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Brain Amyloid-β and Slow Gait in Older Adults without Dementia: Influence of Cognition and APOE-ε4 Genotype

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Abstract

Importance—Motor slowing appears in preclinical Alzheimer's disease (AD), progresses with AD progression and is associated with AD pathology at autopsy. Whether amyloid-beta (Aβ) is associated with gait speed in dementia free elders and whether cognition and apolipoprotein E (*APOE*) ε4 influence this relationship remains unknown.

Objective—To examine the association between Aβ and gait speed in dementia free older adults and study the influence of cognition and *APOE* ε4 status on this relationship.

Design—Cross-sectional.

Setting—University center.

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Author contribution: Dr. Neelesh Nadkarni, Assistant Professor, Division of Geriatric Medicine, Department of Medicine, University of Pittsburgh and Dr. Subashan Perera, Associate Professor, Division of Geriatric Medicine, Department of Medicine and Biostatistics, University of Pittsburgh had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Perera conducted and is responsible for the data analysis.

Participants—183 elders without dementia enrolled in the Ginkgo Evaluation of Memory (GEM) study, including 144 cognitively normal (CN) subsample (mean age: 85 years in both).

Main Outcomes, Measures—We assessed cerebral Aβ on Pittsburgh B (PiB) PET, gait speed over 15-feet and cognition on the Mini-mental Status Examination (MMSE) and Trail-Making-Test, Parts A and B (TMT-A, TMT-B). We grouped participants into high-Aβ [PiB(+)] and low-Aβ [PiB(−)] on standardized global PiB cutoffs and examined group differences. We studied the influence of cognition and *APOE* ε4 on the global and regional associations between gait speed and Aβ in the whole sample and in the CN subsample.

Results—PiB(+) were comparable to PiB(−) individuals on demographics, comorbidities, cognition, hippocampal volume and small-vessel disease but not on gait speed (0.85 vs 0.92 m/sec, p=0.012) or proportion of *APOE* ε4 carriers (29% vs 6%, p<0.001). In this whole sample and in the CN subsample, the association between global PiB retention and slower gait withstood adjustment for covariates (p=0.026 and p=0.042 respectively); however, this relationship was attenuated by MMSE, TMT- A and TMT-B and was rendered statistically nonsignificant by *APOE* ε4 in both samples (both p≥0.1). Several regional associations between gait speed and PiB uptake withstood relevant adjustments; however, *APOE* ε4 rendered only the medial and lateral temporal and occipital regions in the whole sample and, the occipital regions in CN subsample statistically significant.

Conclusion—Cerebral Aβ deposition is associated with slower gait speed in older adults without dementia; however, this association is weaker in CN elders. Cognition and *APOE ε4* carrier status influence the relationship between Aβ and gait speed in dementia free older adults.

Introduction

Motor slowing appears during the preclinical stages of Alzheimer's disease (AD),[1] accelerates in those who subsequently go on to develop mild cognitive impairment (MCI)/AD[2,3] and is associated with severity of AD pathology at death.[4] In older adults without dementia, elevated levels of fibrillar amyloid-beta (Aβ) are seen in 30%-65% of adults between 80 and 88 years of age.[5–8] Recent evidence suggests that high levels of Aβ increases fall risk in these populations.[9] Slowing of gait speed is an important determinant of falls and mortality in older adults[10] and is associated with cerebral small-vessel disease and cortical atrophy.[11] However, cerebral Aβ may also play a role in gait slowing in older adults without dementia but there is little research to support this association.

Cognitive processes influence gait in cognitively normal (CN) older adults and in those with MCI.[11,12] Deficits in these cognitive processes are associated with greater Aβ deposition in these populations.[13,14] In addition, *APOE ε4* genotype is associated with poor mobility and physical function in older adults[15] and in those with MCI[16] and presence of an *APOE ε4* allele is linked to accelerated motor decline in aging,[17,18] with exceptions.[19,20] Besides age, *APOE ε4* is the largest risk factor for AD and presence of an APOE ε4 allele increases Aβ accumulation in CN older adults,[5,21–24] and in prodromal and clinical AD.[24–26] Therefore, both cognition and *APOE ε4* genotype may influence the association between Aβ and gait speed in dementia free older adults.

We investigated the relationship between cortical and regional Aβ deposition and gait speed in older adults without dementia and assessed whether cognition and *APOE ε4* status influence this relationship. We further examined these relationships in a subsample of older adults deemed CN in the parent study[5] to understand whether the association between Aβ and gait in the entire cohort was driven by those with MCI. We hypothesized that greater cortical Aβ deposition will be associated with slower gait in the whole sample but its magnitude and statistical significance would be weaker in those without MCI, i.e., the CN individuals. In addition, we posited that cognition and *APOE ε4* would independently influence the global and regional relationship between Aβ deposition and gait speed beyond that explained by demographic factors, cardiac risk, cortical atrophy and small-vessel disease, factors known to play a role in age-related motor slowing.[11,12]

