ORIGINAL RESEARCH

Gait in Cerebral Amyloid Angiopathy

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BACKGROUND: Gait is a complex task requiring coordinated efforts of multiple brain networks. To date, there is little evidence on whether gait is altered in cerebral amyloid angiopathy (CAA). We aimed to identify impairments in gait performance and associations between gait impairment and neuroimaging markers of CAA, cognition, and falls.

METHODS AND RESULTS: Gait was assessed using the Zeno Walkway during preferred pace and dual task walks, and grouped into gait domains (Rhythm, Pace, Postural Control, and Variability). Participants underwent neuropsychological testing and neuroimaging. Falls and fear of falling were assessed through self-report questionnaires. Gait domain scores were standardized and analyzed using linear regression adjusting for age, sex, height, and other covariates. Participants were patients with CAA (n=29), Alzheimer disease with mild dementia (n=16), mild cognitive impairment (n=24), and normal elderly controls (n=47). CAA and Alzheimer disease had similarly impaired Rhythm, Pace, and Variability, and higher dual task cost than normal controls or mild cognitive impairment. Higher Pace score was associated with better global cognition, processing speed, and memory. Gait measures were not correlated with microbleed count or white matter hyperintensity volume. Number of falls was not associated with gait domain scores, but participants with low fear of falling had higher Pace (odds ratio [OR], 2.61 [95% CI, 1.59–4.29]) and lower Variability (OR, 1.64 [95% CI, 1.10–2.44]).

CONCLUSIONS: CAA is associated with slower walking, abnormal rhythm, and greater gait variability than in healthy controls. Future research is needed to identify the mechanisms underlying gait impairments in CAA, and whether they predict future falls.

Key Words: accidental falls ■ cerebral amyloid angiopathy ■ cognition ■ gait ■ neuroimaging

Cerebral amyloid angiopathy (CAA) is a type of cerebral small vessel disease (CSVD) affecting the elderly.1 Sporadic age-related CAA is characterized by the accumulation of β-amyloid protein in the medium to small arteries and capillaries of the brain and can cause intracerebral hemorrhage (ICH), lobar cerebral microbleeds (CMB), cortical superficial siderosis, enlarged perivascular spaces, white matter hyperintensities (WMH), and cortical atrophy.2

Gait is a complex task requiring coordinated efforts of multiple motor and cognitive networks of the brain.3 When another brain resource-intensive task, such as a cognitive task, is performed while walking, gait can be slowed. The extent of slowing may be measured by the dual task cost.4 Studies have shown dual task cost is higher in older adults and those with existing gait difficulties.5

To date, there is little evidence of whether gait is altered in individuals with CAA or how it relates to other older populations. One study showed that reduced white matter network efficiency throughout the brain was associated with lower gait speed in CAA.6 In this study, we aimed to compare CAA and similarly aged mild Alzheimer disease (AD), mild cognitive impairment (MCI), and normal control (NC) participants in gait performance, including the dual task cost. We hypothesized that patients with CAA would have impaired gait and greater dual task cost compared with NC and MCI because of the white matter damage that occurs in CAA, and that impaired gait would be associated with fear of falling and number of falls.
METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants

Participants for this cross-sectional analysis were selected from the Functional Assessment of Vascular Reactivity in Small Vessel Disease-II study, an ongoing 2-site prospective longitudinal cohort study. Participants provided written informed consent. The study was approved by institutional review boards at the University of Calgary and University of Alberta.

Patients with CAA without dementia (n=29), mild AD (n=16), MCI (n=24), and NC (n=47) were selected. General inclusion criteria included proficiency in English, having a study partner with whom the participant had regular contact (minimum once per week), Montreal Cognitive Assessment total score ≥13, and absence of other central nervous system disease or a substance abuse disorder.

Probable CAA was diagnosed using modified Boston criteria, based on evidence of lobar, cortical, or cortical–subcortical evidence of ICH, CMB, or cortical superficial siderosis. Patients with CAA presented with a related clinical syndrome (intracerebral or subarachnoid hemorrhage, transient focal neurological episodes, or MCI) and must not have a cognitive status of dementia based on a comprehensive neuropsychological assessment. Diagnosis of AD was based on the National Institute on Aging–Alzheimer’s Association core clinical criteria, which require the presence of cognitive and functional impairment interfering with usual activities without evidence of other causes on routine blood work and neuroimaging. Participants were considered mild AD if they had a Clinical Dementia Rating scale score of 0.5 or 1.0 out of a possible 3. Diagnosis of MCI was based on cognitive impairments while maintaining functional independence, using the National Institute on Aging–Alzheimer’s Association core clinical criteria and could include amnestic or nonamnestic MCI.

Operational definitions for impaired activities of daily living and cognition followed the protocol of the Comprehensive Assessment of Neurodegeneration and Dementia cohort study. Recruitment of NC was based on community advertising, and all were screened for central nervous system diseases or cognitive decline by Montreal Cognitive Assessment and an examination by a neurologist. The age range for the AD, MCI, and NC groups was 60 to 85 years, while for the CAA group it was 55 to 85 years. Participants with AD, MCI, and NC were excluded from the analysis if study magnetic resonance imaging (MRI) revealed multiple lobar microbleeds or superficial siderosis, indicating the potential presence of asymptomatic CAA.

