

RESEARCH ARTICLE

Association of walking energetics with amyloid beta status: Findings from the Baltimore Longitudinal Study of Aging

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Abstract

Introduction: Higher energetic costs for mobility predict gait speed decline. Slow gait is linked to cognitive decline and Alzheimer's disease (AD). Whether the energetic cost of walking is linked to AD pathology is unknown. We investigated the cross-sectional association between the energetic cost of walking, gait speed, and amyloid beta (A β) status (+/–) in older adults.

Methods: One hundred forty-nine cognitively normal adults (56% women, mean age 77.5 \pm 8.4 years) completed customary-paced walking assessments with indirect calorimetry and ¹¹C-Pittsburgh compound B positron emission tomography. Logistic regression models examined associations adjusted for demographics, body composition, comorbid conditions, and apolipoprotein E ϵ 4.

Results: Each 0.01 mL/kg/m greater energy cost was associated with 18% higher odds of being A β + (odds ratio [OR] = 1.18; 95% confidence interval [CI]: 1.04 to 1.34; $P = .011$). These findings were not observed when investigating gait speed (OR = 0.99; 95% CI: 0.97 to 1.01; $P = .321$).

Discussion: High energetic cost of walking is linked to AD pathology and may be a potential target for therapeutic intervention.

KEYWORDS

apolipoprotein E ϵ 4, biomarkers, motor control, risk factor, walking economy, walking efficiency

1 | INTRODUCTION

Amyloid beta (A β) deposition is a defining pathophysiologic feature of Alzheimer's disease (AD) that can be measured in vivo through positron emission tomography (PET). The current research framework for AD identifies A β PET as a biomarker that characterizes the preclinical stage of AD, during which clinical symptoms are absent, but pathophysiological changes are present.^{1–3} Within this research framework, A β PET is dichotomized into A β positive or negative (+/–) based on

normal/abnormal cut points.² Studies, including the Baltimore Longitudinal Study of Aging (BLSA), have demonstrated A β + adults experience accelerated cognitive decline and are more likely to convert from mild cognitive impairment to AD than A β - adults.^{4–6} Further, cognitively normal adults who harbor the strongest genetic risk factor for sporadic AD, the ϵ 4 allele of the apolipoprotein E gene (APOE ϵ 4), have higher A β deposition, which commences at an earlier age compared to adults without this genetic risk.^{7,8} Because A β tends to accumulate during the preclinical stage of AD, 10 to 20 years prior to cognitive

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impairment, this biomarker is of heightened importance for early detection and perhaps treatment of AD.^{2,3}

In older adulthood, slow and declining gait speed has been linked to poor physical and cognitive health outcomes.^{9,10} Recent PET studies investigating associations between A β and changes in gait (e.g., speed, variability) generally report associations, suggesting gait may become abnormal with the onset and progression of AD pathology.^{11–13} Specifically, A β burden overall and in specific regions of the brain has been linked with future mobility decline, independent of age and APOE ϵ 4.¹³ Thus, the emergence of slowed and altered gait in late life may represent brain pathology that is already fairly advanced.¹⁴ A better understanding of the association between subclinical physiological changes that precede gait dysfunction may afford earlier opportunities to detect the progression of abnormal brain pathology.

Throughout early- to mid-adulthood, gait speed tends to average 1.1 to 1.3 meters per second (m/s), declining in later life.^{15,16} The energy needed for customary walking increases with advancing age^{17–19} and in those with gait disturbances.^{20,21} The exact mechanisms contributing to these increased energy demands are unknown, but may include accumulation of brain pathology in motor function regions. Moreover, a higher energetic cost of walking (i.e., poor walking efficiency) has been identified as a key marker of impending gait speed decline in older adults.²² Given the emergence of studies connecting gait characteristics with cognition^{23–28} and brain pathology^{29–32} in mid–late adulthood, the energetic cost of walking may, thus, reflect early pathophysiological brain changes along shared neural pathways for ambulation and cognitive function.