Design and Methods

Population

Gingko Evaluation of Memory study (GEMS), a randomized double-blind, placebo-controlled trial of Ginkgo biloba targeted to prevent dementia, particularly AD, recruited CN older adults and older adults with MCI.[27,28] Participants free of dementia at study entry were followed annually from 2000 to 2009 in the GEMS. Approximately 10±3 months following the GEMS closeout visit, 194 dementia free participants enrolled at the University of Pittsburgh site were recruited for the GEMS Imaging Substudy that included a brain MRI and Pittsburgh-B compound (PiB) positron emission tomography (PiB-PET).[5,29] Eligibility criteria for the GEMS Imaging Substudy was described previously.[5,29] Eleven participants were not included in this analyses due to technical issues relating to their PiB-PET (n=3) and MRI (n=8) scans. This study analyzed data from 183 GEMS participants who had complete brain MRI and PiB-PET data along with physical performance measures.

Cognitive Assessment and Adjudication of MCI

All participants underwent detailed neuropsychological assessments annually as part of the GEMS[27,28] a subset of which were included in the GEMS Imaging Substudy.[5,29] We assessed global cognitive function on the Mini-mental Status Examination and attention and executive function on the Trail Making Test, parts A (TMT-A) and part B (TMT-B).[28] Adjudication of MCI was conducted by the GEMS Cognitive Diagnostic Center, taking into account all neuropsychological assessments from the GEMS parent study and the GEMS Imaging Substudy. Criteria for MCI included a cutoff of 1.5 standard deviations (SD) below age- and education- adjusted norm on 2–3 tests.[5]

Gait Speed

Time to walk 15-feet was measured using a protocol similar to the one used to assess gait speed in the Short Physical Performance Battery[30] and has been described previously.[31] Briefly, a 15-foot long traverse was demarcated with tape and participants were instructed to begin walking from standing position at the start line and continue walking past the end line. Time was measured using a stop-watch, which was started after the prompt when one foot started to move across the start line and was stopped when the first foot crossed the 15-foot end mark. Two consecutive 15-foot walks were obtained, the first at usual pace and the

second at rapid pace.[31] We used the usual paced timed walk measure to derive gait speed in meters per second. The 15-feet walk (4.57 meter) test is a well validated measure of gait speed in older adults with and without dementia with an excellent test-retest reliability (ICC= 0.973–0.977).[32] Mean duration between gait speed assessment and brain imaging was 16 months (range: 10 to 25 months).

PiB-PET

PiB-PET imaging methodology was reported previously.[5,29] In brief, [C^{11}] PiB ligand (approximately 15 mCi) was injected over 20 seconds and a 10-minute transmission scan was acquired for attenuation correction followed by a 20 minute PiB-PET scan (4 × 5 minute frames) acquired 50 minutes post injection. PiB retention was assessed in the resliced-normalized PET image in the regions of interest (ROIs) encompassing the following bilateral regions:[33] anterior cingulate (ACG, pregenual and subgenual), anteroventral striatum (AVS, anterior caudate and putamen), frontal cortex (FRC, dorsal and ventral), lateral temporal cortex (LTC), parietal (PAR) and precuneus (PRC), mesial temporal cortex (MTC, amygdala and hippocampus), occipital cortex (OCC, primary visual cortex), occipital pole (OCP), pons (PON), sensory-motor cortex (SMC), subcortical white matter (SWM) and thalamus (THL). An iterative outlier cutoff method was used to define subjects as PiB(+) if the atrophy corrected PiB standardized uptake value ratio (SUVR, referenced to the cerebellar value) was >1.57 averaged from PiB SUVR of the ACG, AVS, FRC, LTC, PAR and PRC.[29] A continuous measure of global PiB SUVR represented values in these six ROIs.

APOE genotyping

APOE genotyping was performed using polymerase chain reaction on DNA isolated from whole blood samples as described previously.[34] Participants with at least one *APOE ε4* allele (ε2/ε4, ε3/ε4 or ε4/ε4) were identified as *APOE ε4* carriers.

Covariates

Several age-related changes are linked to gait and cognitive performance in older adults.[11,12] Amongst these, cardiac risk factors are also associated with cerebral Aβ deposition[29] and *APOE ε4* carrier status.[35] Hence, analyses were adjusted for covariates that included demographics (age, gender, race, education), body weight, hypertension, coronary heart disease (presence of a self-reported or chart review based diagnoses angina, myocardial infarction, angioplasty, bypass surgery, pacemaker, valve replacement, heart failure), stroke and MRI measures of cortical atrophy and small-vessel disease (bilateral hippocampal volume and total volume of white matter hyperintensities (WMH), both presented as a proportion of intracranial volume).[29]

Statistical analyses

We compared PiB(+) and PiB(−) groups on demographic, health and key brain measures using independent samples *t*-tests. We examined the association between global PiB retention and gait speed using multiple regression adjusting for the above covariates. We included cognitive measures (MMSE, TMT-A and TMT-B) and *APOE ε4* carrier status,

separately as additional independent variables in the unadjusted and adjusted models. We repeated the analyses using a subsample of participants deemed CN after excluding those with MCI. We included an interaction term in the models to examine whether the association between PiB SUVR and gait speed was different in *APOE ε4* carriers and non-carriers, based on our observations in other setting.[36] However, recognizing that interaction terms have low statistical power, we *a priori* planned an exploratory analysis stratified by *APOE ε4* carrier status. Finally, we performed an another exploratory analysis of regional association between PiB SUVR and gait speed initially adjusting for all covariates including cognition and then with further adjusting for *APOE ε4* status. To assess whether the time between gait assessment and PiB PET scan influenced the overall results we performed a sensitivity analysis by including the duration of time between gait assessment and PiB-PET as a covariate.

