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## Title: The Aortic-Femoral Arterial Stiffness Gradient: An Atherosclerosis Risk in Communities (ARIC) Study

**Running Title:** Aortic-Femoral Arterial Stiffness Gradient

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There are no conflicts of interest to declare.

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**ABSTRACT**

The aortic to femoral arterial stiffness gradient (af-SG) may be a novel measure of arterial health and cardiovascular disease (CVD) risk, but its association with CVD risk factors and CVD status, and whether or not they differ from the referent measure, carotid-femoral pulse-wave velocity (cfPWV), is not known. Accordingly, we compared the associations of the af-SG and cfPWV with, (1) age and traditional CVD risk factors, and (2) CVD status. We evaluated 4,183 older-aged (75.2±5.0 years) men and women in the community-based Atherosclerosis Risk in Communities (ARIC) Study. cfPWV and femoral-ankle PWV (faPWV) were measured using an automated cardiovascular screening device. The af-SG was calculated as faPWV divided by cfPWV. Associations of af-SG and cfPWV with age, CVD risk factors (age, body mass index, blood pressure, heart rate, glucose and blood lipid levels) and CVD status (hypertension, diabetes, coronary heart disease, heart failure, stroke) were determined using linear and logistic regression analyses. (1) The af-SG and cfPWV demonstrated comparable associations with age and CVD risk factors, except body mass index. (2) A low af-SG was associated with diabetes, coronary heart disease, heart failure and stroke, whilst a high cfPWV was only associated with hypertension. Although future studies are necessary to confirm clinical utility, the af-SG is a promising tool that may provide a unique picture of hemodynamic integration and identification of CVD risk when compared to cfPWV.

**KEY WORDS**

Pulse-Wave Velocity Ratio; Risk Factors; Cardiovascular Disease.

## INTRODUCTION

Carotid-femoral pulse-wave velocity (cfPWV), a measure of central aortic stiffness, predicts cardiovascular disease (CVD) risk in both general[1,2] and patient populations[3] independent of traditional risk factors. In contrast, upper extremity (arms) and lower-extremity (legs) peripheral measures of arterial stiffness are used infrequently because of their limited or inconsistent prognostic value[3-5]. However, the central to peripheral arterial stiffness gradient (SG) may reflect the hemodynamic integration of the cardiovascular system and confer unique and prognostic information[6]. To date, the few studies that have investigated the utility of the SG have focused on the aortic to brachial SG (ab-SG), defined as the ratio of carotid-radial PWV (crPWV) and cfPWV[6-11]. However, the aortic to femoral SG (af-SG), defined as the ratio of femoral-ankle PWV (faPWV) and cfPWV, incorporates the lower extremities in the assessment of vascular stiffness and may thus provide a more comprehensive picture of hemodynamic integration.

In a healthy cardiovascular system, the arterial vasculature progressively stiffens between the elastic ascending aorta and the muscular conduit arteries of the periphery[12,13]. This gradient, or impedance mismatch, is physiologically advantageous, permitting the transformation of the highly pulsatile stroke volume into a smooth consistent blood flow, including during diastole[14]. The gradual attenuation of the forward pressure wave prevents the transmission of pulsatile forces to the micro-circulation and moderates wave reflections back towards the myocardium[14-16]. Although no clinical threshold has been identified, reversal of the SG can increase pressure transmission, leading to end-organ damage, and augment reflected wave pressure, increasing myocardial load[6,14,17]. The available literature suggests that most of the change in the SG is attributable to the aortic-iliac pathway, and not the peripheral vasculature[11,18]. Aortic stiffness increases with age and can be accelerated by lifestyle factors[19] and disease[20]. Age or disease related changes in the upper extremities are less marked[5], and the upper extremities represent only a small portion of the vasculature. In contrast, the lower extremities make up a significant

portion of the arterial tree, are more prone to athero- and arterio-sclerotic processes than the upper extremities[5,21], and are major sites of wave reflections[22]. However, the association of the af-SG with age, traditional CVD risk factors and CVD status, and whether these associations differ to those of cfPWV, is not known.

The primary aims of the current study were to compare the associations of af-SG and cfPWV with; 1) age and traditional CVD risk factors, and, (2) CVD status. These aims were undertaken using a well characterized population of older men and women from the Atherosclerosis Risk in Communities (ARIC) Study cohort.

## **METHODOLOGY**

This observational study is reported in accordance with STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines[23]. Participants provided written informed consent, and the study was approved by the Institutional Review Boards at all field centers, coordinating center, and central labs and reading centers.

## **STUDY POPULATION**

The ARIC Study is a population-based, longitudinal study of 15,792 men and women aged 45–64 years enrolled between 1987 and 1989 from 4 US communities (Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland). Details of the baseline visit have been previously described[24]. Prior to exclusions, the current analysis includes 6,538 participants who attended visit 5 between 2011 and 2013 and had PWV measures completed (5,683 total participants at visit 5).

