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Original Article

# Lifetime walking and Alzheimer's pathology: A longitudinal study in older adults

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## ABSTRACT

*Importance:* While many studies have shown that greater amounts or longer durations of walking are associated with a lower risk of Alzheimer's disease (AD) or cognitive decline in older adults, the neuropathological basis for this is not yet fully understood.
*Objective:* To examine the relationship between walking intensity and duration and longitudinal changes in Alzheimer's disease (AD)-related brain pathologies, including A$\beta$ and tau accumulation, neurodegeneration, and white matter hyperintensity (WMH).
*Design:* Data were drawn from the Korean Brain Aging Study for the Early Diagnosis and Prediction of AD, a longitudinal cohort study (initiated in 2014).
*Setting:* Community and memory clinic setting.
*Participants:* One hundred fifty-one older adults.
*Main Outcome and Measures:* Participants underwent baseline and 4-year follow-up neuroimaging assessments. Lifetime walking, as measured using the Lifetime Total Physical Activity Questionnaire, was categorized by intensity (high vs. low) and duration (short ≤360 min/week vs. long >360 min/week), forming four combined walking groups. A$\beta$ and tau deposition, neurodegeneration, and WMH volume were assessed via PET/MRI.
*Results:* Long-duration or high-intensity walking was associated with significantly reduced A$\beta$ accumulation over 4 years. The high-combined walking group showed similar benefits, while medium-combined groups did not.

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The effect was significant only in the early life-initiated walking subgroup. No associations were found with tau, neurodegeneration, or WMH volume.
*Conclusions:* Long-duration, high-intensity walking may reduce brain A$\beta$ accumulation, potentially lowering AD risk, particularly when initiated before late life.

## 1. Introduction

Alzheimer's disease (AD), the leading neurodegenerative condition among the older adults, is fundamentally characterized by the buildup of beta-amyloid (A$\beta$) outside neurons and the clustering of hyperphosphorylated tau proteins within them[1]. With no effective medications to prevent AD, evidence-based lifestyle interventions like physical activity are gaining attention. Increasing research suggests that physical activity may reduce the risk of AD and cognitive decline[2–6]. While most research has focused on the overall impact of physical activity in preventing AD and cognitive impairment [2,3], there is growing recognition that specific forms of exercise may offer unique protective benefits[6,7].

Walking is a universally accessible exercise suitable for all ages, sustainable over time, and requiring no special equipment. Its gentle nature minimizes injury risks, making it especially safe for older adults and those with health issues. Notably, many studies have shown an inverse relationship between walking speed or intensity and dementia risk[8,9]. Several studies have shown that greater amounts or longer durations of walking are associated with a lower risk of AD or cognitive decline in older adults[7,10–12].

Nonetheless, the neuropathological basis for the link between walking and reduced cognitive decline or AD risk is not yet fully understood. Animal studies suggest that regular aerobic exercise, like treadmill workouts, can influence AD pathophysiology by reducing A$\beta$ deposition, attenuating astrocyte activation, and affecting brain insulin signaling[13–17]. As for human studies, a few cross-sectional studies have associated overall physical activity or habitual exercise with reduced cerebral A$\beta$ load in non-demented older adults[18,19]. While a recent study investigated the association between regular physical activity and longitudinal changes in cerebral A$\beta$ deposition resulting in negative results [20], data on the specific relationship between walking—a safe and easily accessible form of physical activity—and longitudinal changes in AD pathologies remain scarce.

Taken together, this study aimed to test the hypothesis that high-intensity and long-duration walking activity is associated with reduced longitudinal changes in vivo core AD pathologies, including cerebral A$\beta$ and tau accumulation, in physically capable, non-demented older adults. We also examined the relationship between the intensity and duration of walking activity and longitudinal changes in AD-related neurodegeneration and white matter injury. Additionally, we explored whether the timing of walking activity initiation (early life-initiated vs. late life-initiated) influences the association between walking activity and changes in pathology, considering previously reported variations in the relationship between physical activity and AD-related cognitive decline[6,7].

## 2. Methods

### 2.1. Participants

This study is part of the Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease (KBASE), which is an ongoing cohort study that began in 2014[21]. As of March 2019, a total of 151 non-demented participants, comprising cognitively normal (CN) individuals and those with mild cognitive impairment (MCI), who had completed both baseline and 4-year follow-up MRI and PET scans for brain A$\beta$ deposition, were included (eFigure 1).

Participants were recruited from four sites in Seoul, South Korea, including two public dementia prevention centers and two university-affiliated memory clinics. Potentially eligible individuals were informed about the study, and those expressing interest underwent eligibility screening. Community volunteers were also recruited through online advertisements, printed materials, and referrals from participants or their acquaintances. The CN group consisted of participants with a Clinical Dementia Rating (CDR) score of 0 and no diagnosis of MCI or dementia. All participants with MCI met the current consensus criteria for amnestic MCI, including: 1) memory complaints confirmed by an informant; 2) objective memory impairments; 3) preservation of global cognitive function; 4) independence in functional activities; and 5) absence of dementia. Regarding Criterion 2, the age-, education-, and gender-adjusted z-score was $< -1.0$ [22,23] for at least one of four episodic memory tests: Word List Memory, Word List Recall, Word List Recognition, and Constructional Recall tests included in the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) neuropsychological battery. All MCI individuals had a CDR score of 0.5. The exclusion criteria were the following: 1) presence of a major psychiatric illness; 2) significant neurological or medical condition or comorbidity that could affect mental functioning; 3) contraindications for an MRI scan (e.g., pacemaker or claustrophobia); 4) illiteracy; 5) presence of significant visual/hearing difficulties and/or severe communication or behavioral problems that would make clinical examinations or brain scans difficult; 6) pregnancy or lactation; and, 7) use of an investigational drug. Further details on the KBASE cohort recruitment are provided in our previous report[21]. The institutional review boards of Seoul National University Hospital (C-1401–027–547) in Seoul, South Korea, approved the study protocol. The study adhered to the latest guidelines of the Declaration of Helsinki, and written informed consent was obtained from all participants.

### 2.2. Clinical assessment

The participants were comprehensively evaluated at the beginning of the study using the KBASE protocol [21], which included the CERAD-K assessment battery, by trained psychiatrists. In addition, nutritional markers, including serum albumin, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, fasting glucose, and homocysteine, were measured to account for potential confounding effects in the relationship between walking and AD-related brain pathologies. Blood samples were collected after an overnight fast and analyzed using standardized methods. Details are described in the supplementary materials (eMethods).