Results

Sample characteristics

In the whole sample (N=183, 85.5±3 years, 42% female), the mean MMSE was 28, 20% were *APOE ε4* carriers and 54.6% were designated as PiB(+). The characteristics of the whole group and subgroups divided on global PiB SUVR are shown in Table 1. Both PiB(+) and PiB(−) subgroups were similar in terms of their demographic, body weight, comorbidities, MMSE, TMT-A, TMT-B, physical performance measures, number of falls and, hippocampal and WMH volumes. PiB(+) group had greater proportion of *APOE ε4* carriers compared to the PiB(−) group (29% vs 6%, p<0.001). Also, we found that the PiB(+) group had a slower gait speed than the PiB(−) group (0.85 vs 0.92 m/sec, p=0.012).

Sample characteristics of the CN subsample (n=144, 85.4 years) are shown in Table 2. PiB(+) and PiB(−) groups were similar on all above characteristics except on prevalence of hypertension (42% vs 22%, p=0.01), the proportion of *APOE ε4* carriers (28% vs 7%, p=0.003) and gait speed (0.87 vs 0.94 m/sec, p=0.036).

There were no differences in gait speed between the placebo and Gingko biloba arms of the study in the whole sample (0.89 m/sec vs 0.87 m/sec, p=0.6) or in the CN subsample (0.89 m/sec vs 0.92 m/sec, p=0.4).

Association between global PiB SUVR and gait speed

Table 3 shows the association between global PiB binding and gait speed. In the whole sample, greater global PiB SUVR was associated with slower gait (regression coefficient (β)= −0.086, p=0.005) and this association remained significant after adjustment for above covariates (β=−0.068, p=0.026). MMSE correlated with gait speed (r=0.24, p=0.002); TMT-A and TMT-B correlated with both global PiB SUVR (r= 0.3, p=0.005 and r=0.18, p=0.02, respectively) and gait speed (r=−0.3, p=<0.001 and r=−0.19, p=0.01, respectively). The association between PiB SUVR and gait speed was attenuated but tended to persist after adjusting for MMSE (p=0.06), TMT-A (p=0.06) and TMT-B (p=0.08). Accounting for *APOE ε4* in the model rendered the association between PiB SUVR and gait speed

nonsignificant and contributed to approximately 16% of the additional explained variance in the entire sample (Table 3).

In the CN older adults, greater global PiB SUVR was associated with slower gait speed (β=-0.072, p=0.04) and even after adjusting for above covariates (β=-0.074, p=0.042); however, this association was no longer significant after additional adjustments for MMSE, TMT-A, TMT-B or *APOE ε4* status. *APOE ε4* explained approximately 10% of the additional explained variance in the association between PiB SUVR and gait speed (Table 3).

We did not find a statistically significant interaction with *APOE ε4* and global PiB with respect to gait speed. We found no significant relationships between APOE ε4 carrier status and gait speed (eTable 1). The stratified analysis by *APOE ε4* carrier status suggested that the associations between gait speed and PiB SUVR, MMSE, TMT-A and TMT-B were stronger in the *APOE ε4* non-carriers than carriers in both the samples (eTable 2).

We performed a sensitivity analysis to examine whether the duration between gait assessment and PiB-PET had any bearing on the relationship between Aβ and gait speed. With time period between MRI and gait assessment as a covariate in the regression analysis, the strength of unadjusted relationship between global PiB SUVR and gait speed was unchanged (whole sample: beta = −0.09, p=0.005; CN subsample: beta=−0.072, p=0.04).

Association between regional PiB SUVR and gait speed

Figure 1a depicts an exploratory analysis showing the coefficient of the association between regional PiB SUVR for global PiB SUVR and regional PiB SUVR for the whole group and for the subsample limited to CN individuals adjusted for demographics variables, body weight, hypertension, coronary heart disease, stroke, MMSE and normalized hippocampal and WMH volume but not adjusted for *APOE ε4*. In the whole sample, slower gait was significantly associated with regional PiB SUVR in AVS (p=0.027), LTC (p=0.012), MTC (p=0.015), PAR (p=0.027), PRC (p=0.019), SMC (p=0.02) and SWM (p=0.031) and, showed a trend with PiB SUVR in ACG, FRC, OCC (all p=0.06) and OCP (p=0.05). However, in CN elders, slower gait was significantly associated with greater regional PiB SUVR in the FRC (p=0.05), AVS (p=0.039), LTC (p=0.023), PRC (p=0.024) and SMC (p=0.021). The association between gait speed and regional PiB SUVR was marginally statistically significant in the ACG (p=0.07) and the MTC, PAR, OCC and OCP (all p=0.05) ROIs (Figure 1a). Gait speed was not significantly associated with regional PiB SUVR in any other ROIs in the whole group or in the subsample of CN older adults.

