LONGITUDINAL RELATIONSHIPS OF SUBCLINICAL CARDIOVASCULAR DISEASE WITH PHYSICAL FUNCTION IN OLDER ADULTS

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Low ankle-arm index (AAI), a marker of peripheral arterial disease, predicts incident disability in older adults. Elevated pulse wave velocity (PWV), a measure of arterial stiffness, increases risk of cardiovascular events and mortality. However, the relationship between PWV and mobility has not been well characterized in older adults. To evaluate the potential local and systemic influences of vascular disease on physical function, we compared the associations of AAI and PWV with usual gait speed over eight years in the Health, Aging and Body Composition (Health ABC) Study. The study population consisted of 2,066 participants (mean age $\pm$ SD 73.6 $\pm$ 2.8 years, 48.1% men, 37.8% black) with valid PWV, AAI and gait speed data at baseline after exclusion of those with either revascularization or angioplasty of the leg arteries. Random coefficient models were used to evaluate the relationships of both subclinical vascular disease measures with gait speed decline over time. After adjustment for risk factors and comorbidities, each SD higher PWV was associated with a 0.008 m/s slower gait speed over the study period (SE 0.004, p = 0.03). Compared to high-normal AAI (>1.3-1.4), low AAI and noncompressible arteries were each associated with slower gait speed over the study period: Beta (SE) = -0.10 (0.03), p < 0.001 for AAI <0.7, and Beta (SE) = -0.16 (0.04), p < 0.001 for noncompressible arteries. The public health relevance of these findings is the potential contribution of subclinical vascular disease, particularly low AAI and noncompressible arteries, to poor physical function in aging.

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1.0   INTRODUCTION

Beginning in 1997, the Health, Aging and Body Composition (Health ABC) Study enrolled 3,075 Medicare-eligible nondisabled men and women aged 70-79 years living in Pittsburgh, PA and Memphis, TN. The study was designed to prospectively evaluate factors that may be associated with loss of strength and muscle mass and incident functional limitation in a large, biracial population of well-functioning older adults. Currently in its 12th year of funding, Health ABC provides a unique opportunity to characterize the relationship between two measures of subclinical vascular disease and mobility decline in older adults.

Recent research has identified significant associations of both overt and subclinical cardiovascular disease with frailty in older adults [1]. While contributions of clinical cardiovascular disease to frail health are expected, the functional consequences of subclinical disease are under recognized. Often asymptomatic and undiagnosed, peripheral arterial disease (PAD) may lead to physical impairment via local disabling effects, including muscle weakness, impaired nerve function and leg pain [2]. Low values of AAI (<0.9) reflect obstructive atherosclerosis in the leg arteries [2] and predict functional decline and mortality in older adults. However, it is unclear whether high AAI (>1.3) or noncompressible arteries, which may reflect arterial calcification, are also associated with greater risk of mobility decline.

A second measure of subclinical vascular disease available in Health ABC, aortic pulse wave velocity (PWV) has not been characterized in relation to functional decline. Higher values

of PWV represent systemic vascular stiffness, which may cause injury to the fragile small vessels of target organs. Recently, elevated PWV was identified as an important risk factor for cerebral small-vessel disease identified on brain MRI. This cerebrovascular pathology may preferentially disrupt frontal-subcortical tracts involved in the execution of motor tasks such as walking [3]. However, it is not known whether arterial stiffness may influence physical function, and whether this relationship may be explained by reduced cognitive function.

1.1   STATEMENT OF THE PROBLEM

The purpose of this study is to evaluate the associations of two measures of subclinical cardiovascular disease, AAI and PWV, with physical function in older adults. The primary outcome is decline in usual gait speed, a reliable and valid measure of physical function that predicts incident disability in older adults [4]. The study population consists of 2,066 Health ABC participants (mean age ± SD 73.6 ± 2.8 years, 48.1% men, 37.8% black). Random coefficient models are used to evaluate the relationships of both subclinical vascular disease measures with gait speed decline over eight years. Results may clarify the local and systemic influences of subclinical vascular disease on physical function in advancing age.

2.0   REVIEW OF THE LITERATURE

Recent research has identified associations of both clinical and subclinical PAD with functional decline in older adults. Among individuals with clinically diagnosed PAD, AAI and leg symptoms predicted 2-year decline in physical function [5]. For these analyses, generalized estimating equations (GEE) were used to perform repeated-measures analysis of covariance (ANCOVA). The models compared annual changes in physical performance, including walking distance, across patient groups defined by three AAI categories or severity of leg symptoms. Results indicated that lower baseline AAI and leg symptoms each predicted greater decline physical function over two years. These findings demonstrate the clinical value of AAI to identify those with asymptomatic PAD who are at risk for functional decline.

More recently, low AAI was found to predict incident disability and gait speed decline in older adults living in the community [2]. In contrast to the previous study, the study population included individuals without clinically diagnosed PAD. Cox proportional hazards models were used to test the associations of four categories of AAI with self-reported incident disability. Additionally, marginal models were used to analyze the associations of AAI categories with gait speed decline over six years. The results suggested an inverse, dose-response relationship between AAI and risk of incident disability. Participants with an AAI less than 0.9 declined on average 0.12 m/s over 6-year follow-up, an amount considered a clinically meaningful decline in physical function [6].

While these findings suggest local influences of PAD on mobility, it is unclear whether systemic vascular disease may influence physical function in older age. In a recent study of this relationship, ultrasound imaging was used to measure carotid intima-media (IMT) thickness, a surrogate marker of subclinical atherosclerosis [7]. The authors identified an inverse association of IMT with walking speed in older adults without self-reported PAD. This relationship was partially attenuated by adjustment for cognitive performance, in line with hypothesized mediation by cognitive function. However, these results may be confounded by subclinical or undiagnosed PAD. To clarify the potential local and systemic influences of vascular disease on mobility, we evaluated the associations of both AAI and PWV with gait speed decline over eight years in Health ABC.