### 2.3. Assessment of walking, exercise, and MET values

All participants underwent structured interviews to assess their lifetime exercise and sport activities, including walking, through the exercise and sport activities section of the Lifetime Total Physical Activity Questionnaire (LTPAQ), which is recognized for its reliability and validity[24,25]. Following the questionnaire's comprehensive user guide (https://www.cepr.ca/wp-content/uploads/2017/12/LTPAQ_Users-Guide.pdf), a trained nurse asked participants to report all exercise and sports activities, including walking, since childhood. Participants were reminded of the minimum number of hours required for an activity to be included (32 hours total per year, 40 min per week per year, or 2 hours per week for 4 months, if seasonal). For each activity, participants reported the age at which they started and stopped, the

frequency (months per year, weeks per month, and days per week), and the time spent on the activity (hours). Activities were categorized into three intensity levels: light (minimal physical effort), moderate (slight increase in heart rate and light perspiration), and vigorous (significant increase in heart rate and heavy sweating). Based on walking activity data from the LTPAQ, participants were categorized into three groups: no-walking (not meeting the minimum level), low-intensity walking (below moderate intensity), and high-intensity walking (moderate to vigorous intensity). They were also categorized by walking duration into no-walking (not meeting the minimum level), short-duration (≤360 min per week), and long-duration (>360 min per week) groups. The threshold of 360 min per week was adopted based on criteria utilized in previous studies that investigated differences in cognition or other health-related indicator according to walking duration categories[7,26]. To explore the potential synergistic effects of intensity and duration on brain pathology, participants were further categorized into four groups: no-walking, low-combined level walking (low-intensity & short-duration), medium-combined level walking (low-intensity & long-duration or high-intensity & short-duration), and high-combined level walking (high-intensity & long-duration). Furthermore, participants were divided into two groups based on the timing of walking activity initiation: early life-initiated walking (before age 65) and late life-initiated walking (age 65 and above), considering previous studies suggesting that the timing of activity onset influences its protective effects against dementia and AD[27,28]. Using data from the exercise and sporting activities section of the LTPAQ, a metabolic equivalent (MET) value was assigned to each activity based on the Compendium of Physical Activities. The MET value of other lifetime exercise and sports activities except walking was calculated as the sum of average MET-hours per week spent on these activities during lifetime.

### 2.4. Measurement of in vivo AD pathologies and white matter hyperintensities

At both baseline and 4-year follow-up visits, all participants received [11C] Pittsburgh compound B (PiB)-PET and T1-weighted MRI scans using a 3.0T Biograph mMR (PET-MR) scanner. A subset of 108 participants underwent [18F] AV-1451 PET scans using a Biograph Truepoint 40 PET/CT scanner approximately 2.5 years after baseline, with 48 participants receiving follow-up scans 2 years later. For longitudinal analysis, cerebrum white matter was used as the reference region for intensity normalization, with adjustments made to the reference region in the partial volume correction code. AD-signature cortical thickness (AD-CT) was calculated from regions including the entorhinal, inferior temporal, middle temporal, and fusiform gyrus. White matter hyperintensitiy (WMH) volumes were derived from FLAIR images using validated procedures. Full details of imaging acquisition, preprocessing, and analysis are provided in the supplementary materials (eMethods).

### 2.5. Assessment of other potential confounders

To account for various factors that could influence the relationship between walking and AD pathologies, we assessed several potential confounders. Depression levels were measured using the Geriatric Depression Scale (GDS) [29], while cognitive activity was evaluated with a 39-item questionnaire[30]. Occupational complexity was classified based on participants' longest-held jobs, according to the International Standard Classification of Occupations. Income levels were categorized using the minimum cost of living standards set by the Ministry of Health and Welfare, Republic of Korea. Vascular risk factors, including hypertension, diabetes, coronary artery disease, hyperlipidemia, transient ischemic attack, and stroke, were identified through interviews and verified sources. Additionally, dietary patterns, including intake of protein and fruits/vegetables, were assessed using mini nutritional tools[31]. Extrapyramidal motor signs were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS), focusing on total and gait item scores, due to the impact of motor function on walking[32]. Detailed descriptions of these assessments are provided in the supplementary materials (eMethods).

### 2.6. Statistical analyses

To examine the associations between walking groups and longitudinal changes in brain pathologies, we first performed multiple linear regression analyses. Longitudinal changes in neuroimaging markers, computed as the difference between baseline and follow-up values, served as the dependent variable, while walking groups were included as the independent variable, with the no-walking group as the reference category. Covariates were included to adjust for potential confounding factors. The first model controlled for age, sex, apolipoprotein E $\varepsilon$4 allele (APOE4) positivity, education level, GDS score, LCA score, occupational complexity, annual income, alcohol intake, smoking status, dietary patterns (e.g., protein and fruit/vegetable intake), clinical diagnosis (CN vs. MCI), BMI, serum nutritional markers (albumin, glucose, HDL-/LDL-cholesterol, hemoglobin, homocysteine, or malnutrition status), hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia, transient ischemic attack, and UPDRS score. The second model included all covariates from the first model and additionally adjusted for the index of other lifetime exercise and sports activities to disentangle a walking-specific effect that is distinct from general physical activity. Neuroimaging changes were computed as the difference between baseline and follow-up values. Linear mixed-effects model analyses were additionally employed to assess time × walking group interaction effects, as well as within- and between-subject effects, on neuroimaging markers. The same covariates included in the second model for linear regression analyses were adjusted in the linear mixed-effects model analyses. For each type of analysis, a Bonferroni-corrected $P$ ($P_B$ = 0.05/number of analyses) was applied as the threshold for statistical significance; the $P_B$ was < 0.0125 (0.05/4). Additionally, we investigated whether the timing of walking activity initiation (i.e., early life-initiated vs. late life-initiated) influenced the relationship between walking activity and longitudinal changes in neuroimaging markers. We also conducted moderation analyses to explore whether potential modifiers—such as age, sex, APOE4 positivity, GDS score, BMI, clinical diagnosis, and vascular burden—alter the association between walking activity and AD-related brain pathologies. These variables were selected based on prior studies, which suggest their potential influence on the neuroprotective effects of physical activity in aging and AD[27,33–36]. To investigate this, we incorporated interaction terms into the regression models. All statistical analyses were performed using IBM SPSS Statistics 28 software (IBM, Armonk, NY, USA).

## 3. Results

### 3.1. Participant characteristics

Table 1 displays the demographic and clinical characteristics of the participants, categorized by four combined level walking groups. All participants were physically capable, meaning they could walk unassisted (with UPDRSm gait item score of 2 or less).