We excluded participants with the following conditions due to concerns of PWV data quality: BMI  $\geq 40$  kg/m<sup>2</sup>, major arrhythmias (Minnesota codes 8-1-3, 8-3-1, and 8-3-2), Minnesota code 8-1-2

with evidence of biased PWV waveforms, aortic aneurysms, abdominal aorta  $\geq 5$  cm, history of aortic or peripheral revascularization or aortic graft, aortic stenosis, and moderate or greater aortic regurgitation. Additionally, we excluded participants whose race was other than white or African American (due to small sample size), with missing PWV or vascular risk factor data, as well as those with outlying PWV values, defined as PWV values 3 standard deviations above or below the mean.

Participants were asked not to consume food or drink, and refrain from tobacco and vigorous physical activity after midnight prior to the clinic visit or for 8 hours prior to the visit. Visit 5 study examination included interviewer-administered questionnaires to obtain demographic data, medical history and lifestyle information, blood and urine collection, and assessment of vascular risk factors and cardiovascular phenotypes, including PWV.

## **EXPERIMENTAL MEASURES**

### **PULSE WAVE VELOCITY**

After participants were supine for 5–10 minutes, technicians measured cfPWV and faPWV following a standardized protocol, using the automated cardiovascular screening device VP-1000 Plus (Omron, Kyoto, Japan)[25]. The device simultaneously measured bilateral brachial blood pressures, and carotid, femoral and posterior tibial arterial pulse waves. PWV was estimated as the distance between two arterial recording sites divided by transit time (TT): distance/TT. For cfPWV assessments, arterial waveforms were simultaneously acquired for 30 seconds by applanation tonometry sensors attached on the left common carotid artery (via neck collar) and left common femoral artery. The distance from the carotid to the femoral artery was directly measured with a segmometer (Rosscraft, Surrey, Canada) and calculated as the carotid to femoral distance minus the distance between the suprasternal notch to the carotid applanation site. For faPWV assessments, bilateral posterior-tibial arterial pressure waveforms were detected

over 10 seconds by extremities cuffs connected to plethysmographic and oscillometric pressure sensors wrapped on both ankles. Distance for faPWV was automatically calculated by the VP-1000 Plus using height-based formulas, as previously described[26]. A minimum of two PWV measurements were taken per participant and the last two measurements were averaged. The average of left and right faPWV measures was included for analysis.

The validity and reliability of the automatic device for measuring PWV have previously been described[25,27]. Quality assurance for PWV included central training and recertification, quarterly equipment calibration, and ongoing quality control reviews by one of the authors (H.T.) on a stratified random sample of 40 records per month with feedback provided to technicians. Approximately 78% of records were considered optimal quality, 17% were good quality, 3% were acceptable, and none were poor or unacceptable.

**Aortic-Femoral Arterial Stiffness gradient.** The af-SG was calculated by dividing femoral-ankle PWV (faPWV) by carotid-femoral PWV (cfPWV). This method emphasizes the model arterial system, whereby in a healthy cardiovascular system arterial stiffness increases between central and distal arteries [14]. Although no clinical threshold has been identified, to give greater context, an af-SG greater than 1.0 (i.e.  $\text{faPWV} > \text{cfPWV}$ ) can be considered physiologically normal, whereas an af-SG of 1.0 or less (i.e.  $\text{cfPWV} \geq \text{faPWV}$ ) can be considered pathological[11].

## COVARIATE MEASUREMENTS

All covariate measures were collected as part of ARIC visit 5.

**Demographics.** Age was calculated from date of birth. Sex and race were self-reported. History of smoking was self-reported and analyzed as dichotomous (current versus noncurrent).

**Anthropometrics.** Body weight was measured to the nearest 0.1 kg, and height was recorded to the nearest centimeter. Body mass index (BMI) was calculated as body mass (kg) divided by height squared ( $m^2$ ).

**Blood Pressure.** Three seated blood pressure (BP) measurements were obtained after a 5-minute rest using an oscillometric automated sphygmomanometer (Omron HEM-907 XL, Omron, Kyoto, Japan), and the average of the last two measurements was used. Hypertension was defined as systolic BP (SBP)  $\geq 140$  mm Hg, diastolic BP (DBP)  $\geq 90$  mm Hg, or antihypertensive medication use. Mean arterial pressure (MAP) was calculated as:  $(SBP + (2 * DBP)) / 3$ .