The purpose of this study was to examine the association between the energetic cost of walking and A β status in cognitively normal men and women aged 59 to 95 years. We hypothesized that a higher energetic cost of walking would be associated with A β positivity. Further, based on previous work describing a connection between A β and gait speed, we conducted exploratory analyses to compare the strength of the association between A β and the energetic cost of walking to that of A β and usual gait speed.

2 | METHODS

2.1 | Participants

The BLSA is a study of human aging initiated in 1958. All BLSA participants are community-dwelling adults free of major chronic conditions and cognitive and functional impairment at the time of enrollment. Once enrolled, participants are followed for life and undergo comprehensive health, cognitive, neuroimaging, and functional assessments every 1 to 4 years depending on age (<60: every 4 years, 60 to 79: every 2 years, \geq 80: every year). A subset of participants receives ¹¹C-Pittsburgh compound B positron emission tomography (PiB-PET) scans as part of the BLSA neuroimaging substudy.³³ Trained staff administers all assessments following standardized protocols. Additional study enrollment and design details have been previously described.³⁴ The sample for the current study consists of cognitively normal participants

RESEARCH IN CONTEXT

1. Systematic review: The authors performed a traditional literature review related to energetic cost of walking, gait speed, and amyloid beta (A β) deposition. There is evidence that gait speed is associated with A β in cognitively impaired older adults. However, whether a higher energetic cost of walking, which has been shown to precede gait speed decline, is linked to A β in cognitively normal adults is currently unknown.
2. Interpretation: Within a cognitively normal cohort of community-dwelling older adults, greater energetic cost of walking, but not gait speed, is associated with higher odds of A β positivity. These data suggest the physiological underpinnings of walking could be a meaningful measure of early Alzheimer's disease pathology and a potential target for therapeutic intervention.
3. Future directions: Longitudinal studies that assess the temporality of the association and biological mechanisms connecting walking energetics and A β are needed to better elucidate causality and directionality of the observed associations.

free of Parkinson's disease or stroke who underwent physical examinations, health history assessments, functional testing, and neuroimaging between September 2007 and May 2019. The institutional review boards of the Intramural Research Program of the National Institutes of Health and the Johns Hopkins Medical Institutions approved the study protocol, and all participants provided written informed consent.

2.2 | Energetic cost of walking

The energetic cost of walking was assessed as the energy expended during an overground customary-paced walking test. Participants were instructed to walk at their "usual comfortable pace" for 2.5 minutes in a continuous loop around a 20-meter course laid out in an uncarpeted corridor marked by traffic cones. At the start, participants stood with their feet behind a taped starting line. After a command of "Go," timing was initiated with the first foot-fall over the line and stopped after 2.5 minutes of walking. Oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), minute ventilation ($\dot{V}E$), respiratory exchange ratio (RER), and metabolic work rate were obtained during the walking test using a portable indirect calorimeter (Cosmed K4b², Cosmed) and two-way non-rebreathing mask. The Cosmed K4b² unit continuously collects and analyzes $\dot{V}O_2$ and $\dot{V}CO_2$ using breath-by-breath measurement and averages these measures over 30-second intervals to reduce variability. The Cosmed K4b² unit was calibrated using standard procedures prior to each test to ensure accuracy (i.e., volumetric/gas). To calculate average customary walking $\dot{V}O_2$ (mL/kg/min), readings from

the first 1.5 minutes of testing were discarded to allow the participant to adjust to the workload. The average $\dot{V}O_2$ (mL/kg/min) recorded during the final minute was expressed per meter walked ($\dot{V}O_2$, mL/kg/m) to standardize to gait speed and derive a single energetic cost of walking measure.