### 3.2. Association between walking levels and in vivo longitudinal changes in brain pathologies

Both the long-duration and high-intensity walking groups demonstrated a significant association with reduced A$\beta$ deposition over 4 years compared to the no-walking group (i.e., reference group), even after applying the Bonferroni correction ($P_B$ < 0.0125) (Table 2). In contrast, neither the short-duration nor the low-intensity walking group showed a significant difference in 4-year change in A$\beta$ deposition compared to the no-walking group (Table 2). For the combined level of walking, while the high-combined level group (characterized by both long-duration and

**Table 1**
Participant characteristics.

| Characteristic | Overall |
|---|---|
| N | 151 |
| Age, y | 69.70 (7.42) |
| Female, No. (%) | 89 (58.94) |
| Education | 11.15 (4.69) |
| MMSE | 25.97 (3.18) |
| APOE4 positivity, No. (%) | 29 (19.21) |
| Clinical diagnosis, CN, No. (%) | 119 (78.81) |
| **Duration of walking**, No. (%) | |
| None | 92 (60.93) |
| Short | 37 (24.50) |
| Long | 22 (14.57) |
| **Intensity of walking**, No. (%) | |
| None | 92 (60.93) |
| Low | 16 (10.60) |
| High | 43 (28.48) |
| **Combined level of walking**, No. (%) | |
| None | 92 (60.93) |
| Low-combined level | 14 (9.27) |
| Med-combined level | 25 (16.56) |
| High-combined | 20 (13.33) |
| **Walking timing, onset**, No. (%) | |
| None | 92 (60.93) |
| Early life (≤ 64 y) | 39 (25.83) |
| Young life (≤ 39 y) | 10 (6.62) |
| Midlife (40–64 y) | 29 (19.21) |
| Late life (≥ 65 y) | 20 (13.25) |
| **Lifetime leisure activity**, average MET-h/week | |
| Overall | 10.44 (16.66) |
| Walking | 2.41 (8.03) |
| Others | 8.03 (15.87) |
| **Lifetime cognitive activity score** | |
| **Occupational complexity,** No. (%) | |
| None | 23 (15.23) |
| Skill level 1 | 11 (7.28) |
| Skill level 2 | 53 (35.10) |
| Skill level 3 | 18 (11.92) |
| Skill level 4 | 46 (30.46) |
| **Annual income**, No. (%) | |
| <MCL | 10 (6.62) |
| ≥MCL, <2 × MCL | 58 (38.41) |
| ≥2 × MCL | 83 (54.97) |
| **Vascular risk**, No. (%) | |
| Hypertension | 67 (44.37) |
| Coronary artery disease | 9 (5.96) |
| Diabetes mellitus | 29 (19.21) |
| Hyperlipidemia | 52 (34.44) |
| Transient ischemic attack | 2 (1.32) |
| Stroke | 0 (0.00) |
| UPDRSm, gait disturbance requiring assistance, No. (%) | 0 (0.00) |
| UPDRSm, sum | 0.55 (1.80) |
| Geriatric depression scale, No. (%) | |
| Normal (<9) | 114 (75.50) |
| Depressed (≥10) | 37 (24.50) |
| **Dietary nutritional markers** | |
| Protein, No (%) | |
| High | 18 (11.92) |
| Moderate | 60 (39.74) |
| Low | 71 (47.02) |
| Fruit & Vegetables, No (%) | |
| High | 92 (60.93) |
| Low | 57 (37.75) |
| Alcohol intake, SD per week, lifetime | 5.36 (13.97) |
| Smoking, pack per day, lifetime | 0.29 (0.53) |
| **Blood nutritional markers** | |
| Albumin | 4.47 (0.25) |
| Glucose, fasting | 103.83 (22.60) |
| HDL-Cholesterol | 54.81 (14.75) |
| LDL-Cholesterol | 109.15 (31.65) |
| Hemoglobin, g/dL | 13.95 (1.28) |
| Homocysteine | 14.39 (5.72) |
| Malnutrition, No.(%) | 23 (15.23) |
| Body mass index, kg/m$^2$ | 24.34 (2.93) |
| **Neuroimage markers** | |
| A$\beta$, SUVR | |
| Baseline A$\beta$, SUVR | 0.83 (0.20) |
| ΔA$\beta$, SUVR | <0.01 (0.07) |
| Tau, SUVR ($n$ = 48) | |
| Baseline AV-1451, SUVR | 1.11 (0.20) |
| ΔAV-1451, SUVR) | 0.02 (0.20) |
| AD-CT, mm | |
| Baseline AD-CT, mm | 2.85 (0.19) |
| ΔAD-CT, mm | −0.09 (0.25) |
| WMH volume, cm$^3$ | |
| Baseline WMH volume, cm$^3$ | 13.23 (11.66) |
| ΔWMH volume, cm$^3$ | <0.01 (11.25) |

(*continued on next page*)

**Table 1** (*continued*)

MMSE=mini-mental state examination, APOE4=apolipoprotein $\varepsilon$4, CN=cognitively normal, MET= metabolic equivalent, MCL=minimum cost of living, UPDRSm=motor subscale of the unified Parkinson's disease rating scale, SD=standard drink, HDL=high density lipoprotein, LDL=low density lipoprotein, A$\beta$=beta-amyloid, AD=Alzheimer's disease, AD-CT=Alzheimer's disease signature cortical thickness, SUVR=standardized uptake value ratio, WMH=white matter hyperintensities, NA=not applicable.
Data are expressed as mean±standard deviation, unless otherwise indicated.
[a]by one-way analysis of variance,.
[b]by chi-square test.
[c]by fisher exact test.

high-intensity walking) showed a significant association with reduced A$\beta$ deposition over 4 years compared to the no-walking group. In contrast, no significant differences in A$\beta$ deposition were observed between the low- or medium-level groups and the no-walking group (Table 2). There were no significant differences among the walking groups in other brain pathological markers, including tau deposition, AD-CT, and WMH volume (Table 2). The linear mixed effects model analyses similarly showed a significantly negative time × walking group interaction effect on A$\beta$ deposition as well as a significant walking group effect

(Table 2, Fig. 1A-C), but did not reveal a time × walking group interaction effect on any other pathologies (Table 2).

### *3.3. Differential association between walking levels and longitudinal change in A$\beta$ pathology based on the initiation timing of walking activity*

The association between high-intensity (or long-duration or high-combined level) walking activity and the change in A$\beta$ deposition over a 4-year period was significant only in the early life-initiated walking subgroup, but not in the late life-initiated walking subgroup (Table 3).

### *3.4. Influence of potential moderators on the association between walking levels and A$\beta$ pathology*

No significant interactions were found between walking activity (combined walking levels) and any of the potential moderators, such as age, sex, APOE $\varepsilon$4 status, GDS score, BMI, clinical diagnosis, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, or transient ischemic attack (eTable 1).