Stroke-related signs were captured for CAA participants using the National Institutes of Health Stroke Scale.

Gait Assessment

Objective gait measurements were obtained using the 6-m Zeno Walkway and the accompanying data collection software, ProtoKinetics Movement Analysis Software (ProtoKinetics LLC, Havertown, PA). Participants completed 6 separate walks down the full length of the walkway: 3 walks at a preferred pace (to be averaged for analysis) and 3 more walks while performing a different secondary task (dual task gait) in a fixed order: counting backward by ones, naming animals, and counting backward by sevens. Walking aids were permitted. We assessed test–retest reliability to determine the consistency of the results from the walkway.
Specific gait parameters analyzed, in accordance with previous studies with similar populations, were stride length (distance between heel points of 2 consecutive footfalls of same foot, in cm), stride width (distance between midpoint of 2 consecutive footfalls of the same foot and midpoint of the opposite footfall, in cm), stride time (time elapsed between first contacts of 2 consecutive footfalls of the same foot, in seconds), and cadence (number of steps per minute), and where available, variability for each parameter. Variability was defined as the percent coefficient of variance of the variable. Because gait speed and cadence are measured across the whole walk and not per step, it is not possible to report a coefficient of variance for these parameters.

Individual gait variables can be grouped as a smaller number of broad gait domains that describe gait characteristics and reduce redundancy among individual variables. We grouped the gait variables into 4 domains:

1. **Rhythm**, representing temporal gait measurements consisting of stride time and cadence;
2. **Pace**, representing distance-related gait measurements, consisting of the average of gait speed, stride length, and double support percent;
3. **Postural Control**, representing width-related gait measurements, consisting of stride width and stride width variability; and
4. **Variability**, representing variability measures of gait, consisting of stride time variability, stride length variability, and double support percent variability.

Dual task cost for velocity was calculated using a previously described formula: \( \text{Dual task velocity} = \left( \frac{\text{single task velocity} - \text{dual task velocity}}{\text{single task velocity}} \right) \times 100 \).

**Neuroimaging**

Brain MRIs were acquired using 3T scanners (Calgary: MR 750, General Electric Healthcare, Waukesha, WI or Edmonton: Siemens Skyra, Erlangen, Germany) at baseline visit (ie, within 3 months of gait and cognitive assessments). T2* gradient recalled echo (GRE; slice thickness 3.0 mm; TR/TE=650/20 ms; flip angle=20 degrees; acquisition matrix 256x256; field of view 240 mm), T1-weighted (slice thickness 1.0 mm; TR/TE 6/2.7 ms; flip angle=11 degrees, acquisition matrix 256x256; field of view 240 mm), and T2-weighted fluid attenuated inversion recovery (slice thickness 3.0 mm; TR/TE 9000/140 ms; flip angle=90 degrees; acquisition matrix 256x256; field of view 240 mm) sequences were obtained to assess measures of lobar CMB count and WMH volume.

WMH volume was measured from T2-weighted fluid attenuated inversion recovery images using the semi-automated, seed-based region growing method in Cerebra Lesion Extraction Tool (Calgary Image Processing and Analysis Centre, Calgary, Canada). Intracranial volume was estimated from T1-weighted images processed through Freesurfer v6.0, and WMH volumes were analyzed as the percent of the intracranial volume occupied by WMH. A qualified radiologist with >15 years experience counted the number of lobar CMBs, defined as hypointense signals of <10 mm in diameter on T2* GRE, in accordance with criteria for Standards for Reporting Vascular Changes on Neuroimaging, which provides standardized terminology for and identification of lesion types in MRI.

**Cognitive Assessment**

Participants completed a neuropsychological assessment covering the cognitive domains of processing speed, executive function, and memory, as well as the Montreal Cognitive Assessment to assess global cognition. Processing speed was measured by the Digit Symbol Coding task and Trail Making Test Part A, executive function by the Trail Making Test Part B and phonetic verbal fluency tasks, and memory by the delayed recall sections of the Rey Auditory Verbal Learning Test and Brief Visuospatial Memory Test-Revised. Standardized individual test scores were combined to determine domain scores.

**Falls Assessment**

Number of falls over the year before baseline visit was determined using a self-report questionnaire. Participants were asked if they had sustained any falls over the previous year and, if so, how many. Fear of falling was reported by participants on a scale of 0 to 10 based on their response to the following question: “Using a scale from 0 to 10, where 0 is “not afraid” and 10 is “extremely afraid”, how afraid of falling are you?”

**Statistical Analysis**

Test–retest reliability was assessed by calculating the intraclass correlation coefficient (ICC) for each of the 10 gait parameters comprising the gait domains using the 3 trials of the preferred pace walks.