3.0   METHODS

3.1   POPULATION

From 1997 to 1998 the Health ABC Study enrolled 3,075 Medicare-eligible nondisabled men and women aged 70-79 from Pittsburgh, Pa. and Memphis, Tenn., USA. The population was 52% women and 58% white with a mean age of 73.6 years. Participants were recruited from a random sample of Medicare-eligible adults provided by the Health Care Financing Administration and other household members aged 70-79 were also eligible for recruitment. Exclusion criteria were difficulty walking without an assistive device, walking one quarter of a mile or climbing 10 steps without resting. Both Institutional Review Boards of the University of Pittsburgh, Pa., as well as University of Tennessee at Memphis approved the study and written, informed consent was obtained from each volunteer. Of the 3,075 participants enrolled in Health ABC, 2,103 had PWV, AAI and gait speed data at baseline. Of these participants, we excluded those with either self-reported lower extremity revascularization or angioplasty (n = 37), leaving 2,066 participants for analysis (mean age ± SD 73.6 ± 2.8 years, 48.1% men, 37.8% black).

3.2   ANKLE-ARM INDEX

All Health ABC participants were eligible for ankle-arm index measurement except those with rashes, open wounds, bilateral amputations, or those unable to lie at 45 degrees or less. According to previously reported standard protocol [8], certified technicians measured pressures in the left or right arm and both ankles. Participants were asked to lie recumbent or semirecumbent for at least 5 minutes before measuring blood pressure. Standard blood pressure cuffs were applied to the right arm and each ankle (posterior tibial artery). If blood pressures could not be obtained in the right arm, then the left arm was used (50 cases). After palpation of the arteries, ultrasound gel was applied and an 8-MHz pencil Doppler probe (Parks Medical Electronics, Inc) was used with a standard manometer to measure systolic blood pressures. The systolic blood pressure of the ankle was divided by the systolic blood pressure of the arm to create the ankle-arm index. Measures were performed twice and the results were averaged. The lower average value between the two legs was used to define the ankle-arm index.

3.3   PULSE WAVE VELOCITY

Aortic PWV was measured noninvasively via simultaneous Doppler-recorded carotid and femoral pulse waveforms (model 810A, 9.0- to 10-MHz probes, Parks Medical Electronics, Inc). A minimum of ten beats were recorded for each simultaneous recording site. Three separate runs were recorded for each participant, and all usable runs were averaged to calculate the final PWV measure. The distance between the carotid and femoral recording sites was measured above the surface of the body with a tape measure. The time delay between the feet of the pressure waves

at each site was divided by the associated distance to calculate PWV in cm/s. Replicate measures of PWV in 14 subjects revealed intraclass correlations of 0.88 between sonographers and 0.84 between readers [9].

3.4   GAIT SPEED

Usual speed is a reliable, valid measure of physical function that predicts incident disability in older adults [4]. In Health ABC gait speed was assessed over a 20-meter straight course at baseline and annual (except for Year 7) follow-up over seven years. Participants were instructed to walk at their usual pace from the starting point to the end of the course. Timing began at the first footfall over the starting line and ended with the first footfall over the finishing line.

3.5   RANDOM COEFFICIENT ANALYSIS

Random coefficient analysis, a type of linear mixed model, provides the advantage of correcting for the correlation of observations within a subject over time. The models account for heterogeneity between subjects by allowing the regression coefficients to vary randomly between subjects. The responses for each subject are assumed to be independent observations conditional on the random effects. Also, the random coefficients are assumed to have a multivariate normal distribution and the residuals a normal distribution [10].

This approach corrects for correlation within the data by dividing the total variance in the outcome variable into several components: variance explained by predictors, variance explained

by the random intercept and slope(s), and remaining variance. Ignoring the correlation within data would lead to overestimated standard errors for within-subject factors, and underestimated standard errors for between-subject effects [11].

In the simplest form of the model, only the intercept is random:

$$Y_{it} = B_{0i} + B_{1t} + \varepsilon_{it}$$

where Y_{it} is the observation for subject i at time t, B_{0i} is the random intercept, B_{1t} is the coefficient for time, and ε_{it} is the error for subject i at time t.

The model may additionally allow the relationship of the outcome with time, or the slope with time, to vary randomly between subjects:

$$Y_{it} = B_{0i} + B_{1it} + \varepsilon_{it}$$

where Y_{it} is the observation for subject i at time t, B_{0i} is the random intercept, B_{1t} is the random coefficient for time, and ε_{it} is the error for subject i at time t.

Random coefficient models often consider a coefficient relating a predictor and an outcome as fixed, or constant between subjects. In general, a factor is designated as fixed if it is one of a specific set of treatments or levels of interest. If the levels of a factor are considered to be random sample from a larger population, the factor may be considered random [12]. The coefficients for both types of factors may be interpreted as population-averaged or subject-specific; in reality, each coefficient combines both types of effects. However, coefficients estimated by random coefficient analysis are often considered conditional, or within-subject effects. This approach is often preferred over marginal, or population-averaged methods when inference is subject-specific, or when there is significant variation in the responses that cannot be explained by the covariates [11].