## 4. Discussion

The present study revealed that both high-intensity (moderate to vigorous) and long-duration (averaging more than 360 min per week) walking activities were associated with a reduction in A$\beta$ accumulation over a 4-year period among physically capable, non-demented older adults. Notably, when considering both intensity and duration of walking, only the group that engaged in both high-intensity and long-duration walking exhibited a reduced accumulation of A$\beta$ over the 4-year follow-up period compared to the no-walking group, whereas the medium combined group, characterized by either high-intensity or long-duration walking

**Table 2**
Longitudinal results for the associations between walking duration, intensity, or a combination of both, and brain pathologies.

| | ΔA$\beta$, SUVR | | ΔAV-1451, SUVR | | ΔAD-CT, mm | | ΔWMH volume, $cm^3$ | |
|---|---|---|---|---|---|---|---|---|
| | $\beta$ | $p$ | $\beta$ | $p$ | $\beta$ | $p$ | $\beta$ | $p$ |
| *Independent variable: walking duration group* | | | | | | | | |
| **Model 1** | | | | | | | | |
| Long-duration | -0.310 | **<0.001** | -0.199 | 0.374 | -0.141 | 0.220 | 0.107 | 0.448 |
| Short-duration | -0.124 | 0.153 | -0.110 | 0.558 | -0.008 | 0.949 | -0.067 | 0.586 |
| None | Ref. | | Ref. | | Ref. | | Ref. | |
| **Model 2** | | | | | | | | |
| Long-duration | -0.306 | **0.001** | -0.132 | 0.575 | -0.205 | 0.064 | 0.132 | 0.355 |
| Short-duration | -0.121 | 0.175 | -0.095 | 0.615 | -0.048 | 0.696 | -0.035 | 0.785 |
| None | Ref. | | Ref. | | Ref. | | Ref. | |
| *Independent variable: walking intensity group* | | | | | | | | |
| **Model 1** | | | | | | | | |
| High-intensity | -0.253 | **0.007** | -0.283 | 0.171 | -0.116 | 0.371 | 0.014 | 0.915 |
| Low-intensity | -0.096 | 0.277 | 0.075 | 0.725 | -0.035 | 0.771 | -0.084 | 0.516 |
| None | Ref. | | Ref. | | Ref. | | Ref. | |
| **Model 2** | | | | | | | | |
| High-intensity | -0.246 | **0.011** | -0.235 | 0.272 | -0.173 | 0.162 | 0.042 | 0.759 |
| Low-intensity | -0.091 | 0.314 | 0.079 | 0.711 | -0.099 | 0.390 | -0.055 | 0.677 |
| None | Ref. | | Ref. | | Ref. | | Ref. | |
| *Independent variable: combined level walking group* | | | | | | | | |
| **Model 1** | | | | | | | | |
| High-combined level | -0.310 | **<0.001** | -0.227 | 0.294 | -0.064 | 0.584 | 0.068 | 0.620 |
| Med-combined level | -0.084 | 0.354 | -0.147 | 0.455 | -0.172 | 0.160 | 0.011 | 0.934 |
| Low-combined level | -0.104 | 0.222 | 0.011 | 0.958 | 0.103 | 0.384 | -0.123 | 0.326 |
| None | Ref. | | Ref. | | Ref. | | Ref. | |
| **Model 2** | | | | | | | | |
| High-combined level | -0.308 | **<0.001** | -0.167 | 0.461 | -0.147 | 0.202 | 0.092 | 0.511 |
| Med-combined level | -0.082 | 0.369 | -0.131 | 0.508 | -0.181 | 0.120 | 0.029 | 0.822 |
| Low-combined level | -0.102 | 0.242 | 0.019 | 0.924 | 0.034 | 0.769 | -0.094 | 0.468 |
| None | Ref. | | Ref. | | Ref. | | Ref. | |