Data from the disease groups (ie, MCI, CAA, and AD) were standardized to the NC group by calculating z-scores for each gait variable using means and SDs of the respective variable within the NC group. Standardized scores for stride time, double support percent, stride width, and variability scores were inverted so that higher scores indicate better performance. All scores were then combined into gait domains. Demographic variables were compared using 1-way ANOVA for continuous variables and Pearson’s \( \chi^2 \) test for categorical data, using Fisher exact test when expected counts were low.
To identify differences in gait ability and dual task cost of gait speed across groups, we used linear regression models, controlling for age, sex, and height. Gait domains and dual task cost were the dependent variables in the model, and group was the independent variable of interest. Least-square means were used to estimate adjusted means for each group and 95% CIs, using the Tukey–Kramer method post hoc to adjust for multiple comparisons.

Linear regression was used to examine the associations between gait, MRI features associated with CAA (ie, WMH volume and CMB count) and cognitive performance, in the CAA group and in all participants. Gait domains and dual task cost were the dependent variables in the model. All of the models were adjusted for age, sex, and height. Models including cognitive domains were additionally adjusted for education, and the models including all participants were additionally adjusted for group. Because cognition and gait were associated with each other, an additional analysis was done to investigate whether cognition mediates relationship between CAA and gait impairment by recalculating standardized domain scores for CAA, with additional adjustments for each of processing speed, memory, and global cognition in separate models.

Number of falls over the past year (before study visit) and fear of falling score (out of a maximum score of 10) were dichotomized as follows: low falls was defined as 1 fall or no falls, based on prior literature, and low fear of falling was defined as a questionnaire score of 2 or lower to represent the most commonly reported scores. Associations between gait domains and low number of falls and low fear of falling were assessed using logistic regression. All of the models were adjusted for age, sex, height, and the models including all participants were additionally adjusted for group.

A significance threshold of $P<0.05$ was applied for all analyses. All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC) with the exception of the test–retest reliability calculation, which was done using SPSS version 26 (IBM Corp, Armonk, NY).

Deidentified participant data and analytic code will be shared on request to the corresponding author.

### Table 1. Participant Characteristics

|                       | All participants | NC   | MCI  | CAA   | AD    | $P$ value† |
|-----------------------|------------------|------|------|-------|-------|------------|
| No.                   | 116              | 47   | 24   | 29    | 16    |            |
| Female, n (%)         | 60 (51.7)        | 34 (72.3) | 9 (37.5) | 12 (41.4) | 5 (31.3) | <0.01*     |
| Age, y (SD)           | 71.8 (7.3)       | 70.0 (6.3) | 72.8 (8.3) | 75.1 (7.7) | 69.8 (6.2) | 0.01*      |
| Height, cm (SD)       | 168.5 (10.3)     | 165.8 (9.7) | 170.0 (9.8) | 171.0 (10.8) | 169.7 (11.2) | 0.14       |
| Education, y (SD)     | 15.3 (3.5)       | 15.8 (3.2) | 15.5 (4.2) | 13.9 (3.3) | 16.0 (3.4) | 0.09       |
| MoCA, total (SD)      | 23.3 (4.9)       | 26.9 (1.9) | 23.2 (2.9) | 20.5 (5.7) | 18.1 (4.0) | <0.001*    |

Clinical information

|                        |                  |      |      |       |       |         |
|------------------------|------------------|------|------|-------|-------|---------|
| Hypertension, n (%)    | 43 (37.1)        | 13 (27.7) | 6 (25.0) | 18 (62.1) | 6 (37.5) | 0.01*   |
| Hypercholesterolemia, n (%) | 47 (40.1)    | 19 (40.4) | 14 (58.3) | 10 (34.5) | 4 (25.7) | 0.19     |
| Diabetes, n (%)        | 9 (7.8)          | 4 (8.5) | 3 (12.5) | 1 (3.5) | 1 (6.3) | 0.02*‡   |
| Osteoarthritis, n (%)  | 54 (47.0)        | 28 (60.9) | 9 (37.5) | 13 (44.8) | 4 (25.0) | 0.06     |

MRI characteristics

|                         |                  |      |      |       |       |         |
|-------------------------|------------------|------|------|-------|-------|---------|
| WMH volume, % ICV (SD)  | 0.9 (1.2)        | 0.4 (0.4) | 0.8 (0.9) | 2.1 (1.7) | 0.5 (0.8) | <0.001*  |
| CMB count, (SD)         | 21.3 (114.7)     | 0.2 (0.6) | 0.9 (3.0) | 84.1 (220.3) | 0.1 (0.3) | <0.01*   |

Walking aids

|                        |                  |      |      |       |       |         |
|------------------------|------------------|------|------|-------|-------|---------|
| None, n (%)            | 106 (92.2)       | 44 (95.7) | 24 (100) | 23 (79.3) | 15 (93.8) | ...     |
| Cane, n (%)            | 6 (5.2)          | 1 (2.2) | 0 (0) | 4 (13.8) | 1 (6.3) | ...     |
| Walker, n (%)          | 3 (2.6)          | 1 (2.2) | 0 (0) | 2 (6.9) | 0 (0) | ...     |

Falls

|                     |                  |      |      |       |       |         |
|---------------------|------------------|------|------|-------|-------|---------|
| Low number of falls, n (%) | 95 (83.3)      | 38 (84.4) | 17 (70.8) | 24 (82.8) | 16 (100) | ...     |
| Low fear of falling, n (%) | 79 (69.3)    | 31 (68.9) | 17 (70.8) | 19 (65.5) | 12 (75.0) | ...     |

Values represent means (SD) for continuous variables and count (%) for categorical variables. Low number of falls is no falls or 1 fall in the year before baseline visit. Low fear of falling is a self-reported score of 2 or less out of 10. AD indicates Alzheimer disease; CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed; ICV, intracranial volume; MCI, mild cognitive impairment; MoCA, Montreal cognitive assessment; NC, normal controls; and WMH, white matter hyperintensity.