Figure 1b shows the associations between regional PiB SUVR and gait speed adjusted for *APOE ε4* status. In the models adjusted for the above covariates (Figure 1a), we found that additional inclusion of *APOE ε4* rendered the regional association between gait speed and PiB SUVR in the FRC, PRC, AVS and ACG nonsignificant (p>0.1, Figure 1b) in the whole sample and in the subsample of individuals without MCI (the CN individuals) The statistically significant associations between gait speed and PiB SUVR in the MTC, OCC, OCP, SWM, and LTC were retained in the whole sample; however, in the sample without MCI, this association was limited to the OCC.

Discussion

In this sample of dementia free older adults, in the category that we term “oldest old”, brain Aβ deposition was present at high levels in 55% and was associated with slower gait speed, independent of demographic, cardiac risk, hippocampal volume and small-vessel disease. The association between brain Aβ and gait speed was influenced by global cognitive and executive function capabilities as well as *APOE ε4* carrier status. Gait speed was associated with regional Aβ in the frontal, striatal, temporal, parietal, anterior cingulate, precuneus and occipital cortices. However, *APOE ε4* attenuated the associations between gait speed and global Aβ and the Aβ deposition in several anterior brain regions, particularly in the CN sample. This is the one of the first reports highlighting the influence of cognition and *APOE ε4* on the association between global and regional Aβ and gait speed in dementia free and in CN older adults.

Prior studies have linked Aβ pathology to physical performance measures in aging and in neurodegenerative diseases. In population studies, Aβ plaques and neurofibrillary tangles, hallmarks of AD pathology, are associated more strongly with motor performance measures than are other changes in the aging brain such as small cerebral infarcts or Lewy body pathology.[17] While both Aβ plaques and NFT are associated weakly with gait speed in cross-sectional studies they are associated more strongly with gait slowing over 6.4 years of longitudinal assessments.[37] In dementia free older adults, elevated levels of Aβ are associated with a 5-fold increase in falls.[9] These studies support our findings indicating that greater Aβ deposition in the brain is associated with mobility decline in older adults.

APOE ε4 increases Aβ deposition in preclinical AD and in CN individuals.[21,24,35,38] *APOE ε4* also has other effects on the brain such facilitating tau hyperphosphorylation[35] Moreover, *APOE ε4* carriers have more severe gait impairments[15] and worsened gait speed decline[17,18] than *APOE ε4* non-carriers. *APOE ε4* status is also associated with gait speed in MCI, although not with other physical performance measures such as grip strength, chair stands or cardiorespiratory status.[16] This body of literature suggests that *APOE ε4* may influence cortical control of gait by influencing both Aβ related and unrelated processes; this may explain why controlling for *APOE ε4* in the statistical analyses led to diminution of the magnitude of relationship between Aβ and gait speed. The association between Aβ and gait speed appears to have been driven by 34 and 27 *APOE ε4* carriers in the whole sample and the CN subsample respectively – this small sample of *APOE ε4* carriers may have also precluded any interaction between *APOE ε4* and interpretation of the association between global PiB retention and gait speed within *APOE ε4* subgroups. However, our findings complement the growing body of literature showing that *APOE ε4* status may play a role in the association between global cortical Aβ deposition and gait speed in dementia free older adults and in CN individuals.

Cognition plays an important role in motor planning and gait control in older adults, including in those without dementia.[39] In CN older adults, slower gait is associated with worse attention, executive function, visuospatial processing and memory.[39–41] In dementia free elders, Aβ is associated with global cognitive function,[13,14,42] memory[13,42–44], attention/executive function,[14,45] and visual-spatial processing.[14,42] We found that both

global cognitive function and executive function measures attenuated the relationship between global PiB SUVR and gait speed in the whole sample, and rendered the relationship between Aβ and gait speed statistically nonsignificant in the CN subsample - suggesting that Aβ may influence higher level cognitive processes that play an important role in gait control in these populations. Furthermore, *APOE ε4* modulates the association between global Aβ and global cognition, memory and visual-spatial processing[14,42] albeit with exceptions.[13] Therefore, our findings suggest that *APOE ε4* may influence the cognitive processes involved in the control of gait, and influence gait slowing in older adults.