*(Continued on next page)*

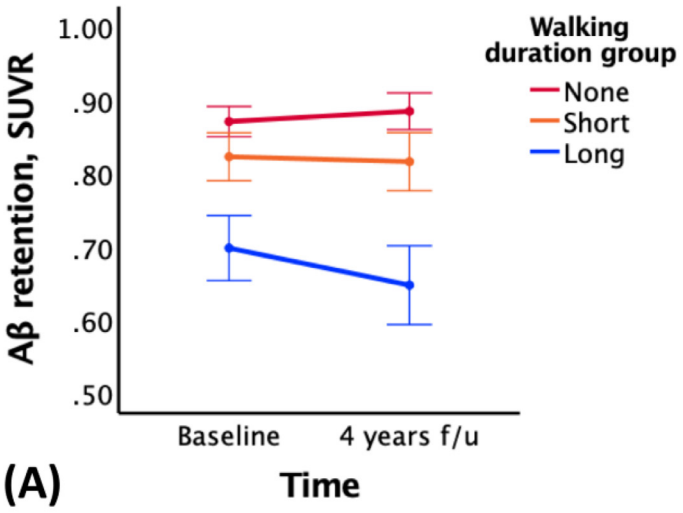
***Table 2*** *(Continued)*

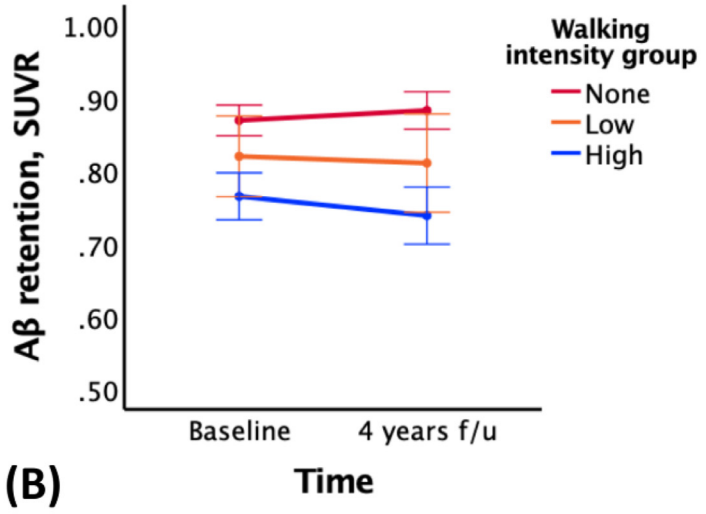
| | Aβ retention, SUVR | | | | AV-1451, SUVR | | | | AD-CT, mm | | | | WMH volume, $cm^3$ | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SS | MS | F | *p* | SS | MS | F | *p* | SS | MS | F | *p* | SS | MS | F | *p* |
| *Independent variable: walking duration group* | | | | | | | | | | | | | | | | |
| **Between subjects** | | | | | | | | | | | | | | | | |
| Walking group | 1.014 | 0.507 | 6.609 | 0.002 | 0.216 | 0.108 | 1.768 | 0.190 | 0.204 | 0.102 | 1.507 | 0.229 | 327.250 | 163.630 | 1.604 | 0.209 |
| Error | 8.593 | 0.077 | | | 1.648 | 0.061 | | | 4.672 | 0.068 | | | 6220.993 | 101.983 | | |
| **Within subjects** | | | | | | | | | | | | | | | | |
| Time | 0.012 | 0.012 | 5.328 | 0.023 | 0.001 | 0.001 | 0.001 | 0.992 | 0.001 | 0.001 | 0.040 | 0.842 | 62.857 | 62.857 | 1.496 | 0.226 |
| Time × Walking group | 0.025 | 0.012 | 5.678 | **0.004** | 0.011 | 0.005 | 0.239 | 0.789 | 0.052 | 0.026 | 0.720 | 0.490 | 20.535 | 10.268 | 0.244 | 0.784 |
| Error | 0.251 | 0.002 | | | 0.613 | 0.023 | | | 2.500 | 0.036 | | | 2563.880 | 42.031 | | |
| **Total** | | | | | | | | | | | | | | | | |
| *Independent variable: walking intensity group* | | | | | | | | | | | | | | | | |
| **Between subjects** | | | | | | | | | | | | | | | | |
| Walking group | 0.610 | 0.305 | 3.799 | 0.025 | 0.108 | 0.054 | 0.832 | 0.446 | 0.145 | 0.072 | 1.069 | 0.349 | 590.501 | 295.251 | 1.441 | 0.244 |
| Error | 8.997 | 0.080 | | | 1.755 | 0.065 | | | 4.740 | 0.068 | | | 13113.344 | 204.896 | | |
| **Within subjects** | | | | | | | | | | | | | | | | |
| Time | 0.010 | 0.010 | 4.202 | 0.043 | 0.002 | 0.002 | 0.083 | 0.775 | 0.002 | 0.002 | 0.053 | 0.819 | 25.017 | 25.017 | 0.391 | 0.534 |
| Time × Walking group | 0.016 | 0.008 | 3.470 | **0.034** | 0.032 | 0.016 | 0.736 | 0.488 | 0.076 | 0.038 | 1.064 | 0.351 | 22.302 | 11.151 | 0.174 | 0.840 |
| Error | 0.260 | 0.002 | | | 0.592 | 0.022 | | | 2.491 | 0.036 | | | 4091.562 | 63.931 | | |
| **Total** | | | | | | | | | | | | | | | | |
| *Independent variable: combined level walking group* | | | | | | | | | | | | | | | | |
| **Between subjects** | | | | | | | | | | | | | | | | |
| Walking group | 1.214 | 0.405 | 5.350 | 0.002 | 0.248 | 0.083 | 1.333 | 0.285 | 0.026 | 0.026 | 0.373 | 0.773 | 719.388 | 359.694 | 1.773 | 0.178 |
| Error | 8.394 | 0.076 | | | 1.615 | 0.062 | | | 4.807 | 0.070 | | | 12984.457 | 202.882 | | |
| **Within subjects** | | | | | | | | | | | | | | | | |
| Time | 0.012 | 0.012 | 5.546 | 0.020 | 0.001 | 0.001 | 0.019 | 0.891 | 0.003 | 0.003 | 0.087 | 0.769 | 6.685 | 6.685 | 0.105 | 0.747 |
| Time × Walking group | 0.027 | 0.009 | 4.031 | **0.009** | 0.021 | 0.007 | 0.295 | 0.829 | 0.154 | 0.051 | 1.472 | 0.230 | 42.978 | 21.489 | 0.338 | 0.715 |
| Error | 0.249 | 0.002 | | | 0.604 | 0.023 | | | 2.412 | 0.035 | | | 4070.887 | 63.608 | | |
| **Total** | | | | | | | | | | | | | | | | |

Aβ=beta-amyloid, AD Alzheimer's disease, AD-CM Alzheimer's disease signature cerebral glucose metabolism, AD-CT Alzheimer's disease signature cortical thickness, SUVR standardized uptake value ratio, WMH white matter hyperintensities, SS=sum of squares, MS=mean square, GDS=geriatric depression scale, APOE4=apolipoprotein ε4, LCA=lifetime cognitive activity, BMI=body mass index, LPA=lifetime physical activity, UPDRSm=motor subscale of the unified Parkinson's disease rating scale.

[a] Adjusted for age, sex, APOE4, education, clinical diagnosis, vascular risks, UPDRSm sum, GDS score, LCA score, occupational complex, annual income status, BMI, alcohol intake, smoking, dietary pattern including food types, and serum nutritional markers.

[b] Adjusted for covariates in Model 1 plus other leisure LPA score.



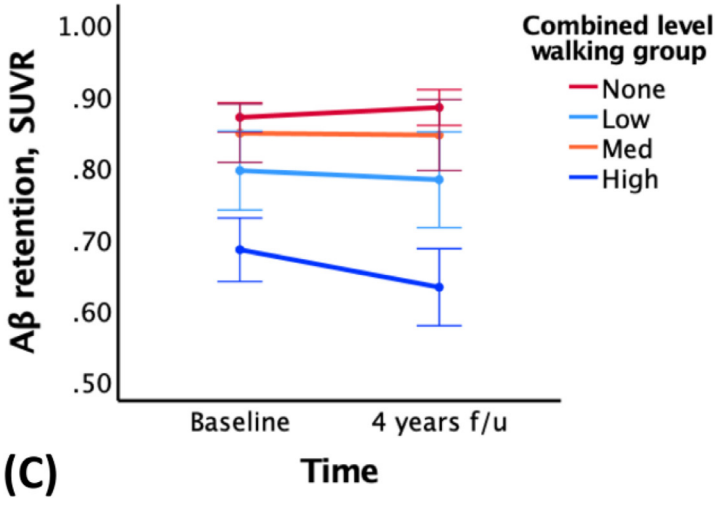




**Fig. 1.** Plots of the longitudinal associations (A-C) between walking groups and A$\beta$ deposition: (A) walking duration group vs. A$\beta$ deposition, (B) walking intensity group vs. A$\beta$ deposition, (C) combined level walking group vs. A$\beta$ deposition.
*A$\beta$* beta-amyloid. For A-C plots adjusting all potential covariates are presented. For A-C values are presented as the mean of A$\beta$ deposition values and error bars represent standard errors.

**Table 3**
Four-year changes in A$\beta$ deposition based on walking duration, intensity, and combined effects: a comparison of early life-initiated and late life-initiated walking.