*Significant difference ($P<0.05$) between study groups based on ANOVA and $\chi^2$ as appropriate.

†Comparisons between groups, not including all participants.

‡Results from Fisher exact test.
RESULTS

Study Participant Characteristics

Of 119 participants, 3 did not complete the gait walk (2 declined, and 1 had difficulty with ambulation), leaving 116 for analysis (NC=47, MCI=24, CAA=29, and AD=16). Participant characteristics are presented in Table 1. Patients with CAA were older with a mean age of 75.1 (SD 7.7) and consisted of 41.4% females. Patients with CAA were more likely to have a history of hypertension and had greater WMH volumes and CMB counts. Global cognition scores in CAA were lower than NC (mean 20.5 [SD 5.7]). Patients with CAA presented with lobar ICH (12 participants [41.4%]), transient focal neurological episodes (12 [41.4%]), or cognitive decline (5 [17.2%]), and 1 (3.5%) had a history of CAA-related inflammation, which had resolved at the time of the study assessments. Among the patients with CAA with lobar ICH, median National Institutes of Health Stroke Scale was 0 (interquartile range 0–0); and none had examination findings of motor weakness in the leg or limb ataxia.

Gait Performance

Assessment of test–retest reliability across study groups and in the full study sample is shown in Table 2. There was excellent test–retest reliability (ICC>0.9) in the Pace and Rhythm domains, and moderate (ICC, 0.5–0.75) to good (ICC, 0.75–0.9) test–retest reliability in the Postural Control domain. However, the test–retest reliability in the Variability domain ranged from poor (ICC, <0.5) to good.

Performance on each of the walks, as measured by standardized gait domain scores, is displayed in Figure 1. In analyses adjusted for age, sex, and height, compared with NC, CAA was associated with impairments in Rhythm, Pace, and Variability (P≤0.001), but not Postural Control, when walking at preferred pace and when walking while counting backwards. Similarly, there were impairments in Rhythm and Pace when walking while naming animals (P≤0.001). In contrast, there was no difference compared with NC when walking while subtracting 7 serially. Like CAA, AD was also associated with impairments in Rhythm, Pace, and Variability, but not Postural Control, compared with NC (P≤0.05). There were no significant differences between CAA and AD on any of the walks (also see Table 3). CAA was associated with lower gait scores than MCI for Rhythm, Pace, and Variability for most walks (Table 3). In a sensitivity analysis removing 9 participants with walking aids, the relationships between CAA and other study groups with gait domains were unchanged (data not shown). A further comparison of gait performance between CAA participants with ICH (n=16) and without (n=13) ICH on preferred pace walk found no differences. Standardized score differences for individuals with ICH in reference to those without ICH were as follows: Rhythm 0.12 (95% CI −1.35, 1.58), Pace −0.20 (−1.43, 1.04), Postural Control: −0.15 (−0.66, 0.36), and Variability: −0.56 (−1.81, 0.68).

Dual Task Cost

Comparisons of dual task cost between groups are shown in Figure 2. CAA had a greater dual task cost of gait speed than NC during counting backwards (loss of 10.43% of the single task gait speed; 95% CI, 3.36–17.50) and naming animals walks (loss of 10.65%; 95% CI, 0.85–20.45), adjusting for age, sex, and height. Dual task cost did not differ significantly between CAA

Table 2. Test–Retest Reliability of the Protokinetics Zeno Walkway

| Gait variable                  | Total sample | NC     | MCI    | CAA     | AD     |
|-------------------------------|--------------|--------|--------|---------|--------|
| Pace                          |              |        |        |         |        |
| Gait speed                    | 0.976        | 0.967  | 0.970  | 0.980   | 0.965  |
| Stride length                 | 0.986        | 0.981  | 0.989  | 0.989   | 0.977  |
| Double support percent        | 0.973        | 0.968  | 0.950  | 0.976   | 0.979  |
| Rhythm                        |              |        |        |         |        |
| Cadence                       | 0.973        | 0.964  | 0.966  | 0.969   | 0.952  |
| Stride time                   | 0.969        | 0.960  | 0.956  | 0.961   | 0.957  |
| Variability                   |              |        |        |         |        |
| Double support percent variability | 0.412    | 0.028  | 0.140  | 0.592   | 0.521  |
| Stride time variability       | 0.645        | 0.698  | 0.532  | 0.598   | 0.553  |
| Stride length variability     | 0.653        | 0.302  | 0.659  | 0.517   | 0.771  |
| Postural control              |              |        |        |         |        |
| Stride width                  | 0.723        | 0.852  | 0.925  | 0.562   | 0.484  |
| Stride width variability      | 0.590        | 0.597  | 0.537  | 0.733   | 0.316  |

Values represent intraclass correlation coefficient of gait variables across 3 trials of the preferred pace walks for full study sample (Total Sample) and separated by study group. AD indicates Alzheimer disease; CAA, cerebral amyloid angiopathy; MCI, mild cognitive impairment, and NC, normal control.
Figure 1. Gait performance on single and dual task walks by gait domain obtained through general linear models, controlling for age, sex, and height, and Tukey–Kramer method post hoc to adjust for multiple comparisons.

