10.1016/j.trci.2016.02.003
30. Taylor HL, Jacobs DR, Schucker B, Knudsen J, Leon AS, Debacker G. A questionnaire for the assessment of leisure time physical activities. *J Chronic Dis*. 1978;31(12):741-755. doi:10.1016/0021-9681(78)90058-9
31. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol*. 2006;5(9):735-741. doi:10.1016/S1474-4422(06)70537-3
32. Salvadó G, Brugulat-Serrat A, Sudre CH, et al. Spatial patterns of white matter hyperintensities associated with Alzheimer's disease risk factors in a cognitively healthy middle-aged cohort. *Alzheimers Res Ther*. 2019;11:12. doi:10.1186/s13195-018-0460-1
33. Brugulat-Serrat A, Salvadó G, Sudre CH, et al. Patterns of white matter hyperintensities associated with cognition in middle-aged cognitively healthy individuals. *Brain Imaging Behav*. 2020;14(5):2012-2023. doi:10.1007/s11682-019-00151-2
34. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361-370. doi:10.1111/j.1600-0447.1983.tb09716.x
35. Klunk WE, Koeppe RA, Price JC, et al. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimers Dement*. 2015;11(1):1-15.e4. doi:10.1016/j.jalz.2014.07.003
36. Salvadó G, Molinuevo JL, Brugulat-Serrat A, et al. Centiloid cut-off values for optimal agreement between PET and CSF core AD biomarkers. *Alzheimers Res Ther*. 2019;11(1):27. doi:10.1186/s13195-019-0478-z
37. Desikan RS, Ségonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*. 2006;31(3):968-980. doi:10.1016/j.neuroimage.2006.01.021
38. Fischl B, Salat DH, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002;33(3):341-355. doi:10.1016/s0896-6273(02)00569-x
39. Jack CR, Wiste HJ, Weigand SD, et al. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. *Alzheimers Dement J Alzheimers Assoc*. 2017;13(3):205-216. doi:10.1016/j.jalz.2016.08.005
40. Dickerson BC, Stoub TR, Shah RC, et al. Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults. *Neurology*. 2011;76(16):1395-1402. doi:10.1212/WNL.0b013e3182166e96
41. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B Methodol*. 1995;57(1):289-300. doi:10.1111/j.2517-6161.1995.tb02031.x
42. Arnardottir NY, Koster A, Van Domelen DR, et al. Association of change in brain structure to objectively measured physical activity and sedentary behavior in older adults: age, Gene/Environment Susceptibility-Reykjavik Study. *Behav Brain Res*. 2016;296:118-124. doi:10.1016/j.bbr.2015.09.005
43. Colcombe SJ, Erickson KI, Scalf PE, et al. Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci*. 2006;61(11):1166-1170. doi:10.1093/gerona/61.11.1166
44. Rosano C, Guralnik J, Pahor M, et al. Hippocampal response to a 24-month physical activity intervention in sedentary older adults. *Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry*. 2017;25(3):209-217. doi:10.1016/j.jagp.2016.11.007
45. Sun Y, Chen C, Yu Y, et al. Replacement of leisure-time sedentary behavior with various physical activities and the risk of dementia incidence and mortality: a prospective cohort study. *J Sport Health Sci*. 2023;12(3):287-294. doi:10.1016/j.jshs.2022.11.005
46. 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(5):636-643. doi:10.1001/archneurol.2011.845
47. De la Rosa A, Olaso-Gonzalez G, Arc-Chagnaud C, et al. Physical exercise in the prevention and treatment of Alzheimer's disease. *J Sport Health Sci*. 2020;9(5):394-404. doi:10.1016/j.jshs.2020.01.004
48. Erickson KI, Raji CA, Lopez OL, et al. Physical activity predicts gray matter volume in late adulthood. *Neurology*. 2010;75(16):1415-1422. doi:10.1212/WNL.0b013e3181f88359
49. Geda YE, Roberts RO, Knopman DS, et al. Physical exercise and mild cognitive impairment: a population-based study. *Arch Neurol*. 2010;67(1):80-86. doi:10.1001/archneurol.2009.297
50. Piercy KL, Troiano RP, Ballard RM, et al. The physical activity guidelines for Americans. *JAMA*. 2018;320(19):2020-2028. doi:10.1001/jama.2018.14854

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: Akinci M, Aguilar-Domínguez P, Palpatzis E, et al. Physical activity changes during midlife link to brain integrity and amyloid burden. *Alzheimer's Dement*. 2025;21:e70007. https://doi.org/10.1002/alz.70007