Finally, random coefficient models provide several advantages in longitudinal data analysis. In addition to flexibly correcting for correlation within data, the models accommodate unequal spacing between time points. The method also utilizes all available data throughout the study period, rather than excluding individuals with missing data as in the Analysis of Variance (ANOVA) method. Finally, missing data in random coefficients models allowed to be missing at random (MAR), where the probability that an observation is missing is unrelated to the value of each covariate after controlling for another covariate. This condition is less restrictive than the requirement of missing completely at random (MCAR), where the probability of missingness is assumed to be independent of unobserved or observed data [11].

3.6 COVARIATES

In addition to demographic variables (age, race, sex, and clinic site), we considered as potential confounders variables that were associated with both subclinical vascular disease and gait speed in the literature but did not lie on the expected causal pathway. These included smoking status, body-mass index, physical activity, prevalent coronary heart disease (CHD), diabetes, and hypertension. We evaluated differences in these variables across quartiles of PWV, AAI and gait speed in the Health ABC cohort (Tables 1-3) using Chi-squared tests for categorical variables and analysis of variance for continuous variables. Variables that were associated with either PWV or AAI and with gait speed at a significance level of 0.15 were selected as covariates in the adjusted models. These included all variables except smoking status and CHD, which were not associated with gait speed. Additionally, because peripheral arterial disease and PWV are important predictors of cerebrovascular disease [13] [9], we considered as potential mediators

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prevalent cerebrovascular disease and performance on the Digit Symbol Substitution Test (DSST), a test of attention and psychomotor speed.

Presence of comorbid conditions was determined from participant reports from the baseline visit. BMI was calculated as measured weight in kilograms divided by measured height in meters squared. Physical activity was assessed by questionnaire and used to calculated the kilocalories expended walking for exercise in the previous week. Participants with at least 1,000 kcal walking for exercise were defined as active. Finally, the DSST is a paper-and-pencil task which requires participants are asked to copy as many symbols corresponding to numbers as possible in 90 s. This test predicts morbidity and mortality in older adults [14] [15] and may be a marker of cerebral small vessel disease [15]. In these analyses, DSST performance is evaluated as a potential mediator of the relationships between PWV, AAI, and gait speed over time.

4.0   ANALYSIS

We evaluated the relationships of baseline pulse wave velocity and ankle arm index with 20 meter gait speed over time in 2, 066 Health ABC participants. Gait speed was additionally measured at annual follow-up (except Year 7) through Year 8, for a total of seven measurements. All analyses were performed using STATA (College Station, TX).

Plots of baseline gait speed by the subclinical vascular disease measures indicated that gait speed (m/s) decreased linearly with increasing PWV (cm/s) (Fig 1). By contrast, we identified an inverted U-shaped relationship between AAI category and baseline gait speed. The >1.3 – 1.4 AAI category had the fastest gait speed (mean (SD) 1.45 (0.22) m/s), while the lowest AAI (>0.7) and noncompressible categories had the slowest (mean (SD) 1.23 (0.22) m/s and mean (SD) 1.24 (0.22) m/s respectively). To account for this nonlinear relationship, analyses of AAI in the whole sample categorized AAI in 0.1 increments and including noncompressible arteries. Random coefficient models of AAI categories used the >1.3 – 1.4 category as the reference because participants in this category had the highest performance at baseline.

Gait Speed by Quintile of PWV
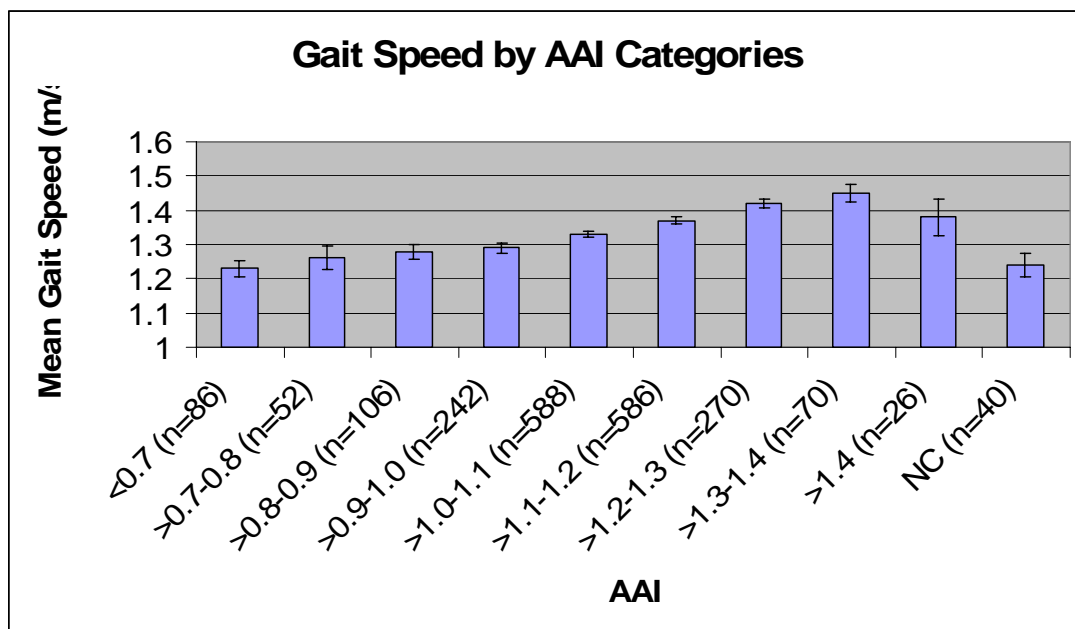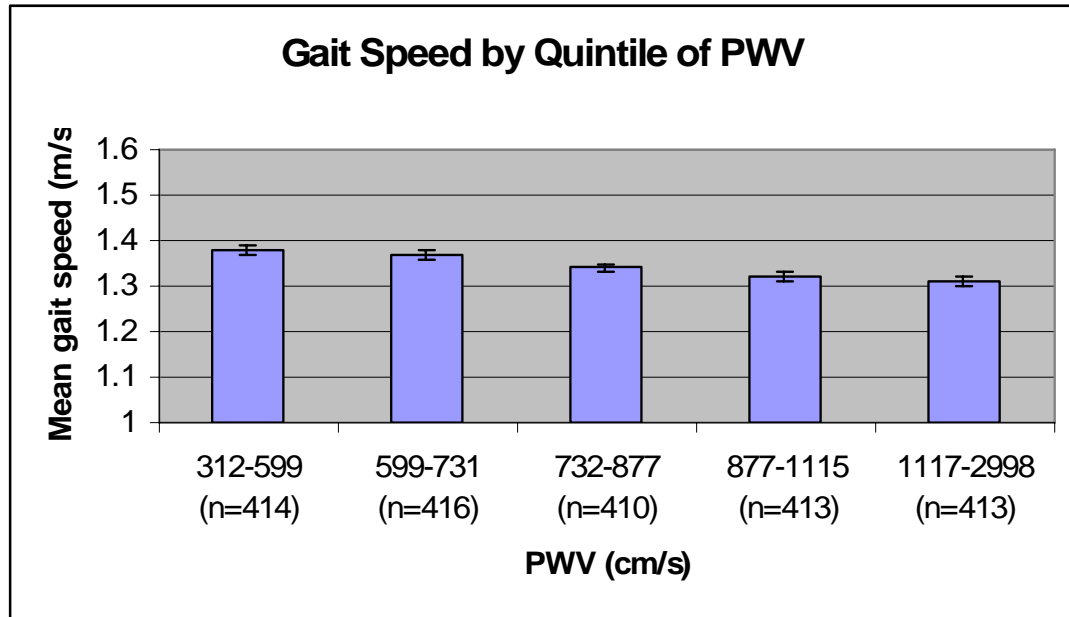