Bars represent standardized differences between disease groups, as displayed (MCI, CAA, and AD), and control group (NC) with error bars representing 95% CIs. AD indicates Alzheimer disease; CAA, cerebral amyloid angiopathy; MCI, mild cognitive impairment; and NC, normal controls. *Significant difference (P<0.05) compared with NC.
and NC during serial 7’s walk. There were no significant differences between CAA and MCI or between CAA and AD in dual task cost of gait speed.

**MRI Markers of CAA**
In CAA participants, no associations between WMH volume and CMB were found, nor were there associations found in the full study sample after controlling for group (Table 4).

**Cognitive Performance**
Associations between gait and cognitive performance are shown in Table 4. In CAA participants, the dual task cost of naming animals was associated with memory (estimated 7.66% greater dual task cost for each SD decrease in memory, 95% CI −15.01% to −0.32%). Among all participants, controlling for group, Pace was associated with global cognition, processing speed, and memory; Variability was associated with processing speed; the dual task cost of counting backwards was associated with processing speed; and dual task cost of naming animals was associated with global cognition. After additional adjustment for processing speed and memory, several associations between CAA and gait impairment became nonsignificant, particularly in the Pace and Variability domains (Table 5).

**Falls**
Falls characteristics are shown in Table 6. There was no association between gait domains, dual task cost, and higher number of falls. However, among CAA participants, low fear of falling was associated with higher Pace score (odds ratio [OR], 4.17 per 1 SD increase [95% CI, 1.26–13.82]) and better Variability score (OR, 2.33 [95% CI, 1.08–5.00]) in univariate analyses, but these relationships were no longer significant after adjusting for age and sex: Pace OR 2.81 (95% CI, 0.84–9.45) and Variability OR 1.65 (95% CI, 0.67–4.02). Among all study participants, low fear of falling was associated with higher Pace and better Variability score in both univariate (Pace: OR 2.47 per 1 SD increase [95% CI, 1.59–3.84]; Variability: OR 1.49 [95% CI, 1.07–2.06]) and multivariable-adjusted analyses (Pace: OR 2.80 [95% CI, 1.59–4.91]; Variability: OR 1.06 [95% CI, 1.01–2.54]).

**DISCUSSION**
The current study is the first to examine domain-specific differences in gait between CAA and other similar-aged groups using an instrumented walkway. There was generally good to excellent test–retest reliability, depending on the domain, with Pace and...
Rhythm being excellent and Variability ranging from good to poor. Although conclusions were limited by sample size, the current study found that gait in CAA is impaired compared with NC across single and dual task walks, particularly in the Pace domain, which consists of gait speed, stride length, and double support percent. A similar pattern was seen when comparing CAA to MCI. CAA and AD performed similarly across all domains on both single and dual task walks. The dual task cost was greater in CAA than NC and MCI, and similar to AD, on the counting backwards and animal naming walks. However, there were no differences between groups in the dual task cost of serial sevens. No associations were found between gait and CMB count or WMH volume in either CAA participants or all participants. However, in CAA participants, we found associations between dual task cost of naming animals and memory, while in all participants, we found that Pace was associated with all cognitive domains measured except executive function. Finally, we failed to find an association between poor gait and a greater number of falls, but we did find that greater performance in Pace and Variability were associated with low fear of falling. Associations with fear of falling were not significant when looking at CAA alone, again possibly because of the smaller sample size.

While gait has been studied extensively in older populations, there is very little published work looking at gait in CAA specifically. One study showed that decreased whole-brain white matter network efficiency in CAA was associated with reduced gait speed. All generally, normal control of gait requires the integrated functioning of several regions of cerebral cortex, including prefrontal, occipital, and temporal cortices. CAA may disrupt cerebral cortical function by causing microinfarction and thinning of the cortex. In future work we plan to use multimodal MRI to better define the neural mechanisms underlying gait dysfunction in CAA.

Consistent with our findings in CAA, gait performance has also been shown to be impaired in individuals with other causes of CSVD. The exception to this is Postural Control, which studies do not report being consistently related to CSVD. Dual task cost has been associated with presence of MCI, and in participants with MCI, dual task cost was higher in amnestic than nonamnestic MCI and predicted risk for dementia. Future studies are needed to determine whether higher dual task cost is associated with future gait decline or cognitive decline in CAA.

In contrast to our prespecified hypothesis, we failed to find that higher WMH was associated with gait impairment even though prior studies in the general population or in persons with CSVD generally find that higher WMH is associated with slower gait. Therefore, other mechanisms may be at play. There may be subtler alterations in white matter microstructure that underlie gait impairments. We did not find that abnormal gait was associated with CMB count, although as noted, this may be because of small sample size.