2.3 | Neuroimaging protocol

All participants underwent PET (GE Advance or Siemens HRRT) and magnetic resonance imaging (MRI; 3T Philips Achieva) procedures. Details on the acquisition and processing of the PiB-PET and structural images have been fully described elsewhere.³⁵ Briefly, PET scans were acquired in 3D mode after an intravenous injection of ≈ 555 MBq of PiB. Scans acquired on the GE Advance were reconstructed using filtered back-projection with a ramp filter, yielding a spatial resolution of ≈ 4.5 mm full width at half max (FWHM) at the center of the field of view; image matrix = 128×128 , 35 slices, pixel size = 2×2 mm, slice thickness = 4.25 mm. Scans acquired on the Siemens HRRT were reconstructed using ordered subset expectation-maximization, yielding a spatial resolution of ≈ 2.5 mm FWHM at the center of the field of view (image matrix = 256×256 , 207 slices, voxel size = 1.22 mm isotropic). For both scanners, dynamic images were reconstructed according to the following protocol for the duration of the frames: 4×0.25 , 8×0.5 , 9×1 , 2×3 , and 10×5 min, resulting in 33 frames over 70 minutes. Post-reconstruction, HRRT scans were smoothed with a 3 mm FWHM isotropic Gaussian kernel to bring their spatial resolution closer to that of the GE Advance scans and resampled to match their voxel size. Distribution volume ratio (DVR) images were calculated in the native space of each PET image using the cerebellar gray matter as reference tissue.³⁶ The mean cortical DVR was calculated as the average DVR values from the cingulate, frontal, parietal (including precuneus), lateral temporal, and lateral occipital cortices, excluding the sensorimotor strip. Leveraging longitudinal PiB-PET data available in the larger BLSA data set on both GE Advance and HRRT scanners for 79 participants, we estimated the parameters of a linear model mapping mean cortical DVR values between the GE Advance and HRRT scanners and applied this mapping to all HRRT values to harmonize them with the GE Advance values. Participant's $A\beta$ status (+/–) was determined using a mean cortical DVR threshold of 1.06, which was derived from a two-class Gaussian mixture model fitted to harmonized mean cortical DVR values at first PiB-PET assessment.

2.4 | Covariate measures

All participants completed a variety of health-related questionnaires and measurements at each study visit. Variables investigated as potential confounders included age, sex, race, years of education, height, body composition, comorbid conditions, and APOE $\epsilon 4$ carrier status. Age, sex, race, and years of education were determined by self-report. Height was measured according to a standard protocol. Body composition, specifically fat, and lean mass (kg) were estimated using a dual-

energy x-ray absorptiometry (DEXA) scan. Comorbid conditions were defined as a history of two or more of the following: cardiovascular disease, lung disease, liver disease, kidney disease, peripheral neuropathy, hypertension, diabetes, cancer, and lower extremity arthritis pain. Presence of the APOE $\epsilon 4$ allele was determined through restriction isotyping using standard procedures.³⁷

2.5 | Gait speed

Usual gait speed was measured over a 6-m course in an uncarpeted corridor. Participants stood with their feet behind a taped starting line and were asked to walk at a “normal comfortable pace.” After a command of “Go,” timing was initiated with the first foot-fall over the starting line and stopped after the first foot-fall over the finish line. Two timed trials were conducted to derive usual gait speed in m/s; the faster of the two trials was used for analyses.

2.6 | Statistical analyses

Participant characteristics were summarized with means, standard deviations, and frequencies and independent-sample *t*-tests (or χ^2 tests, as applicable) were used to compare demographics between $A\beta$ groups (+/–). Multivariable logistic regression models were used to test the association between the energetic cost of walking and odds of $A\beta+$. A series of unadjusted and adjusted models that controlled for the effects of demographics, body composition, comorbid conditions, and APOE $\epsilon 4$ carrier status were performed—Model 1: adjusted for age, sex, race, education, height, lean body mass and fat mass; Model 2: additional adjustment for comorbid conditions and APOE $\epsilon 4$. We conducted logistic and linear regression subanalyses, using 6-m usual gait speed as the predictor for the logistic models and $A\beta$ status as the predictor for the separate linear models to compare the strength of the association between $A\beta$ and the energetic cost of walking to that of $A\beta$ and gait speed using standardized beta coefficients. To improve the interpretability, both the energetic cost of walking (mL/kg/m) and gait speed (m/s) were scaled to 0.01 units in the regression models.