Gait Speed by AAI Categories

Figure 1. Mean gait speed (m/s) by PWV quintile and AAI category at baseline.

For additional analyses of AAI as a continuous variable, we excluded participants with AAI > 1.4 (n = 26) or noncompressible arteries (n = 40), to preserve the linear relationship between AAI and gait speed in the remaining sample (AAI < 1.4, n = 2000) (Fig 1). For these

analyses, we standardized AAI to allow comparison of the strengths of the relationships of AAI and PWV with gait speed.

To evaluate the relationships between PWV and AAI with gait speed decline, we calculated the least squares means of gait speed at each year according to quartiles of baseline PWV and AAI, adjusted for age, race, sex, and site (Fig 2). We then used random coefficient models to evaluate the relationships of PWV (SD) and AAI with gait speed over time. Continuous covariates were centered to simplify interpretation of model coefficients and to reduce multicollinearity.

Gait Speed Decline by Quartiles of PWV

Gait Speed (m/s)

Year

- PWV 312-636
- PWV 636-799
- PWV 799-1045
- PWV 1046-2988

Gait Speed Decline by Quartiles of AAI

Mean Gait Speed (m/s)

AAI

- AAI 0.32 - 1.01
- AAI > 1.01 - 1.09
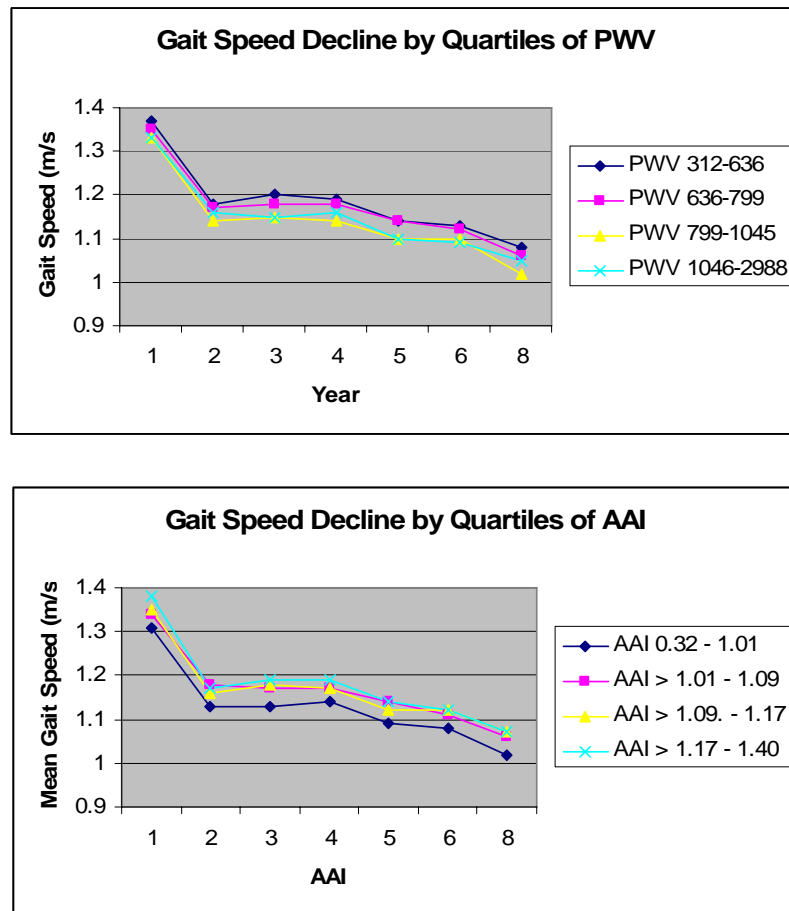- AAI > 1.09. - 1.17
- AAI > 1.17 - 1.40

Figure 2. Gait speed (m/s) decline over 8 years, by quartiles of PWV and AAI. The figure gives least squares means for gait speed adjusted for age, race, sex, and site. AAI quartiles were calculated after excluding those with either AAI > 1.40 (n=26) or noncompressible arteries (n=40).