A systematic review examining the links between gait and cognition in older people showed that, similar to our results in the full study sample, Pace was associated with global cognition and individual cognitive domains, including processing speed and memory. However, reported associations of Rhythm and Variability were more variable, with only some studies finding associations. Likewise, we found Variability was only associated with processing speed and did not find links between Rhythm and cognition. Additionally, we found that impaired processing speed and memory may mediate the relationship between CAA and gait impairment, particularly in the Pace and Variability domains. This is in line with a prior study, which found...
Table 4. Associations Between Preferred Pace Walks and MRI and Cognitive Characteristics

| Rhythm* | Pace* | Postural control* | Variability* | DTC counting backward† | DTC naming animals† | DTC serial sevens† |
|---------|-------|------------------|--------------|------------------------|---------------------|-------------------|
| MRI markers: CAA only |
| WMH     | 0.05 (−0.37, 0.48) | −0.17 (−0.52, 0.18) | 0.02 (−0.13, 0.17) | −0.20 (−0.56, 0.16) | 1.97 (−2.02, 5.96) | 0.24 (−4.85, 5.34) |
| CMB     | 0.0003 (−0.003, 0.003) | 0.001 (−0.002, 0.003) | 0.0002 (−0.001, 0.001) | 0.001 (−0.001, 0.003) | 0.004 (−0.02, 0.03) | 0.003 (−0.03, 0.03) |
| MRI markers: all participants |
| WMH     | 0.10 (−0.12, 0.33) | −0.19 (−0.40, 0.02) | 0.01 (−0.10, 0.11) | −0.21 (−0.42, 0.01) | 1.23 (−0.88, 3.33) | 0.07 (−3.13, 3.27) |
| CMB     | 0.006 (−0.001, 0.003) | 0.009 (−0.001, 0.003) | 0.0001 (−0.001, 0.001) | 0.001 (−0.001, 0.003) | 0.003 (−0.01, 0.02) | 0.004 (−0.02, 0.03) |
| Cognitive domains: CAA only |
| Global cognition | 0.02 (−0.13, 0.16) | 0.04 (−0.07, 0.16) | −0.02 (−0.07, 0.03) | −0.04 (−0.17, 0.08) | −0.23 (−1.63, 1.17) | −0.49 (−2.25, 1.28) |
| Processing speed | 0.08 (−0.63, 0.79) | 0.50 (−0.02, 1.02) | 0.12 (−0.13, 0.37) | 0.41 (−0.17, 0.90) | −2.58 (−8.84, 3.67) | −2.40 (−10.46, 5.67) |
| Executive function | 0.19 (−0.42, 0.79) | 0.30 (−0.18, 0.77) | 0.09 (−0.13, 0.31) | −0.06 (−0.59, 0.47) | −1.52 (−6.56, 3.51) | −3.14 (−9.41, 3.12) |
| Memory | −0.14 (−0.84, 0.56) | 0.30 (−0.25, 0.85) | 0.10 (−0.16, 0.35) | 0.01 (−0.60, 0.62) | −5.30 (−11.27, 0.66) | −7.66 (−15.01, −0.32) |
| Cognitive domains: all participants |
| Global cognition | 0.02 (−0.05, 0.09) | 0.07 (0.01, 0.14) | −0.002 (−0.03, 0.03) | 0.03 (−0.03, 0.10) | −0.89 (−1.49, −0.29) | −0.94 (−1.84, −0.05) |
| Processing speed | 0.07 (−0.14, 0.29) | 0.41 (0.22, 0.59) | 0.06 (−0.04, 0.16) | 0.33 (0.13, 0.53) | −3.21 (−5.13, −1.30) | −1.83 (−4.59, 0.92) |
| Executive function | 0.17 (−0.02, 0.37) | 0.17 (−0.002, 0.35) | −0.01 (−0.10, 0.08) | 0.09 (−0.10, 0.28) | −1.55 (−3.37, 0.26) | −2.41 (−4.87, 0.06) |
| Memory | −0.003 (−0.22, 0.22) | 0.23 (0.03, 0.43) | 0.02 (−0.08, 0.12) | 0.09 (−0.20, 0.23) | −1.87 (−3.91, 0.18) | −2.28 (−5.10, 0.53) |

Data shown represent β coefficients (95% CI). The β coefficient for WMH represents the change in outcome per 1% increase in WMH as a percentage of intracranial volume, and the β coefficient for CMBs represents the change in outcome per additional CMB. All models are adjusted for age, sex, and height. Models including all participants are also adjusted for group, and models including cognitive domains are additionally adjusted for years of education. CAA indicates cerebral amyloid angiopathy; CMB, cerebral microbleeds; DTC, dual task cost; MRI, magnetic resonance imaging; and WMH, white matter hyperintensities.

*β coefficients in these columns represent the SD change in gait domain score for each 1% increase in WMH as a percent of intracranial volume, each additional CMB, or each SD change in cognitive domain.

†β coefficients in these columns represent the change in percent dual task cost for each 1% increase in WMH as a percent of intracranial volume, each additional CMB, or each SD change in cognitive domain.