| | Early life-initiated walking | | Late life-initiated walking | |
|---|---|---|---|---|
| | ΔA$\beta$, SUVR | | ΔA$\beta$, SUVR | |
| | $\beta$ | $p$ | $\beta$ | $p$ |
| *Independent variable: walking duration group* | | | | |
| **Model 1**[a] | | | | |
| Long-duration | -0.316 | **<0.001** | -0.175 | 0.134 |
| Short-duration | -0.148 | 0.113 | -0.071 | 0.535 |
| None | Ref. | | Ref. | |
| **Model 2**[b] | | | | |
| Long-duration | -0.312 | **0.001** | -0.168 | 0.155 |
| Short-duration | -0.145 | 0.123 | -0.057 | 0.631 |
| None | Ref. | | Ref. | |
| *Independent variable: walking intensity group* | | | | |
| **Model 1**[a] | | | | |
| High-intensity | -0.324 | **0.002** | -0.087 | 0.452 |
| Low-intensity | -0.038 | 0.685 | -0.157 | 0.145 |
| None | Ref. | | Ref. | |
| **Model 2**[b] | | | | |
| High-intensity | -0.318 | **0.002** | -0.071 | 0.557 |
| Low-intensity | -0.028 | 0.769 | -0.152 | 0.160 |
| None | Ref. | | Ref. | |
| *Independent variable: combined level walking group* | | | | |
| **Model 1**[a] | | | | |
| High-combined level | -0.320 | **<0.001** | -0.167 | 0.137 |
| Med-combined level | -0.165 | 0.104 | 0.031 | 0.779 |
| Low-combined level | -0.045 | 0.626 | -0.145 | 0.157 |
| None | Ref. | | Ref. | |
| **Model 2**[b] | | | | |
| High-combined level | -0.315 | **0.001** | -0.157 | 0.167 |
| Med-combined level | -0.165 | 0.105 | 0.048 | 0.673 |
| Low-combined level | -0.039 | 0.681 | -0.139 | 0.180 |
| None | Ref. | | Ref. | |

| | Early life-initiated walking | | | | Late life-initiated walking | | | |
|---|---|---|---|---|---|---|---|---|
| | Change of A$\beta$, SUVR | | | | Change of A$\beta$, SUVR | | | |
| | SS | MS | F | $p$ | SS | MS | F | $p$ |
| *Independent variable: walking duration group* | | | | | | | | |
| **Between subjects** | | | | | | | | |
| Walking group | 0.891 | 0.445 | 5.185 | 0.007 | 0.302 | 0.151 | 1.953 | 0.149 |
| Error | 7.990 | 0.086 | | | 5.714 | 0.077 | | |
| **Within subjects** | | | | | | | | |
| Time | 0.012 | 0.012 | 5.148 | 0.026 | 0.017 | 0.017 | 6.704 | 0.012 |
| Time × Walking group | 0.026 | 0.013 | 5.815 | **0.004** | 0.006 | 0.003 | 1.056 | 0.353 |
| Error | 0.208 | 0.002 | | | 0.193 | 0.003 | | |
| *Independent variable: walking intensity group* | | | | | | | | |
| **Between subjects** | | | | | | | | |
| Walking group | 0.523 | 0.261 | 2.908 | 0.060 | 0.255 | 0.128 | 1.641 | 0.201 |
| Error | 8.358 | 0.090 | | | 5.760 | 0.078 | | |
| **Within subjects** | | | | | | | | |
| Time | 0.009 | 0.009 | 3.813 | 0.054 | 0.017 | 0.017 | 6.566 | 0.012 |
| Time × Walking group | 0.023 | 0.011 | 4.988 | **0.009** | 0.005 | 0.003 | 1.048 | 0.356 |
| Error | 0.211 | 0.002 | | | 0.193 | 0.003 | | |
| *Independent variable: combined level walking group* | | | | | | | | |
| **Between subjects** | | | | | | | | |
| Walking group | 0.891 | 0.297 | 3.420 | 0.021 | 0.447 | 0.149 | 1.954 | 0.129 |
| Error | 7.990 | 0.087 | | | 5.569 | 0.076 | | |
| **Within subjects** | | | | | | | | |
| Time | 0.011 | 0.011 | 4.769 | 0.032 | 0.017 | 0.017 | 6.662 | 0.012 |
| Time × Walking group | 0.027 | 0.009 | 4.006 | **0.010** | 0.012 | 0.004 | 1.508 | 0.220 |
| Error | 0.207 | 0.002 | | | 0.187 | 0.003 | | |

A$\beta$=beta-amyloid, SS=sum of squares, MS=mean square, GDS=geriatric depression scale, APOE4=apolipoprotein $\varepsilon$4, LCA=lifetime cognitive activity, BMI=body mass index, LPA=lifetime physical activity, UPDRSm=motor subscale of the unified Parkinson's disease rating scale.

[a] Adjusted for age, sex, APOE4, education, clinical diagnosis, vascular risks, UPDRSm sum, GDS score, LCA score, occupational complex, annual income status, BMI, alcohol intake, smoking, dietary pattern including food types, and serum nutritional markers.

[b] Adjusted for covariates in Model 1 plus other leisure LPA score.

alone, did not demonstrate this effect. Additionally, no significant associations were observed between walking intensity or duration levels and other brain pathologies, including tau deposition, AD-related neurodegeneration, or white matter changes.

Our findings on the inverse relationship between walking activity and A$\beta$ accumulation over time align with previous studies[18,19] that showed a cross-sectional link between physical activity or habitual exercise and lower cerebral A$\beta$ deposition. However, unlike these earlier studies, which were limited by their cross-sectional design, our study provides an evidence of a longitudinal association between walking activity and a reduction in A$\beta$ accumulation, supporting the potential causal relationship. In contrast to our findings, a recent study failed to find significant link between regular physical activity and changes in cerebral A$\beta$ deposition[20]. The discrepancy may stem from differences in assessment periods and activity types (overall activities versus walking alone). The earlier study[20] measured physical activity over 7 days, focusing on current activity. In contrast, our study assessed lifetime walking activity, particularly during midlife and late-life, to capture long-term cumulative effects on A$\beta$ deposition. Furthermore, our study supports this possibility, as significant results were found only in the subgroup that began walking in midlife, not in late life. Earlier studies also linked midlife physical activity to lower AD risk [27] and less cognitive decline[37]. Those who started walking earlier had more years of activity than those who started later. However, our analysis of cumulative years of walking and A$\beta$ deposition showed no significant findings (eTable 2). These results suggest that the benefits of early walking on A$\beta$ deposition are tied more closely to the timing of initiation rather than the total duration of activity.

When considering both intensity and duration of walking activity simultaneously, we found significant benefits (i.e., reduced A$\beta$ deposition) exclusively in individuals who engaged in both high-intensity and long-duration walking, but not in those who engaged in only one of these activities. This suggests that both components are critical and may have a synergistic effect on reducing A$\beta$ deposition, offering important insights for AD prevention strategies. Although earlier studies [7,10,11] have examined the effects of walking intensity and/or duration on AD and related cognitive decline, the combined or synergistic impact of these two aspects of walking has not been previously demonstrated.