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4.1   RANDOM COEFFICIENT MODEL

We evaluated the associations of PWV (continuous) and AAI (both continuous and categorical) with gait speed over time using separate random coefficient models for each measure. Reduced models included a random intercept for subject, a random slope with time, clinic site and PWV or AAI as fixed effects, and an interaction term for PWV or AAI with time. In a second model, we additionally adjusted for demographics (age, sex, and race) and the interaction of each covariate with time. To build a full model, we additionally adjusted for confounders that were each significantly associated ($p < 0.05$) with gait speed in an unadjusted random intercept model. Covariates that remained significant in a model adjusted for all others were retained in the model. Controlling for these covariates, we then tested the significance of interactions of each covariate with time by fitting separate models for each interaction. All significant interaction terms were included in a full model. Interaction terms that remained significant in the full model were retained in a final parsimonious model. Finally, to evaluate cognitive function as a possible mediator, we additionally adjusted each final model for prevalent cerebrovascular disease and Digit Symbol score.

Using this stepwise selection procedure we obtained identical final models for both PWV (SD) and AAI (0.1 categories) as predictors of gait speed over time. These models are provided for PWV below.

Model 1: Gait speed$_{it}$ = B$_{0i}$ + B$_{1it}$ + B$_2$PWV + B$_3$site + B$_4$PWV*time + ε_{it}

Model 2: Gait speed$_{it}$ = B_{0i} + $B_{1i}t$ + B_2PWV + B_3site + B_4PWV*time + B_5age + B_6sex +

B_7race + B_8age*time + B_9sex*time + B_{10}race*time + ε_{it}

Model 3: Gait speed$_{it}$ = B_{0i} + $B_{1i}t$ + B_2PWV + B_3site + B_4PWV*time + B_5age + B_6sex +

B_7race + B_8age*time + B_9sex*time + B_{10}race*time + B_{11}BMI + B_{12}physical activity +

B_{13}diabetes + B_{14}hypertension + B_{15}hypertension*time + ε_{it}

where Y_{it} is the observation for subject i at time t, B_{0i} is the random intercept, B_{1t} is the random

coefficient for time, and ε_{it} is the error for subject i at time t.

No correlation structure was specified for the random coefficient models. Because the

correlations between repeated responses are of similar magnitude (Figure 2), the exchangeable

structure is appropriate. However, because specifying a random slope is equivalent to

designating an exchangeable correlation structure, the unstructured option was selected to avoid

'over-correction.' [8]

4.2   RESULTS

Tables 1-4 give the baseline characteristics of the cohort by quartiles of PWV, AAI, and gait

speed. Participants in higher quartiles of PWV were older, more likely to be male, black,

exercise less, and have higher BMI, a history of smoking and comorbidities. Those with low

AAI or noncompressible arteries were older, more likely to be black and to have comorbidities.

Those in lower quartiles of gait speed were older, more likely to be female, black, have higher

BMI, exercise less, and have comorbidities.

Figure 1 gives the least squares means for gait speed at each year according to baseline quartiles of PWV and AAI, adjusted for age, race, sex and site. For these analyses, participants with high AAI (>1.4) and noncompressible arteries were excluded. Participants with PWV below the median and those with AAI in the lowest quartile performed consistently worse throughout the study period.

In the random coefficient model adjusted for site, gait speed declined on average 0.041 m/s per year (p<0.001) and each SD higher PWV was associated with a 0.019 m/s slower gait speed throughout the study period (p<0.001). The relationship of PWV with gait speed over time was modestly attenuated after additional adjustment for age, sex, race, and the interaction of each covariate with time (Beta (SE) = -0.014 (0.004), p<0.001). The associations of PWV with gait speed were further attenuated, but remained significant, after additional adjustment for BMI, physical activity, diabetes, hypertension, and the interactions of each covariate with time (Beta (SE) = -0.008 (0.004), p=0.03). Finally, the interaction of PWV and time was nonsignificant in all models, indicating that the rate of gait speed decline did not differ by baseline PWV.

To evaluate whether cerebrovascular disease may mediate the relationship between PWV and gait speed over time, we additionally adjusted the final model for Digit Symbol Substitution (DSS) score and prevalent cerebrovascular disease. Adjustment for DSS attenuated the association of PWV with gait speed (Beta (SE) = -0.007 (0.004), p=0.08). However, the relationship remained unchanged after adjustment for prevalent cerebrovascular disease.

Random coefficients models of AAI (SD) indicated a stronger relationship of AAI with gait speed over time, compared to PWV. In participants with AAI < 1.4, each SD lower AAI was associated with a 0.046 m/s slower gait speed throughout the study period (p<0.001). The relationship was substantially attenuated after adjustment for demographic variables and their

interactions with time (Beta (SE) = 0.022 (0.004), p<0.001). The coefficient for AAI was unchanged after further adjustment for risk factors and comorbidities and the interactions of covariates with time.

Similar to results at baseline (Fig 1), analyses of AAI categories in the whole sample indicated an inverse U-shaped relationship of AAI with gait speed over time. Participants with lowest AAI (≤ 0.7) and those with noncompressible arteries had the slowest gait speed over time: Beta (SE) = -0.21 (0.04), and Beta (SE) = -0.20 (0.04) respectively, compared to the reference category AAI >1.3 – 1.4 (p<0.001 for both). These relationships were attenuated after adjustment for demographics and the interaction of each covariate with time: Beta (SE) = -0.12 (0.04), Beta (SE) = -0.13 (0.04) respectively (p<0.001 for both). Further adjustment for BMI, physical activity, diabetes, and hypertension, and the interaction of covariates with time did not substantially change the coefficients for AAI.