To verify the robustness of the results, we performed (1) additional linear regression models with mean cortical $A\beta$ as a continuous predictor and (2) bootstrapping analyses with 5000 replications; 95% confidence intervals were quantified using bootstrapped standard deviations and 2.5th and 97.5th percentiles of the bootstrap distribution. Analyses were conducted using Stata IC (15.1, Stata Corporation).

3 | RESULTS

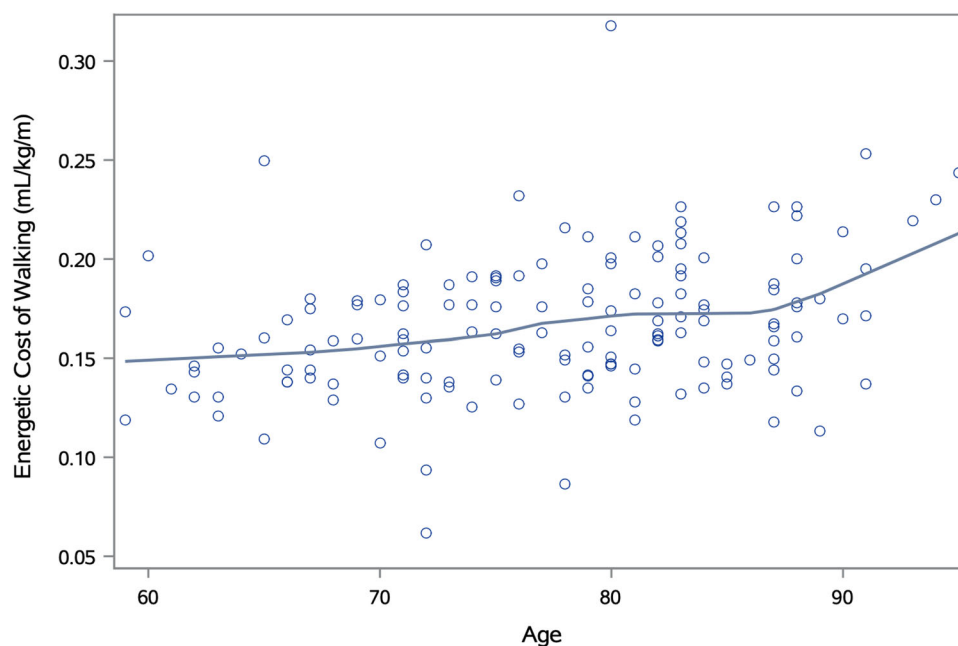
One hundred forty-nine cognitively normal participants (mean age 77.5 ± 8.4 years, 56% women) completed the energetic cost of walking and PiB-PET assessments. The average energetic cost of walking was $.167 \pm .035$ mL/kg/m and 23% of the sample was $A\beta+$.

TABLE 1 Characteristics of study participants

Baseline variables N (%) or mean (SD)	Entire sample N = 149	A β + N = 35	A β - N = 114
Age (y)	77.5 (8.4)	79.6 (7.6)	76.8 (8.6)
Female	83 (56%)	19 (54.3%)	64 (56.1%)
APOE ϵ 4 +	40 (26.8%)	12 (34.3%)	28 (24.6%)
Non-White	37 (24.8%)	9 (25.7)	28 (24.6%)
Education (y)	17.9 (2.5)	17.4 (2.1)	18.1 (2.6)
Fat mass (kg), %	28.2 (10.8)	26.4 (10.4)	28.7 (10.9)
Lean mass (kg), %	45.8 (9.6)	44.7 (8.5)	46.1 (10.0)
Height (cm)	166.7 (9.2)	166.5 (10.1)	166.7 (9.0)
Comorbid conditions (≥ 2)	87 (58.4%)	19 (54.3%)	46 (59.6%)
Energetic cost of walking, $\dot{V}O_2$ (mL/kg/m)	0.167 (0.035)	0.180 (0.032)	0.162 (0.035)
Usual gait speed (m/s)	1.11 (0.25)	1.05 (0.27)	1.13 (0.24)
Mean cortical amyloid beta (DVR)	1.068 (0.144)	1.281 (0.166)	1.002 (0.025)

Notes: Values indicate mean and standard deviation unless indicated otherwise. A β status determined using ^{11}C -Pittsburgh compound B (PiB) positron emission tomography (PET) imaging.