The exploratory regional analysis in the entire cohort, including the 21% with MCI, revealed that Aβ deposition in the AVS, FRC, ACG, MTC, LTC, PAR, SWM, SMC, and PRC was associated with gait speed while in the CN sample, the regional associations were limited to the SMC, AVS, PRC and LTC. These findings are supported by another recent report on the regional associations between Aβ and gait speed.[46] The SMC, AVS, PAR, PRC and related networks play an important role in gait control[47,48] and our data suggest that Aβ in these areas may affect gait speed in older adults. However, we also found that regional associations in the FRC, ACG, AVS, PAR and PRC were not significant after correction for *APOE ε4*. *APOE ε4* allele influences Aβ deposition in the frontal, cingulate, striatal, parietal and precuneus regions.[21,49] In dementia free PiB(+) older adults, regional Aβ distribution is similar to that of AD patients, including nonspecific binding in SWM,[8,49,50] and is associated with cognition – medial temporal Aβ with memory[43,44] and frontal, temporal and parietal Aβ with global cognition.[14] This may explain why *APOE ε4* rendered these predominantly anterior regional associations nonsignificant in the entire sample and in the CN subsample. Our findings differ slightly from the recent study on regional Aβ deposition and gait associations in a heterogeneous sample of older adults selected on basis of memory complaints (99.2%), slow gait (11%) and impaired instrumental activities of daily living (6%) that reported that greater regional Aβ in several frontal, temporal and striatal parietal regions was related to slower gait;[46] these analysis were adjusted for *APOE ε4* status but not for cardiac risk, WMH volume or cortical atrophy.[46] The differences in the two studies could relate to varying inclusion criteria, delineation of ROIs, differences in the study samples and the statistical adjustments used.

Our findings show that Aβ is not strongly associated with gait speed in CN individuals suggesting that Aβ *per se* is not the main driver of slow gait speed in aging or in AD. Aβ may coexist and contribute to other AD-related brain changes such as inflammation, tau aggregation and neurofibrillary tangle pathology, which spreads to the neocortex coinciding with onset of AD symptoms[51] that may include gait slowing.[2,3] In PiB(+) CN individuals, Aβ deposition may be an early event in the AD process and may be weakly associated with gait speed, nevertheless modified by APOE ε4 allele that favors Aβ deposition over tau aggregation in CN aging.[24] Changes in the brain in CN older adults may be independent of Aβ.[52] Given the lack of research in this area, we speculate that gait speed in older adults may be affected by both Aβ dependent and Aβ-independent pathways influenced by *APOE ε4*.

Our study has several limitations. This was an exploratory secondary analysis of data of well-characterized older adults who had PiB PET scans along with physical performance

measures. The smaller sample size, especially in the *APOE ε4* subgroup analyses, resulted in lower statistical power that is required to show meaningful conclusions. We cannot exclude the possibility of other AD-related pathologies such as tau contributing to gait slowing in our sample. The timing of gait speed assessment was not concurrent with PiB-PET, however, we performed a sensitivity analysis that showed that controlling for the duration of time between gait assessment and PiB-PET scan did not affect the overall results. Lastly, this was a cross-sectional analysis that included an exploratory analysis of regional associations on a well characterized sample; therefore, while our findings are hypotheses generating, we cannot address causality or directionality of these associations.

In summary, this study revealed that in older adults without dementia, gait speed was modestly associated with Aβ deposition independent of cardiac risk, hippocampal volume and small-vessel disease burden, and the relationship between Aβ deposition and gait speed was attenuated by *APOE ε4* and cognition.