As in the PWV analyses, the interaction of AAI (continuous and categorical) and time was nonsignificant in adjusted models, indicating that baseline AAI was not associated with the rate of gait speed decline. Further adjustment for DSS score and prevalent CBVD each modestly attenuated the coefficients for AAI.

Residual plots were used to verify the assumptions of the random coefficients models. For the final models of PWV and AAI, plots of residuals vs. time did not suggest that the residual variance varies over time. Normal probability plots of residuals did not reveal substantial departures from normality.

Finally, missing observations were common throughout the study period (Table 8). To evaluate the sensitivity of our models to missing data, we repeated the analyses in the subgroup of participants who had gait speed data at Year 8 (n = 1200). In this subgroup, the coefficient for

PWV in the final model was substantially reduced and no longer significant (Beta (SE) = -0.003 (0.005), p = 0.48). However, the coefficient for AAI (SD) did not change substantially and remained significant (Beta (SE) = -0.020 (0.005), p = 0.000). In the final model of AAI categories, the coefficients for AAI were slightly reduced compared to results in the whole sample. The categories AAI ≤ 0.7, AAI 0.7-0.8 and noncompressible arteries remained significantly worse compared to the 1.3-1.4 category: Beta (SE) = -0.09 (0.04), p = 0.03 for AAI ≤ 0.7; Beta (SE) = -0.09 (0.04), p = 0.04 for AAI 0.7-0.8; Beta (SE) = -0.13 (0.04), p = 0.05 for noncompressible arteries. As in the analyses of the whole sample, none of the interactions of either subclinical measure with time were significant in the sensitivity analyses.

5.0   DISCUSSION

In this well-functioning cohort of community-dwelling older adults, higher PWV and lower AAI were each associated with slower gait speed over time. However, we identified no relationship of either subclinical measure with gait speed decline over eight years.

This study builds on growing evidence of a vascular pathology underlying age-related mobility decline in older adults. Recent research has identified an association of low AAI, a marker of peripheral arterial disease, with gait speed decline and incident functional limitation [2]. PAD may directly contribute to physical impairment via claudicating leg pain, muscle weakness, and reduced nerve function [2].   At the same time, new evidence suggests a potential systemic influence of subclinical atherosclerosis on physical function in nondisabled older adults [7]. This relationship may be mediated by cerebral small-vessel disease, which preferentially disrupts frontal-subcortical tracts involved in the execution of complex tasks such as walking [3].

The current study supports associations of both higher PWV and lower AAI with slower gait speed over time. However, the estimated effect of elevated PWV was largely explained by underlying cardiovascular risk factors. A small independent association of PWV with gait speed was modestly attenuated by adjustment for performance on a test of psychomotor speed. These findings support our hypothesis that elevated arterial stiffness may influence physical function via reduced cognitive function; however, the potential role of arterial stiffness was modest in relation to AAI.

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Our results underscore the local influences of subclinical PAD on mobility in advancing age. Independent of risk factors and comorbidities, each SD lower AAI was associated with a 0.022 m/s slower gait speed. More strikingly, participants with AAI <0.7 and noncompressible arteries had 0.10 and 0.16 slower gait speeds over time, compared to those with AAI <1.3-1.4. An annual decline within this range is considered a disabling change in function [6]. These findings call attention to meaningfully reduced function in those with low AAI or noncompressible arteries.

While both PWV and AAI were associated with gait speed over eight years, we did not identify an association of either measure with the rate of decline. However, our analyses of AAI categories are limited by small sample sizes at the high and low ends of the AAI distribution and in the noncompressible category. It is also possible that PWV and AAI influenced the rate of decline prior to our observation. Our results may then reflect a "horse-racing effect" [16], where fast decliners perform worse at the time of observation. Similarly, we observed consistently slower gait speeds in individuals with higher PWV and lower AAI.

Although AAI and PWV were not associated with the rate of gait speed decline in our study, several covariates predicted accelerated decline over eight years. In separate multivariate models of PWV and AAI as continuous variables, older age, male sex, white race, and hypertension were each associated with a faster rate of gait speed decline. In models of AAI (SD), prevalent diabetes was also associated with faster decline. The finding that men and whites declined faster was unexpected, given the faster baseline gait speed of these participants. These accelerated declines may reflect a floor effect in participants with poorer baseline performance.

Our finding that the high normal AAI category (>1.3-14) had the fastest gait speed was also unexpected. In Health ABC, this category was associated with a higher risk of mortality compared to the >1.2-1.3 category, which carried the lowest risk [13]. This result may reflect arterial stiffness in those with high ankle pressures in the >1.3-1.4 range [13]. In the current study, the high performance observed in the >1.3-1.4 category may be explained by the large proportion of men (80%) in this category, since men were faster than women throughout the study period.

Strengths of our study include a large, community-based population, availability of important covariates, and use of a reliable, valid measure of physical function that predicts mobility limitation [4]. An additional advantage is the analysis of noncompressible arteries, which reflect vascular stiffness due to calcification of the leg arteries. Our study is limited by high proportion of missing observations throughout the study period. Sensitivity analyses which excluded participants with a missing final observation suggest that our analyses of PWV, but not AAI, are sensitive to missing data. Because participants with high PWV were more likely to withdraw from the study, our results may underestimate the associations of PWV with gait speed in the population.