Abbreviations: A β , amyloid beta; APOE, apolipoprotein E; DVR, distribution volume ratio; SD, standard deviation; $\dot{V}O_2$, oxygen consumption.

**FIGURE 1** Unadjusted scatter of the energetic cost of walking and age ($n = 149$). Curve generated through locally weighted smoothing (LOESS)

Additional participant characteristics are detailed in Table 1. The energetic cost ($\dot{V}O_2$ mL/kg/m) of customary walking was positively associated with age ($r = .32$; $P < .001$; Figure 1). A β + participants ($n = 35$) tended to be older ($P = .08$) and have a higher energetic cost of walking ($P = .01$) than A β - participants ($n = 114$); A β groups did not significantly differ on any other measured demographic characteristics (Table 1).

Results from the logistic regression models are presented in Table 2. In the unadjusted model, the energetic cost of walking was positively

associated with A β + (odds ratio [OR] = 1.16; 95% confidence interval [CI]: 1.04 to 1.30; $P = .010$). After adjusting for age, sex, race, education, height, and body composition (Model 1), the association between the energetic cost of walking and odds of A β + persisted (OR = 1.17; 95% CI: 1.03 to 1.32; $P = .015$). These results remained essentially unchanged after additional adjustment for comorbid conditions and APOE ϵ 4 (Model 2); each 0.01 mL/kg/m greater energy cost was associated with 18% higher odds of being A β + (OR = 1.18; 95% CI: 1.04 to 1.34; $P = .011$).

TABLE 2 Logistic regression estimates of the association of energetic cost of walking and gait speed with A β status among 149 adults

	Unadjusted		Model 1		Model 2	
	OR	95% CI	OR	95% CI	OR	95% CI
Energetic cost of walking \rightarrow A β	1.16	1.04–1.30	1.17	1.03–1.32	1.18	1.04–1.34
Gait speed \rightarrow A β	0.99	0.97–1.00	0.99	0.97–1.01	0.99	0.97–1.01

Notes: Model 1: adjusted for age, sex, race, education, height, and body composition. Model 2: Model 1 + adjusted for comorbid conditions and APOE ϵ 4. Abbreviations: A β , amyloid beta; APOE, apolipoprotein E; CI, confidence interval; OR, odds ratio.

TABLE 3 Linear regression estimates (standardized) of the association of A β status with energetic cost of walking and gait speed among 149 adults

	Unadjusted		Model 1		Model 2	
	β	P value	β	P value	β	P value
A β \rightarrow Energetic cost of walking	.2194	0.007	.1934	0.016	.2035	0.011
A β \rightarrow Gait speed	-.1335	0.104	-.0699	0.307	-.0701	0.304

Notes: Model 1: adjusted for age, sex, race, education, height, and body composition. Model 2: Model 1 + adjusted for comorbid conditions and APOE ϵ 4. Abbreviations: A β , amyloid beta; APOE, apolipoprotein E.

In the additional exploratory analyses, gait speed was negatively associated with age ($r = -.52$; $P < .001$) and the energetic cost of walking ($r = -.35$; $P < .001$). Gait speed was not associated with A β in the logistic regression unadjusted model (OR = 0.99; 95% CI: 0.97 to 1.00; $P = .106$), adjusted Model 1 (OR = 0.99; 95% CI: 0.97 to 1.01; $P = .314$) or Model 2 (OR = 0.99; 95% CI: 0.97 to 1.01; $P = .321$). Dichotomizing gait into slow (<1 m/s) and normal (≥ 1 m/s) speed did not change the results. Linear regression models with standardized betas demonstrated a stronger association between A β and energetic cost of walking (all $P < 0.05$) than A β and gait speed (all $P > .05$) in unadjusted and adjusted models (Table 3).