The mechanism underlying the association between high-intensity or long-duration walking and the longitudinal reduction in A$\beta$ accumulation is not yet fully understood. However, several hypothetical explanations on the mechanism can be provided based on the findings from prior studies as follows. First, walking has been shown to increase cerebral blood flow [38], which may facilitate the delivery of oxygen and nutrients to brain tissue, as well as promote the clearance of waste products such as A$\beta$ peptides[39]. Second, walking may contribute to an anti-amyloidogenic pathway through elevating the levels of brain-derived neurotrophic factor (BDNF)[40]. BDNF is known to decrease the production of toxic A$\beta$ peptides by enhancing the $\alpha$-secretase processing of amyloid precursor protein, thereby engaging in an anti-amyloidogenic process[41]. Third, regular walking may reduce A$\beta$ burden via moderating the stress response system in a beneficial way and reducing cortisol levels[42]. Preclinical studies have demonstrated that higher cortisol levels contribute to increase of brain A$\beta$ burden by impairing A$\beta$ clearance or enhancing A$\beta$ production[43–45]. Fourth, walking has been associated with improved sleep quality[46]. Given that glymphatic system is more active in removing waste products including A$\beta$ during slow-wave sleep [47], improved sleep pattern induced by regular walking may plays a beneficial role in A$\beta$ clearance. Lastly, some preclinical evidence suggests that physical activity may enhance the ability of microglia—the brain's innate immune cells—to degrade and clear A$\beta$[48,49]. While these mechanisms are supported by findings from animal studies and indirect evidence from human studies, they remain speculative in the context of our study. Further investigations are still needed to understand the exact mechanism linking walking activity and reduced A$\beta$ accumulation.

Unlike its association with A$\beta$ deposition, walking activity showed no significant relationship with longitudinal changes in tau accumulation, AD-signature neurodegeneration, or WMH volume. While research on walking's impact on tau, cortical degeneration, or white matter in humans is limited, the Cardiovascular Health Cognition Study found that higher walking levels were linked to greater gray matter volume increase over 9 years[50]. This is in contrast to our null finding for the association between walking and the longitudinal change of AD-CT. The differences in methodologies, such as a measure of walking activity, target brain regions (AD-signature cortical region vs. overall gray matter) and follow-up duration (4 year vs. 9 years), and sample size (151 vs. 299 participants at follow-up) may explain the discrepant results.

No significant interaction effects were found between walking activity and any of the potential moderators, including age, sex, APOE4 status, GDS score, BMI, clinical diagnosis, and vascular risk factors (eTable 1). This suggests that the association between walking activity and changes in A$\beta$ deposition over the 4-year period was not meaningfully influenced by these factors. In other words, the observed protective effect of lifetime walking against amyloid accumulation appears to be generally applied to non-demented older adults as a whole, rather than confined to specific subgroups with unique characteristics.

This study, using a longitudinal approach, offers new insights into the neuropathological mechanisms linking walking activity to a reduced risk of AD-related cognitive decline. Nevertheless, the study has several limitations. First, the assessment of lifetime walking activity relied on retrospective self-reported data, which is inherently vulnerable to recall bias. Some individuals with MCI often retain relatively preserved remote memory despite impaired recent memory and may rely on such preserved remote memory when recalling habitual lifestyle patterns from earlier adulthood[51]. However, retrospective reports of physical activity have been shown to be especially prone to error in older adults with cognitive impairment[52]. We employed a categorical classification of walking activity rather than using a numeric value, aiming to minimize recall bias and measurement variability related to self-report. Nonetheless, this categorical approach, based on retrospective recall, poses limitations in modelling a detailed dose-benefit relationship, identifying the optimal level of walking activity, and making causal interpretations. Therefore, further prospective studies utilizing device-based or continuous metrics of walking activity are necessary. Secondly, the 4-year follow-up period (with 2 years for tau measurements) may have been too short to detect changes in tau accumulation, AD-related neurodegeneration, and WMHs, potentially explaining the lack of association with walking activity. Longer follow-up studies are needed to validate these findings. Additionally, the delay in initial tau PET scans (2.5 years after baseline) compared to amyloid PET and MRI scans may have influenced our results, though adjustments for this gap did not change the findings. The small number of participants with tau PET scans may also have limited our ability to detect links between walking and tau deposition.

## 5. Conclusions

Our findings suggest that walking activity with both high-intensity and long-duration may reduce brain amyloid accumulation, potentially lowering the risk of AD and related cognitive decline. This effect appears to be more pronounced when walking activity is initiated before late life.

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## Data availability

The data of the current study are not freely accessible because the IRB of the Seoul National University Hospital prevents public sharing of such data for privacy restrictions. However, the data can be available from the independent data sharing committee of the KBASE research group on reasonable request after approval by the IRB. Requests for data access can be submitted to the administrative coordinator of the KBASE group by e-mail (kbasecohort@gmail.com), who is independent of the authors.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## CRediT authorship contribution statement

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100203.