6.0   CONCLUSIONS

Our results underscore the relationship of subclinical vascular disease, particularly low AAI and noncompressible arteries, with poor mobility in older adults. The association of PWV with gait speed was modest in relation to AAI, emphasizing the potential role of subclinical or undiagnosed PAD in functional decline. Strategies to prevent disability in aging should address the control of subclinical vascular disease, particularly PAD.

Table 1. Baseline characteristics of the cohort by quartiles (range in parentheses) of PWV (cm/s).

	Mean ± SD or %					
	Total (312-2998) n=2066	Q1 (312-636) n=517	Q2 (637-799) n=516	Q3 (799-1045) n=517	Q4 (1046-2998) n=516	p-value
Age, years	73.6 ± 2.8	73.3 ± 2.8	73.4 ± 2.8	73.9 ± 2.9	73.9 ± 2.8	0.000
Men	48.1	44.3	44.4	50.1	53.7	0.004
Black	37.8	32.3	36.8	39.3	42.8	0.005
BMI, kg/m^2	27.3 ± 4.7	26.1 ± 4.4	27.4 ± 4.5	28.1 ± 4.8	27.4 ± 4.8	0.000
Current or former smoker	54.7	48.0	54.3	59.4	57.0	0.002
Physical activity > 1000 kcal/wk	33.3	38.3	33.0	31.7	30.2	0.035
Coronary heart disease	17.4	15.0	16.1	20.6	18.1	0.097
Diabetes	14.0	8.0	12.1	16.7	19.3	0.000
Hypertension	48.2	35.8	45.9	51.7	59.4	0.000

Table 2. Baseline characteristics of the cohort by AAI category.

	Median (IQR) or %											
	Total sample (n=2066)	? 0.70 (n=86)	>0.70 - ?0.80 (n=52)	>0.80 - ?0.90 (n=106)	>0.90 - ?1.00 (n =242)	>1.00 - ?1.10 (n=588)	>1.10 - ?1.20 (n=586)	>1.20 - ?1.30 (n=270)	>1.30 - ?1.40 (n=70)	>1.40 (n=26)	NC (n=40)	p value
Age, years*	73 (5)	74 (5)	74 (4)	74 (5)	74 (5)	73 (5)	73 (4)	73 (4)	74 (4)	72 (3)	75 (4)	0.006
Men	48.1	43.0	46.2	48.1	38.0	39.5	50.2	61.5	80.0	57.7	67.5	0.000
Black	37.8	61.6	53.9	53.8	48.8	41.5	30.7	20.4	24.3	19.2	60.0	0.000
BMI, kg/m^2*	26.7 (5.8)	28.0 (5.6)	26.8 (6.7)	26.5 (5.7)	27.0 (7.1)	26.4 (5.7)	26.6 (5.6)	26.9 (5.4)	28.2 (6.0)	29.2 (5.9)	25.1 (6.0)	0.007
Current or former smoker	54.6	69.8	69.2	65.1	57.4	55.8	51.7	47.4	47.1	46.2	50.0	0.001
Physical activity < 1000 kcal/wk	33.3	24.4	32.7	19.8	29.8	32.5	35.8	37.8	47.1	34.6	30.0	0.005
Coronary heart disease	17.4	24.4	38.0	26.7	18.0	17.1	13.5	16.7	14.5	7.7	28.2	0.000
Diabetes	14.0	26.7	26.9	23.6	16.6	10.2	11.5	12.3	15.7	11.5	30.8	0.000
Hypertension	48.2	64.7	67.3	52.4	54.4	49.5	43.7	38.5	42.9	50.0	57.5	0.000

NC = Noncompressible arteries
*Kruskal-Wallis rank test of equal medians

Table 3. Baseline characteristics of the cohort by quartiles (range in parentheses) of gait speed (m/s).

	Mean ± SD or %					
	Total (0.38-2.47) n=2066	Q1 (0.38-1.18) n=542	Q2 (1.19-1.33) n=515	Q3 (1.34-1.50) n=509	Q4 (1.51-2.47) n=500	p-value
Age, years	73.6 ± 2.8	74.1 ± 3.0	73.8 ± 2.8	73.5 ± 2.8	73.0 ± 2.6	0.000
Men	48.1	33.8	41.0	54.4	64.6	0.000
Black	37.8	61.6	39.6	28.9	19.2	0.000
BMI, kg/m^2	27.3 ± 4.7	28.6 ± 5.7	27.4 ± 4.5	26.8 ± 4.0	26.0 ± 3.6	0.000
Current or former smoker	54.7	54.1	54.8	56.4	53.4	0.799
Physical activity > 1000 kcal/wk	33.3	19.0	25.6	38.7	51.2	0.000
Coronary heart disease	17.4	18.6	15.8	19.0	16.2	0.422
Diabetes	14.0	19.3	15.0	13.0	8.2	0.000
Hypertension	48.2	57.2	50.0	44.5	40.3	0.000

Table 4. Baseline characteristics of the cohort by quartiles (range in parentheses) of gait speed (m/s).

	Mean ± SD, Median (IQR) or %					
	Total (0.38-2.47) n=2066	Q1 (0.38-1.18) n=542	Q2 (1.19-1.33) n=515	Q3 (1.34-1.50) n=509	Q4 (1.51-2.47) n=500	p-value
PWV (cm/s)*	799 (409)	831 (411)	827 (413)	799 (422)	756 (378)	0.0009
AAI % <0.9	11.8	17.9	13.8	8.6	6.4	0.0000
Cerebrovascular disease	7.1	9.6	7.8	6.3	4.6	0.015
DSS score	36.8 ± 14.3	30.6 ± 14.4	36.4 ± 13.8	38.9 ± 13.2	41.8 ± 13.5	0.0000

*Kruskal-Wallis rank test of equal medians

Table 5. Regression coefficients and standard errors (values in parentheses) estimated by random coefficient analysis of PWV as a predictor of gait speed (m/s) over eight years.