‡Values are significant (P<0.05).
Table 5. Association of CAA With Gait Domains According to Walk Type, With and Without Additional Adjustments for Processing Speed, Memory, and Global Cognition (MoCA)

| Walk type          | Rhythm                  | Pace                  | Variability            |
|--------------------|-------------------------|-----------------------|------------------------|
|                    | Original results†       | Adjusted‡             | Original results†       | Adjusted‡             | Original results†       | Adjusted‡             |
| Adjustments for processing speed |                       |                       |                        |                       |                        |                       |
| Preferred pace     | −1.33 (−2.08, −0.58)    | −1.12 (−1.97, −0.27)  | −1.23 (−1.95, −0.52)   | −0.52 (−1.21, 0.17)*  | −1.08 (−1.80, −0.35)   | −0.60 (−1.26, 0.66)*  |
| Counting backwards | −1.71 (−2.60, −0.82)    | −1.13 (−2.12, −0.15)  | −1.42 (−2.12, −0.72)   | −0.59 (−1.25, 0.08)*  | −1.67 (−2.76, −0.58)   | −0.24 (−1.50, 1.01)*  |
| Naming animals     | −1.35 (−2.27, −0.44)    | −0.95 (−1.82, −0.08)  | −1.35 (−2.06, −0.63)   | −0.53 (−1.22, 0.16)*  | ...                    | ...                    |
| Serial 7’s         | ...                     | ...                   | −1.20 (−1.87, −0.53)   | −0.76 (−1.43, −0.09)  | ...                    | ...                    |
| Adjustments for memory |                       |                       |                        |                       |                        |                       |
| Preferred pace     | −1.33 (−2.08, −0.58)    | −1.27 (−2.13, −0.40)  | −1.23 (−1.95, −0.52)   | −0.74 (−1.47, −0.01)  | −1.08 (−1.80, −0.35)   | −1.08 (−1.79, −0.38)  |
| Counting backwards | −1.71 (−2.60, −0.82)    | −1.41 (−2.42, −0.40)  | −1.42 (−2.12, −0.72)   | −0.73 (−1.43, −0.03)  | −1.67 (−2.76, −0.58)   | −0.93 (−2.27, 0.42)*  |
| Naming animals     | −1.35 (−2.27, −0.44)    | −1.09 (−1.98, −0.20)  | −1.35 (−2.06, −0.63)   | −0.56 (−1.27, 0.15)*  | ...                    | ...                    |
| Serial 7’s         | ...                     | ...                   | −1.20 (−1.87, −0.53)   | −0.56 (−1.20, 0.09)   | ...                    | ...                    |
| Adjustments for MoCA total score |                   |                       |                        |                       |                        |                       |
| Preferred pace     | −1.33 (−2.08, −0.58)    | −1.04 (−1.83, −0.25)  | −1.23 (−1.95, −0.52)   | −0.77 (−1.44, −0.10)  | −1.08 (−1.80, −0.35)   | −1.12 (−1.77, −0.47)  |
| Counting backwards | −1.71 (−2.60, −0.82)    | −1.29 (−2.22, −0.37)  | −1.42 (−2.12, −0.72)   | −0.95 (−1.61, −0.28)  | −1.67 (−2.76, −0.58)   | −0.86 (−2.09, 0.37)*  |
| Naming animals     | −1.35 (−2.27, −0.44)    | −0.88 (−1.69, −0.08)  | −1.35 (−2.06, −0.63)   | −0.84 (−1.51, −0.16)  | ...                    | ...                    |
| Serial 7’s         | ...                     | ...                   | −1.20 (−1.87, −0.53)   | −0.94 (−1.57, −0.31)  | ...                    | ...                    |

Values represent gait domain scores in CAA, standardized to the normal control group, adjusting for age, sex, height, and cognitive domain. CAA indicates cerebral amyloid angiopathy; and MoCA, Montreal Cognitive Assessment.

*Indicates the association is no longer significant after additionally adjusting for cognition domain.
†β coefficients for the association between CAA and controls, standardized to the normal control group, after adjusting for age, sex, and height. (Note: Only significant results are displayed.)
‡Standardized β coefficients for the association between CAA and controls, adjusting for age, sex, height, and cognitive domain (either Processing Speed, Memory, or MoCA score as indicated).
that cognition mediated the relationship between white matter damage in CSVD and gait.33

Slow gait speed and shorter stride length, both included in the Pace domain, are known to be major risk factors for future falls.34 Increased WMH volume and greater number of lacunes are associated with greater risk of falls,35,36 in part by causing gait impairments. In this study, gait impairments were related to fear of falls but not when only the CAA participants were considered, probably because of insufficient sample size. Other studies in older people demonstrate that quantitative measures of gait are associated with fear of falling19 and that fear of falls predicts future falls.37 This is in addition to qualitative factors, such as lack of physical activity, impaired activities of daily living, and depressive symptoms.38 The lack of association between frequency of falls and gait, however, is consistent with previous findings that fear of falling may not be related to number of falls. A study by Lavedan et al37 showed that only a minority of older adults who reported fear of falling had a fall. One possible explanation for this is that individuals with a fear of falling may adjust walking patterns to reduce risk of falls. However, another study showed that there was no difference in fear of falling between those with and without a history of falls.38 Therefore, the quantitative gait abnormalities seen in this study may be clinically relevant, indicating that persons with CAA are at risk for falling. However, larger studies will be needed to define the prospective relationship between CAA, gait impairments, falls, and fall-related injuries more precisely.