Finally, linear regression models investigating mean cortical A β levels displayed cortical A β was associated with the energetic cost of walking ($P = .038$) but not gait speed ($P = 0.154$) in the fully adjusted models (Table S1 in supporting information). Further bootstrapping analyses revealed all observed logistic and linear regression associations among the energetic cost of walking, A β , and mean cortical A β remained significant, verifying the robustness of our parameter estimates (Table S2 and S3 in supporting information).

4 | DISCUSSION

We examined the cross-sectional associations of the energetic cost of walking with A β status in a sample of cognitively normal community-dwelling older adults free of neurological disease. Our findings show that a greater energetic cost of customary walking is associated with higher odds of A β positivity. These findings persisted after controlling for the effects of demographics, comorbid conditions, and APOE ϵ 4. Notably, there was no association between usual gait speed and A β status in this sample. Collectively, these data suggest inefficient energy use during walking may be a physiological indicator of emerging AD-related pathology that is more sensitive than gait speed.

The utility of assessing gait speed in older adulthood is evident, with multiple studies demonstrating associations of slow gait speed with accelerated cognitive decline and higher risk of cognitive impairment.^{23–28} Further, research has identified associations between gait speed and neuroimaging markers of brain pathology, suggesting changes in gait may track with the progression of age- and disease-related processes (e.g., neurodegeneration).⁹ However, whether gait speed is cross-sectionally associated with A β measured via PiB-PET is less clear. Studies have reported higher A β is associated with slower gait speed in mid- to late-aged adults,^{29–31,38} though it remains unclear whether these findings are sex-specific²⁹ or persist after covariate adjustment (i.e., APOE ϵ 4).³⁸ In studies that included older adults with self-reported memory complaints³⁰ and cognitive impairment,³¹ greater A β deposition was associated with slower gait speed. However, similar gait speed associations were not found in two separate samples of cognitively normal community-dwelling older adults.^{11,32} Although the available cross-sectional data appear mixed, there is a body of research detailing A β deposition predicts future gait speed decline,^{11–13} suggesting these mobility deficits may manifest years after the emergence of AD pathology. This may in part explain why cross-sectional studies that include cognitively impaired participants observe A β and gait speed associations,^{30,31} but studies of cognitively normal cohorts typically do not.^{11,32} Our finding that the energetic cost of walking, but not gait speed, was cross-sectionally associated with A β fits well with the current research paradigms that postulate A β and walking energetics become abnormal years prior to cognitive and motor impairment.^{2,22}

In our sample, the energetic cost of walking and gait speed were both associated with advancing age. It has been hypothesized that the progressive rise in walking energy costs with aging contributes to slowed gait speed, as older adults attempt to maintain a level of energy expenditure ($\dot{V}O_2$) that optimizes walking energetics.^{16,17,39} Recently, our group demonstrated that older adults with rising energetic costs

for walking displayed greater longitudinal decline in gait speed than more efficient walkers, supporting the hypothesis that changes in walking energetics generally precede gait speed decline. To this end, investigating links between the energetic cost of walking and AD pathology may improve our understanding of the connection between gait and early pathophysiological processes of AD that occur prior to observable motor and cognitive deficits.