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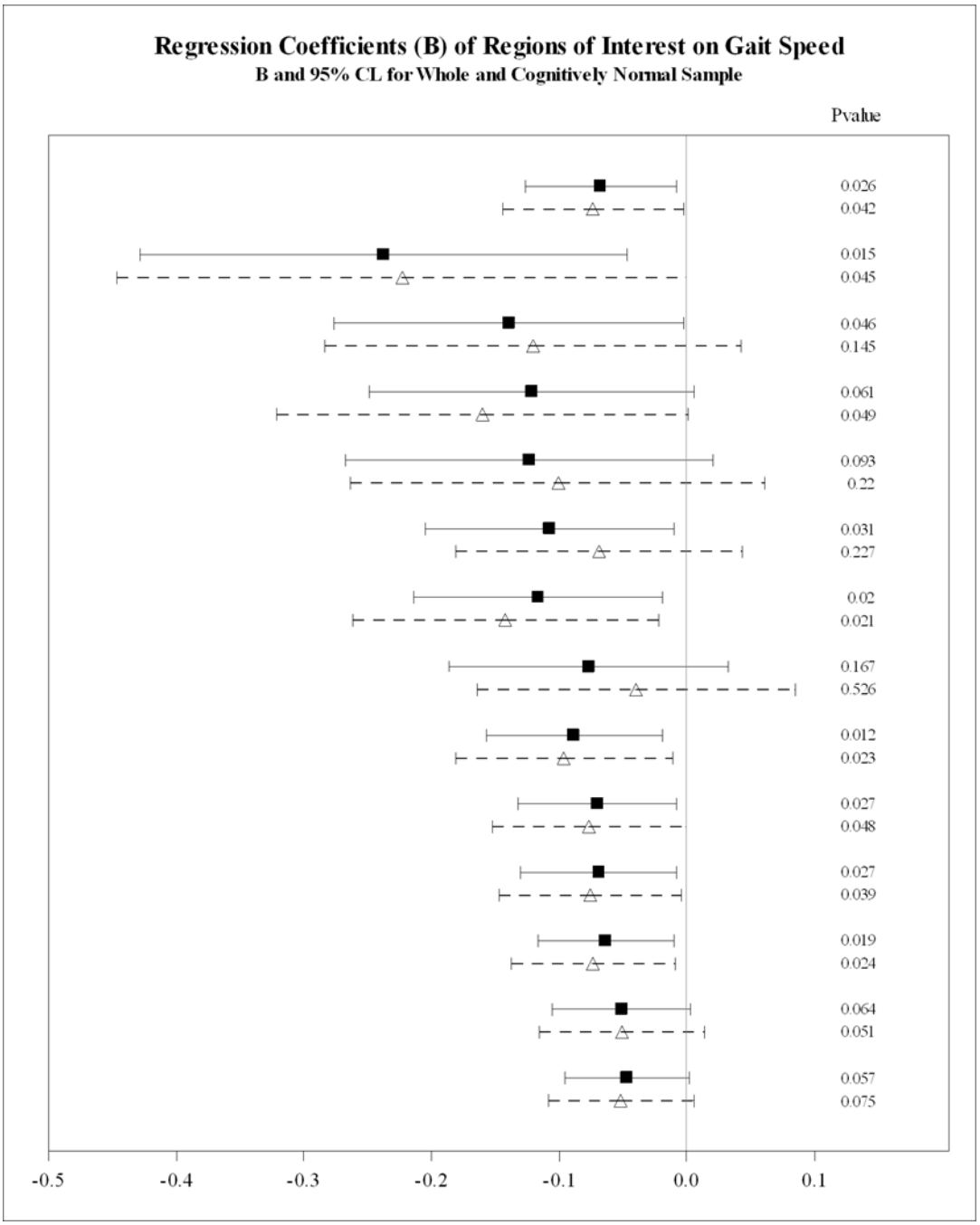