(SD)	Model 1	Model 2	Model 3
PWV	-0.019 (0.005)[+]	-0.014 (0.004)[+]	-0.008 (0.004)*
Time	-0.041 (0.001)[+]	-0.040 (0.001)[+]	-0.038 (0.001)[+]
PWV *Time	-0.001 (0.001)	-0.001 (0.001)	-0.001 (0.001)

* $p<0.05$
[+] $p<0.01$

Model 1 adjusted for site
Model 2 additionally adjusted for age, gender, race, and interaction of each covariate with time
Model 3 additionally adjusted for BMI, physical activity, diabetes, hypertension, and interaction of each covariate with time

Table 6. Regression coefficients and standard errors (values in parentheses) estimated by random coefficient analysis of AAI as a predictors of gait speed (m/s) over eight years, after exclusion of those with AAI > 1.4 or noncompressible arteries.

(SD)	Model 1	Model 2	Model 3
AAI	0.046 (0.005)[+]	0.022 (0.004)[+]	0.022 (0.004) [+]
Time	-0.040 (0.001)[+]	-0.039 (0.001)[+]	-0.037 (0.001) [+]
AAI*Time	0.000 (0.001)	0.001 (0.001)	0.000 (0.001)

* $p < 0.05$
[+] $p < 0.01$
Model 1 adjusted for site
Model 2 additionally adjusted for age, gender, race, and interaction of each covariate with time
Model 3 additionally adjusted for BMI, physical activity, diabetes, hypertension, and interaction of each covariate with time

Table 7. Regression coefficients and standard errors (values in parentheses) estimated by random coefficient analysis of AAI as a predictor of gait speed (m/s) over eight years.

AAI Category	Model 1	Model 2	Model 3
< 0.7	-0.19 (0.03)[+]	-0.10 (0.03)[+]	-0.10 (0.03)[+]
> 0.7 – 0.8	-0.18 (0.04)[+]	-0.10 (0.03)[+]	-0.11 (0.03)[+]
> 0.8 – 0.9	-0.14 (0.03)[+]	-0.06 (0.03)*	-0.08 (0.03)[+]
> 0.9 – 1.0	-0.14 (0.03)[+]	-0.06 (0.03)*	-0.07 (0.02)[+]
> 1.0 – 1.1	-0.10 (0.03)[+]	-0.04 (0.02)	-0.05 (0.02)*
> 1.1 – 1.2	-0.07 (0.03)[+]	-0.03 (0.02)	-0.05 (0.02)*
> 1.2 – 1.3	-0.02 (0.03)	-0.02 (0.02)	-0.02 (0.02)
> 1.4	-0.04 (0.05)	-0.04 (0.04)	-0.04 (0.04)
Noncompressible	-0.20 (0.04)[+]	-0.13 (0.04)[+]	-0.16 (0.04)[+]
Time	-0.046 (0.004)[+]	-0.042 (0.004)[+]	-0.041 (0.004)[+]

Reference: >1.3 – 1.4

* $p < 0.05$
[+] $p < 0.01$
Model 1 adjusted for site
Model 2 additionally adjusted for age, gender, race, and interaction of each covariate with time
Model 3 additionally adjusted for BMI, physical activity, diabetes, hypertension, and interaction of each covariate with time

Table 8. Distribution of missing gait speed observations throughout the study period.

Number of Missing Observations	Participants (N)	%
0	1,012	48.98
1	412	19.94
2	173	8.37
3	129	6.24
4	108	5.23
5	123	5.95
6	109	5.28
Total	2,066	100.00

APPENDIX

STATA CODE

STATA (Version 10) code used for the final random coefficient models is as follows:

I. PWV (SD) as a predictor of gait speed (m/s) over eight years

Model 1

xtmixed gait pwv_stan memphis visit pwv_vis || habcid: visit, cov(unstr) mle

Model 2

xtmixed gait pwv_stan memphis visit pwv_vis age1_cent male black age_visit male_visit

black_visit || habcid: visit, cov(unstr) mle

Model 3

xtmixed gait pwv_stan memphis visit pwv_vis age1_cent male black age_visit male_visit

black_visit bmi_cent physrec pdiab phbp1yn phbp1yn_visit || habcid: visit, cov(unstr) mle

II. AAI (SD) as a predictor of gait speed (m/s) over eight years

Model 1

xtmixed gait minaai_stan visit memphis minaai_vis || habcid: visit, cov(unstr) mle, if aaicat < 10

Model 2

xtmixed gait minaai_stan visit memphis minaai_vis age_cent male black age_visit male_visit black_visit || habcid: visit, cov(unstr) mle, if aaicat < 10

Model 3

xtmixed gait minaai_stan visit memphis minaai_vis age_cent male black age_visit male_visit black_visit bmi_cent phbp1yn physrec pdiab pdiab_visit phbp1yn_visit || habcid: visit, cov(unstr) mle, if aaicat < 10

III. AAI (0.1 categories) as a predictor of gait speed (m/s) over eight years

Model 1

xi: xtmixed gait i.aaicat*visit memphis || habcid: visit, cov(unstr) mle

Model 2

xi: xtmixed gait i.aaicat*visit memphis age_cent male black age_visit male_visit black_visit || habcid: visit, cov(unstr) mle

Model 3

xi: xtmixed gait i.aaicat*visit memphis age_cent male black age_visit male_visit black_visit bmi1_cent phbp1yn physrec pdiab phbp1yn_visit || habcid: visit, cov(unstr) mle

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