The initial adjusted models revealed the energetic cost of walking, but not gait speed, was associated with $A\beta$ positivity. After further adjustment for comorbid conditions and *APOE* $\epsilon 4$, each 0.01 mL/kg/m increase in energy cost was associated with 18% higher odds of being $A\beta+$. These findings were corroborated in the ancillary analyses that found $A\beta$ status and mean cortical $A\beta$ were more strongly associated with the energetic cost of walking than gait speed. Elevated energy costs for walking may result from $A\beta$ affecting descending neuromuscular signaling/recruitment responsible for gait mechanics; however, whether $A\beta$ accumulation in specific motor-related regions influences gait parameters remains unclear.^{12,13,29,32} Disruptions to these corticospinal pathways may lead to subtle motor coordination dysfunction that results in a higher energetic cost of walking but may not be severe enough to interfere with gross motor movements (i.e., gait speed). Another possible mechanistic link may be through mitochondrial function. It has been hypothesized that $A\beta$ impairs neuronal mitochondrial function⁴⁰ and that mitochondrial dysfunction in skeletal muscle is associated with decreased gait speed and cardiorespiratory fitness ($\dot{V}O_{2max}$) in older adults.^{41,42} Therefore, it is possible that neuronal and skeletal mitochondrial impairments may contribute to the link between $A\beta$ deposition and walking energetics in the early stages of AD. Alternatively, these findings may be explained by other AD processes. The current research framework hypothesizes that $A\beta$ is involved in the initial disease process;² therefore, $A\beta+$ participants may be undergoing other disease processes, such as tau accumulation, which may be responsible for neuronal dysfunction/degeneration that affects walking energetics. Although there is support that $A\beta$ is associated with gait speed independent of brain volumes,^{12,29} future research investigating AD-specific biomarkers concomitantly is needed to further delineate the specificity of the current energetics findings.

There is increasing recognition that cardiorespiratory fitness, the integrated ability to deliver oxygen to the musculoskeletal system during exercise, may be an important mitigating factor for developing dementia.⁴³ Our previous research has detailed cardiorespiratory fitness, which relies on the upper limit of energetic capacity, is associated with several indices of brain health in older adulthood;^{44–47} however, less is known about whether the energy required for daily tasks, such as walking, relates to age- and disease-related brain changes. This is in part due to traditional exercise testing methods in which participants are evaluated on a stationary cycle ergometer or treadmill while connected to an immobile metabolic cart. The advent of portable indirect calorimeters allows for metabolic measurement in free-living environmental settings. An important aspect of the current study was measuring the energetic cost of walking during an overground walking test, which allowed participants to walk with usual gait mechanics

(i.e., speed, stride length), which may be compromised with treadmill protocols in which minor biomechanical changes may influence energetic values ($\dot{V}O_2$).⁴⁸ Our findings that the energetic cost of walking was associated with $A\beta$ status is intriguing because similar associations have not been observed with cardiorespiratory fitness.^{49,50} With respect to brain health in old age, these data raise the question whether the lower limit of energetic capacity (i.e., walking energetics) may hold greater predictive value than the upper limit (i.e., cardiorespiratory fitness).

Future longitudinal investigation is warranted to elucidate the temporality of the association and biological mechanisms connecting walking energetics and $A\beta$ deposition. Additionally, studies that systematically compare the energetic cost of walking and cardiorespiratory fitness in larger samples are needed to better understand how the continuum of energy regulation tracks with brain and cognitive health throughout older adulthood. The BLSA is a well-characterized sample of highly educated healthy middle- to older-aged adults, making it uncertain whether our results generalize to more socioeconomic diverse populations. These limitations should be considered in the context of the study strengths which include objectively measured customary-paced walking energetics and examination of $A\beta$ deposition via PiB-PET scans.

In summary, the present study provides evidence that within cognitively normal mid- to late-aged community-dwelling adults, greater energetic cost of customary walking is associated with higher odds of $A\beta$ positivity. Notably, these findings were not observed when investigating gait speed, suggesting the physiological underpinnings of walking could be a meaningful measure of early AD pathology and a potential target for therapeutic intervention. This work contributes to research investigating how gait is interconnected with brain health, and further, provides insight into a physiological measure that may be an early prognostic indicator of emerging AD pathology.

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CONFLICTS OF INTEREST

All authors report no conflicts of interest.

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SUPPORTING INFORMATION

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

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