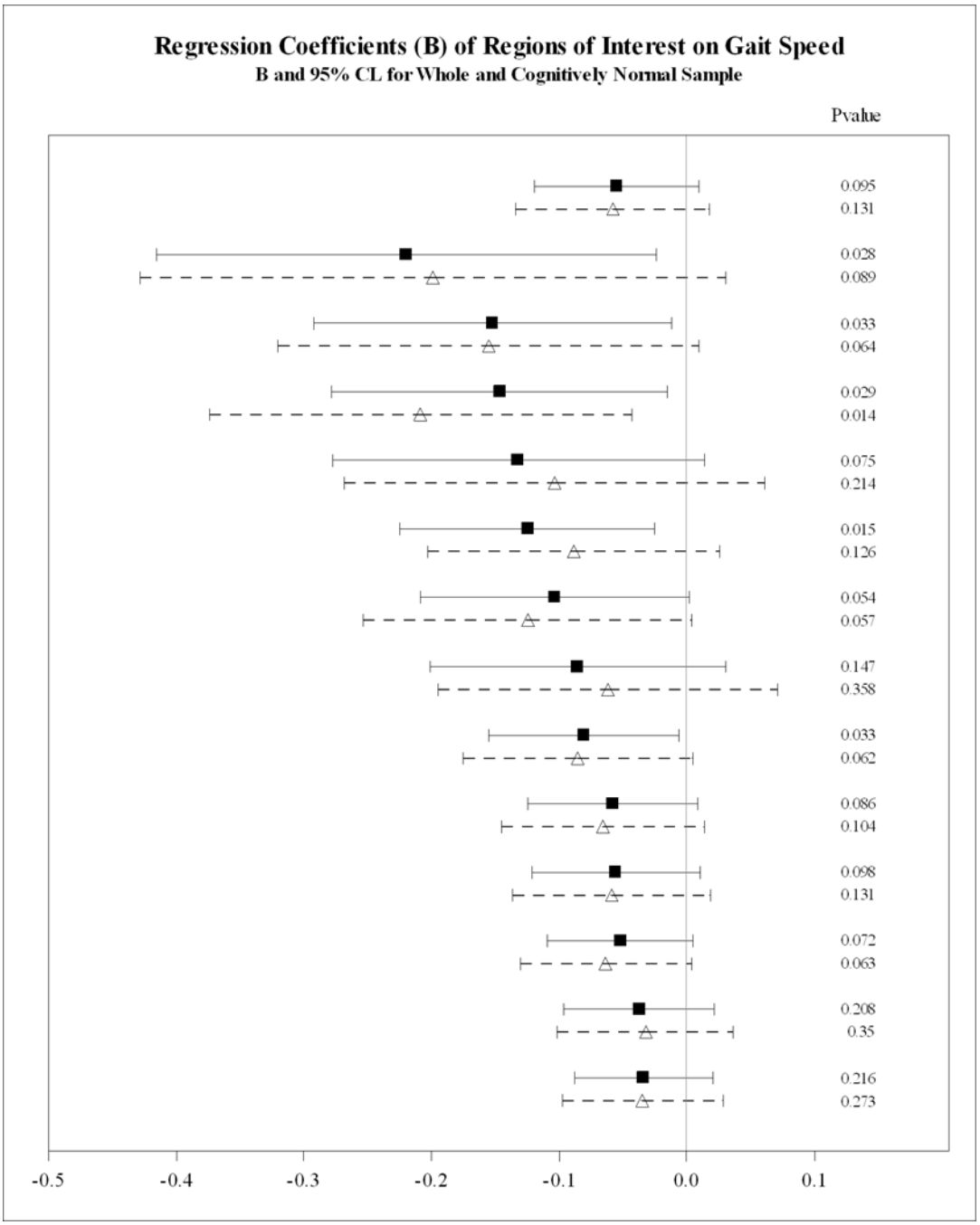

Figure 1.

Association between global and regional Aβ and gait speed in the whole sample and in the cognitively normal subsample.

A: Adjusted for covariates[a] not *APOE ε4* carrier status.

B: Adjusted for covariates[a] including *APOE ε4* carrier status.

Dementia-free older adults in the whole sample shown in filled square and bolded lines. Cognitive normal subsample shown in open triangles and dotted lines. Regions arranged in descending order of magnitude of regression coefficient (β, 95% CI).

[a]covariates: age, gender, race, education, weight, cognition (MMSE), hypertension, coronary heart disease, stroke, bilateral hippocampal volume and white matter hyperintensities on MRI normalized to intracranial volume.

Table 1

Sample characteristics of the whole sample and differences in PiB(+) and PiB(−) groups.

	Whole sample (N=183)	PiB(+) (N=100)	PiB(−) (N=83)	p-value
Age (years)	85.5 ± 2.9	85.7 ± 3.1	85.2 ± 2.5	0.26
Women (n, %)	76 (41.5%)	44 (44%)	32 (38.6%)	0.46
White (n, %)	177 (97%)	97 (98%)	80 (98%)	0.99
Education (years)	14.7 ± 2.6	14.7 ± 2.5	14.6 ± 2.8	0.85
MMSE (range: 0 to 30)	27.6 ± 2.1	27.4 ± 2.0	27.7 ± 2.1	0.36
TMT-A (mean, sec)	48.7 ± 19.2	50 ± 17.4	51.9 + 24.1	0.5
TMT-B (mean, sec)	124.6 ± 52.3	127 ± 50	134 ± 55	0.4
Physical Performance Total score (range: 0 to 12)	8.5 ± 2.3	8.2 ± 2.5	8.8 ± 2.0	0.06
APOE-ε4 carrier status (n, %)	34 (20.1%)	29 (29%)	5 (6%)	<0.001
Standing weight (kg)	74.5 ± 11.4	74.5 ± 11.9	74.5 ± 11	0.99
Heart Disease (n, %)	32 (17.6%)	19 (19%)	13 (15.9%)	0.58
Atrial Fibrillation (n, %)	11 (6.1%)	6 (6.1%)	5 (6.2%)	0.99
Stroke/TIA (n, %)	8 (4.4%)	6 (6%)	2 (2.4%)	0.3
Hypertension (n, %)	63 (35.2%)	39 (39.4%)	24 (30%)	0.19
Diabetes Mellitus (n, %)	10 (5.6%)	7 (7.1%)	3 (3.8%)	0.52
Falls over prior 1 year (n, %)	18 (9.9%)	9 (9%)	9 (11%)	0.66
	Whole sample (N=183)	**PiB(+) (N=100)**	**PiB(−) (N=83)**	**p-value**
White matter hyperintensities (normalized to ICV)	0.009085 ± 0.0059	0.00894 ± 0.00565	0.00925 ± 0.00622	0.72
Hippocampal volume (normalized to ICV)	0.256 ± 0.03	0.255 ± 0.03	0.257 ± 0.03	0.60
PiB SUVR	1.78 ± 0.48	2.136 ± 0.347	1.340 ± 0.141	<0.0001
Gait Speed (m/sec)	0.88 ± 0.2	0.85 ± 0.19	0.92 ± 0.2	0.012

Abbreviations:
PiB SUVR: Pittsburgh B compound standardized value uptake ratio
CN: cognitively normal
MMSE: Mini-mental Status Examination
TMT-A and TMT-B: Part A and Part B of Trail Making Test respectively
APOE ε4 carrier: Presence of at least one ε4 allele on the apolipoprotein-E gene.
ICV: intracranial volume

Table 2

Sample characteristics of the sample restricted to CN older adults with differences in PiB(+) and PiB(−) groups within this sub-sample.