## References

[1] Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Sci. (1979) 2002;297:353–6.
[2] Albert MS, Jones K, Savage CR, et al. Predictors of cognitive change in older persons: macArthur studies of successful aging. Psychol Aging 1995;10:578–89.
[3] Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA 2008;300:1027–37.
[4] Sohn BK, Byun MS, Yi D, et al. Late-life physical activities moderate the relationship of amyloid-beta pathology with neurodegeneration in individuals without dementia. J. Alzheimer's dis.: JAD 2022.
[5] Jeon SY, Byun MS, Yi D, et al. Midlife lifestyle activities moderate APOE epsilon4 effect on in vivo Alzheimer's Disease pathologies. Front Aging Neurosci 2020;12:42.
[6] Ruiz-Muelle A, Lopez-Rodriguez MM. Dance for people with Alzheimer's Disease: a systematic review. Curr Alzheimer Res 2019;16:919–33.
[7] Choe YM, Suh GH, Lee BC, et al. High-intensity walking in midlife is associated with improved memory in physically capable older adults. Alzheimers Res Ther 2023;15:143.
[8] Mayor S. Slow walking speed may be early sign of Alzheimer's in older people, study finds. BMJ 2015;351:h6506.
[9] Hackett RA, Davies-Kershaw H, Cadar D, Orrell M, Steptoe A. Walking speed, cognitive function, and dementia risk in the English longitudinal study of ageing. J Am Geriatr Soc 2018;66:1670–5.
[10] Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K. A prospective study of physical activity and cognitive decline in elderly women: women who walk. Arch Intern Med 2001;161:1703–8.
[11] Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H. Walking and dementia in physically capable elderly men. JAMA 2004;292:1447–53.
[12] Rabin JS, Klein H, Kirn DR, et al. Associations of physical activity and beta-amyloid with longitudinal cognition and neurodegeneration in clinically normal older adults. JAMA Neurol 2019;76:1203–10.
[13] Maesako M, Uemura K, Kubota M, et al. Exercise is more effective than diet control in preventing high fat diet-induced beta-amyloid deposition and memory deficit in amyloid precursor protein transgenic mice. J Biol Chem 2012;287:23024–33.
[14] Zhang J, Guo Y, Wang Y, Song L, Zhang R, Du Y. Long-term treadmill exercise attenuates abeta burdens and astrocyte activation in APP/PS1 mouse model of Alzheimer's disease. Neurosci Lett 2018;666:70–7.
[15] Kang EB, Cho JY. Effects of treadmill exercise on brain insulin signaling and beta-amyloid in intracerebroventricular streptozotocin induced-memory impairment in rats. J Exerc Nutr. Biochem 2014;18:89–96.
[16] Moore KM, Girens RE, Larson SK, et al. A spectrum of exercise training reduces soluble Abeta in a dose-dependent manner in a mouse model of Alzheimer's disease. Neurobiol Dis 2016;85:218–24.
[17] Brown BM, Sohrabi HR, Taddei K, et al. Habitual exercise levels are associated with cerebral amyloid load in presymptomatic autosomal dominant Alzheimer's disease. Alzheimers Dement 2017;13:1197–206.
[18] Liang KY, Mintun MA, Fagan AM, et al. Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. Ann Neurol 2010;68:311–18.
[19] Brown BM, Peiffer JJ, Taddei K, et al. Physical activity and amyloid-beta plasma and brain levels: results from the Australian Imaging. Biomark Lifestyle Study Ageing Mol Psychiatry 2013;18:875–81.
[20] Slee MG, Rainey-Smith SR, Villemagne VL, et al. Physical activity and brain amyloid beta: a longitudinal analysis of cognitively unimpaired older adults. Alzheimers Dement 2024;20:1350–9.
[21] Byun MS, Yi D, Lee JH, et al. Korean Brain Aging Study for the early Diagnosis and prediction of Alzheimer's Disease: methodology and baseline sample characteristics. Psychiatry Investig 2017;14:851–63.
[22] Aisen PS, Petersen RC, Donohue MC, et al. Clinical Core of the Alzheimer's Disease Neuroimaging Initiative: progress and plans. Alzheimers Dement 2010;6:239–46.
[23] Jessen F, Wolfsgruber S, Wiese B, et al. AD dementia risk in late MCI, in early MCI, and in subjective memory impairment. Alzheimers Dement 2014;10:76–83.
[24] Friedenreich CM, Courneya KS, Bryant HE. The lifetime total physical activity questionnaire: development and reliability. Med Sci Sports Exerc 1998;30:266–74.
[25] Gill SJ, Friedenreich CM, Sajobi TT, et al. Association between lifetime physical activity and cognitive functioning in middle-aged and older community dwelling adults: results from the Brain in Motion Study. J Int Neuropsychol Soc 2015;21:816–30.
[26] Imayama I, Alfano CM, Cadmus Bertram LA, et al. Effects of 12-month exercise on health-related quality of life: a randomized controlled trial. Prev Med 2011;52:344–51.
[27] Rovio S, Kareholt I, Helkala EL, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol 2005;4:705–11.
[28] Tolppanen AM, Solomon A, Kulmala J, et al. Leisure-time physical activity from mid- to late life, body mass index, and risk of dementia. Alzheimers Dement 2015;11:434–43 e436.
[29] Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;17:37–49.
[30] Wilson RS, Barnes LL, Krueger KR, Hoganson G, Bienias JL, Bennett DA. Early and late life cognitive activity and cognitive systems in old age. J Int Neuropsychol Soc JINS 2005;11:400–7.
[31] Vellas B, Guigoz Y, Garry PJ, et al. The Mini Nutritional assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition 1999;15:116–22.
[32] Movement Disorder Society. Task Force on Rating Scales for Parkinson's D. The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. Mov Disord 2003;18:738–50.
[33] Etgen T, Sander D, Huntgeburth U, Poppert H, Forstl H, Bickel H. Physical activity and incident cognitive impairment in elderly persons: the INVADE study. Arch Intern Med 2010;170:186–93.

[34] 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;69:636–43.
[35] Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 2011;10:819–28.
[36] Smith JC, Nielson KA, Antuono P, et al. Semantic memory functional MRI and cognitive function after exercise intervention in mild cognitive impairment. J Alzheimers Dis 2013;37:197–215.
[37] Iso-Markku P, Waller K, Vuoksimaa E, et al. Midlife physical activity and cognition later in life: a prospective twin study. J Alzheimers Dis 2016;54:1303–17.
[38] Gligoroska JP, Manchevska S. The effect of physical activity on cognition - physiological mechanisms. Mater Sociomed 2012;24:198–202.
[39] Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. J Neurosci 2005;25:4217–21.
[40] Thoenen H. Neurotrophins and neuronal plasticity. Sci. (1979) 1995;270:593–8.
[41] Nigam SM, Xu S, Kritikou JS, Marosi K, Brodin L, Mattson MP. Exercise and BDNF reduce abeta production by enhancing alpha-secretase processing of APP. J Neurochem 2017;142:286–96.
[42] Churchill R, Teo K, Kervin L, Riadi I, Cosco TD. Exercise interventions for stress reduction in older adult populations: a systematic review of randomized controlled trials. Health Psychol Behav Med 2022;10:913–34.
[43] Kulstad JJ, McMillan PJ, Leverenz JB, et al. Effects of chronic glucocorticoid administration on insulin-degrading enzyme and amyloid-beta peptide in the aged macaque. J Neuropathol Exp Neurol 2005;64:139–46.
[44] Green KN, Billings LM, Roozendaal B, McGaugh JL, LaFerla FM. Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. J Neurosci 2006;26:9047–56.
[45] Ouanes S, Popp J. High Cortisol and the risk of dementia and Alzheimer's Disease: a review of the literature. Front Aging Neurosci 2019;11:43.
[46] Paez A, Frimpong E, Mograss M, Dang-Vu TT. The effectiveness of exercise interventions targeting sleep in older adults with cognitive impairment or Alzheimer's disease and related dementias (AD/ADRD): a systematic review and meta-analysis. J Sleep Res 2024:e14189.
[47] Chen L, Huang J, Yang L, et al. Sleep deprivation accelerates the progression of alzheimer's disease by influencing Abeta-related metabolism. Neurosci Lett 2017;650:146–52.
[48] Liang F, Sun F, He B, Wang J. Treadmill exercise promotes microglial beta-amyloid clearance and prevents cognitive decline in APP/PS1 mice. Neuroscience 2022;491:122–33.
[49] Bolmont T, Haiss F, Eicke D, et al. Dynamics of the microglial/amyloid interaction indicate a role in plaque maintenance. J Neurosci 2008;28:4283–92.
[50] Erickson KI, Raji CA, Lopez OL, et al. Physical activity predicts gray matter volume in late adulthood: the Cardiovascular Health Study. Neurology 2010;75:1415–22.
[51] Leyhe T, Muller S, Milian M, Eschweiler GW, Saur R. Impairment of episodic and semantic autobiographical memory in patients with mild cognitive impairment and early Alzheimer's disease. Neuropsychologia 2009;47:2464–9.
[52] Raffin J, Blennow K, Rolland Y, et al. Associations between moderate-to-vigorous physical activity, p-tau181, and cognition in healthy older adults with memory complaints: a secondary analysis from the MAPT. Lancet Healthy Longev 2025;6:100678.