The main limitation of the study is the relatively small size; although the sample was sufficient to demonstrate differences in quantitative gait measures between CAA and AD and NC, it was not powered to detect associations with falls or neuroimaging markers of CAA. Except for the multiple pairwise comparisons between groups and gait domains, we did not adjust for multiple hypothesis testing. Findings related to fear of falls, cognition, and CAA markers should be considered preliminary and hypothesis-generating, requiring confirmation in future studies. Additionally, the Protokinetics Zeno Walkway system requires further validation to demonstrate that gait metrics collected have clinical relevance, such as with functional impairment or falls risk.

The findings of this study may have implications for clinical care. They suggest that patients with CAA have

### Table 6. Falls Characteristics Based on Preferred Pace Walks

|                      | Number of falls | Fear of falling |
|----------------------|-----------------|-----------------|
|                      | Model 1         | Model 2         | Model 1 | Model 2 |
|                      | OR (95% CI)     | OR (95% CI)     | OR (95% CI) | OR (95% CI) |
| CAA: Gait domains*  |                 |                 |          |         |
| Rhythm               | 0.88 (0.46–1.68) | 0.85 (0.45–1.65) | 0.98 (0.58–1.64) | 1.35 (0.68–2.67) |
| Pace                 | 1.30 (0.61–2.79) | 1.04 (0.44–2.45) | 4.17 (1.26–13.82) | 2.81 (0.84–9.45) |
| Postural control     | 0.22 (0.03–1.61) | 0.16 (0.01–2.40) | 0.59 (0.15–2.35) | 2.06 (0.25–17.20) |
| Variability          | 1.08 (0.53–2.19) | 0.91 (0.36–2.31) | 2.33 (1.08–5.00) | 1.65 (0.67–4.02) |
| CAA: Dual task cost† |                 |                 |          |         |
| Counting backwards   | 0.92 (0.84–1.00) | 0.90 (0.79–1.02) | 0.96 (0.90–1.03) | 0.97 (0.89–1.06) |
| Naming animals       | 0.93 (0.85–1.01) | 0.86 (0.72–1.03) | 0.96 (0.91–1.02) | 0.96 (0.86–1.04) |
| Serial 7’s           | 0.96 (0.91–1.02) | 0.92 (0.83–1.03) | 0.98 (0.93–1.03) | 0.98 (0.92–1.05) |
| All participants: Gait domains* |         |                 |          |         |
| Rhythm               | 0.89 (0.62–1.28) | 0.87 (0.57–1.34) | 0.99 (0.74–1.31) | 1.36 (0.90–2.07) |
| Pace                 | 0.96 (0.63–1.48) | 0.93 (0.60–1.48) | 2.47 (1.59–3.84) | 2.80 (1.59–4.91) |
| Postural control     | 0.65 (0.27–1.53) | 0.72 (0.28–1.84) | 0.96 (0.46–2.00) | 1.98 (0.78–5.06) |
| Variability          | 1.11 (0.75–1.65) | 1.16 (0.76–1.76) | 1.49 (1.07–2.08) | 1.06 (1.01–2.54) |
| All participants: Dual task cost† |         |                 |          |         |
| Counting backwards   | 0.99 (0.95–1.04) | 0.99 (0.95–1.04) | 0.97 (0.93–1.00) | 0.97 (0.93–1.01) |
| Naming animals       | 1.00 (0.97–1.03) | 0.99 (0.96–1.03) | 0.98 (0.96–1.01) | 0.98 (0.95–1.01) |
| Serial 7’s           | 1.01 (0.98–1.04) | 1.01 (0.97–1.04) | 0.99 (0.97–1.01) | 0.98 (0.96–1.01) |

Associations between gait score and odds of low number of falls (<2 falls over previous year) and low fear of falling (self-reported score of 3 or less out of 10). Model 1: Univariate (unadjusted) analysis; Model 2: Multivariable analysis, adjusted for age, sex, and height and, for models including all participants, group. CAA indicates cerebral amyloid angiopathy; and OR, odds ratio.

*β coefficients represent the OR for each SD increase in gait domain.

†β coefficients represent the OR for each 1% absolute increase in dual task cost.

‡Values are significant (P<0.05).
slower walking, abnormal rhythm, and greater gait variability, with a higher fear of falling. Clinicians may wish to question patients with CAA about their fear of falls, observe their gait during the physical examination, and, if there is a concern over falls risk, do a simple bedside test of gait speed such as the Timed Up & Go test. Dual task cost can also be measured relatively simply and reliably in the clinic. Patients at risk for falls could be referred to physical therapy for gait and balance training, and could have their home optimized to reduce falls risk (e.g., by removing hazards and installing assistive devices such as handrails). Future research should attempt to identify the mechanisms underlying gait impairments in CAA, and the utility of quantitative gait measures for predicting future falls.

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