	Normal sample (N=144)	PiB(+) (N=75)	PiB(−) (N=69)	p-value
Age (years)	85.44 ± 2.87	85.33 ± 3.08	85.55 ± 2.65	0.65
Women (n, %)	82 (56.94%)	42 (29.17%)	40 (27.78%)	0.81
White (n, %)	142 (97%)	75 (99%)	68 (99%)	0.99
Education (years)	14.75 ± 2.65	14.79 ± 2.61	14.71 ± 2.71	0.86
MMSE (range: 0 to 30)	28.03 ± 1.65	27.88 ± 1.64	28.21 ± 1.66	0.25
TMT-A (mean, sec)	48.7 ± 19	51 ± 21.4	51 ± 19.8	0.99
TMT-B (mean, sec)	125 ± 52.3	129 ± 50	130 ± 50	0.9
Physical Performance Total score (range: 0 to 12)	8.66 ± 2.29	8.32 ± 2.46	9.01 ± 2.04	0.07
APOE ε4 carrier status (n, %)	27 (20%)	22 (29.3%)	5 (7.2%)	0.001
Standing weight (kg)	75.1 ± 11.1	74.2 ± 11.2	75.8 ± 10.9	0.45
Heart Disease (n, %)	22 (15.3%)	11 (14.7%)	11 (15.9%)	0.99
Atrial Fibrillation (n, %)	10 (6.9%)	5 (6.7%)	5 (7.2%)	0.99
Stroke (n, %)	8 (4.14%)	4 (5.3%)	2 (2.9%)	0.7
Hypertension (n, %)	46 (32.6%)	31 (41.9%)	15 (22.4%)	0.02
Diabetes Mellitus (n, %)	7 (5%)	5 (6.8%)	2 (3%)	0.44
Falls over prior 1 year (n, %)	13 (9.03%)	5 (6.7%)	8 (11.6%)	0.30
Normal sample (N=144)	**PiB(+) (N=75)**	**PiB(−) (N=69)**	**p-value**	**Normal sample (N=144)**
White matter hyperintensities (normalized to intracranial volume)	0.009 ± 0.006	0.008 ± 0.005	0.009 ± 0.006	0.76
Hippocampal volume (normalized to intracranial volume)	0.26 ± 0.03	0.26 ± 0.03	0.26 ± 0.03	0.82
PiB SUVR	1.75 ± 0.47	2.12 ± 0.34	1.35 ± 0.13	<0.0001
Gait Speed (m/sec)	0.90± 0.19	0.87± 0.18	0.94± 0.20	0.036

Abbreviations:
PiB SUVR: Pittsburgh B compound standardized value uptake ratio
CN: cognitively normal
MMSE: Mini-mental Status Examination
TMT-A and TMT-B: Part A and Part B of Trail Making Test respectively
APOE ε4 carrier: Presence of at least one ε4 allele on the apolipoprotein-E gene.
ICV: intracranial volume

Table 3

Unadjusted and adjusted associations between global PiB SUVR and gait speed (dependent variable) in the whole sample and in the CN subsample: influence of cognition (MMSE, TMT-A and TMT-B) and APOE ε4 carrier status on these relationships.

	Whole sample (n=183) β (p value), [95%CI]		CN sample (n=144) β (p value), [95%CI]	
	Unadjusted	**Adjusted***	**Unadjusted**	**Adjusted***
Global PiB SUVR	−0.086 (0.005) [−0.146, −0.027]	−0.068 (0.026) [−0.127, −0.008]	−0.072 (0.04) [−0.140,−0.003]	−0.074 (0.042) [−0.145, −0.003]
Global PiB SUVR + MMSE	−0.073 (0.017) [−0.132, −0.013]	−0.057 (0.056) [−0.115, −0.002]	−0.059 (0.084) [−0.126, 0.008]	−0.055 (0.11) [−0.124, 0.013]
Global PiB SUVR + TMT-A	−0.061 (0.04) [−0.119, −0.002]	−0.055 (0.08) [−0.116, −0.006]	−0.063 (0.07) [0.131, 0.005]	−0.068 (0.06) [−0.14, 0.004]
Global PiB SUVR + TMT-B	−0.071 (0.02) [−0.131, −0.0114]	0.064 (0.038) [−0.125, −0.004]	−0.068 (0.06) [−0.137, 0.002]	−0.077 (0.04) [−0.148, −0.005]
Global PiB SUVR + *APOE ε4* status	−0.062 (0.057) [−0.126, 0.002]	−0.055 (0.095) [−0.119, 0.010]	−0.06 (0.1) [−0.1335, 0.0134]	−0.058 (0.13) [−0.134, 0.018]

Footnote:

* Covariates included in the adjusted model: age, gender, race, education, weight, hypertension, coronary heart disease, stroke and volume of hippocampal and white matter hyperintensities on MRI normalized to intracranial volume.

PiB SUVR: Pittsburgh B compound standardized value uptake ratio
CN: cognitively normal
MMSE: Mini-mental Status Examination
TMT-A and TMT-B: Part A and Part B of Trail Making Test respectively
APOE ε4 carrier: Presence of at least one ε4 allele on the apolipoprotein-E gene.