**Blood Markers.** Blood samples were obtained following a standardized venipuncture protocol and shipped weekly to ARIC central laboratories where assays for total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and fasting glucose concentration were performed. Total plasma cholesterol concentrations were determined enzymatically [28] using a Cobas-Bio analyzer with reagents purchased from Boehringer Mannheim Biochemicals, (Indianapolis, IN). Plasma low-density lipoprotein (LDL) cholesterol, concentration was calculated using the Friedewald equation, [29] and HDL concentrations were measured using the method of Warnick et al. [30]. Diabetes was defined as fasting glucose  $\geq 126$  mg/dl, non-fasting glucose  $\geq 200$  mg/dl, antidiabetic medication use, or self-reported diagnosis of diabetes by a physician.

**Medications.** Participants were asked to bring to the clinical visit all prescription and nonprescription medications taken within the two preceding weeks. That information was transcribed and categorized using MediSPAN prescription codes and classified into medication categories. Participants also self-reported medication use. Medications used included  $\beta$ -blockers,

$\alpha$ -blockers, calcium channel blockers, diuretics, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers.

**Prevalent Cardiovascular Diseases.** Prevalent coronary heart disease (CHD) and stroke were defined by ARIC cohort surveillance data at Visit 5. Prevalent heart failure (HF) was defined as physician reported HF or a hospitalization discharge with an ICD code 428.x.

## STATISTICAL ANALYSIS

Statistical analyses were performed using R Statistical Software. The  $\alpha$ -level was set *a-priori* for all statistical procedures at  $\alpha = 0.05$ . Cumulative frequency and Q-Q plots were used to compare the distributions of cfPWV, faPWV, and af-SG. Participant characteristics were stratified by af-SG quartiles and were estimated as means and standard deviation (SD), or frequencies and percent. Descriptive data across quartiles were compared using one-way analysis of variance (ANOVA) for continuous outcomes and Kruskal-Wallis for categorical outcomes, with Bonferroni correction for multiple comparisons. For linear regression we report unstandardized and standardized  $\beta$  coefficient estimates and 95% confidence intervals (95% CI), and the  $R^2$  values for model fit. When possible, partial  $R^2$  values for dependent variables were determined using semi-partial correlation analysis inherent to the *ppcor* package in R[31]. For logistical regression we report odds ratios and 95% CI.

For the first part of aim 1, linear regression was used explore whether there were sex or race interactions with age for af-SG, cfPWV, and faPWV. In the event of significant sex or race interactions ( $P < 0.05$ ), stratified analysis was used. Subsequently, associations between af-SG, cfPWV, and faPWV with 5-year age groups was determined using Spearman correlations ( $r$ ). For the second part of aim 1, cfPWV, faPWV and af-SG associations with traditional CVD risk factors were evaluated using multivariable linear regression. Independent variables included age, BMI,

current smoking, DBP, SBP, heart rate, glucose, HDL cholesterol, LDL cholesterol, and triglycerides. Variables significantly associated with cfPWV and af-SG ( $P < 0.1$ ) were retained using a backward step-wise method. Linear regression models were adjusted for race, field center, sex, current smoker, medication count and prevalent CVD. For aim 2, we investigated the associations between cfPWV, faPWV and af-SG as continuous variables with CVD status, including CHD, HF, stroke, hypertension and diabetes, using multi-variable binomial logistic regression. To further interrogate associations with disease status, given that no clinical threshold for af-SG has been identified, comparisons were also made whereby cfPWV, faPWV and af-SG measures were entered as categorical variables (quartile 1 to quartile 3 vs. quartile 4 for cfPWV and faPWV, quartile 1 vs. quartile 2 to quartile 4 for af-SG). Logistic regression models were adjusted for age, race, field center, sex, MAP, current smoker and medication count. Assumption of linearity, collinearity, homoscedasticity, and outliers were assessed for every model.

## RESULTS

### CHARACTERISTICS OF THE STUDY POPULATION

Descriptive characteristics, overall and stratified by af-SG quartiles, are reported in **Table 1**. Following exclusions, the sample included 4,183 cohort participants between the ages of 66 and 90 years, of which 59.5% were women and 22.3% were African American. Of the 5,683 participants who attended visit 5 and underwent PWV measurements: 1500 were excluded using the following criteria: pre-existing condition ( $n=579$ ), race other than white or African American ( $n=15$ ), missing PWV data ( $n=529$ ), PWV values 3 SDs above or below the mean ( $n=76$ ), missing risk factor data ( $n=81$ ), and missing covariates ( $n=220$ ).

### AIM 1: ASSOCIATIONS WITH AGE AND CVD RISK FACTORS

There was no significant sex or race by age interactions for cfPWV, faPWV or af-SG (all  $P > 0.05$ ).

**Figure 1** presents cfPWV, faPWV, and af-SG values stratified by age categories. Mean cfPWV increased and mean af-SG decreased across 5-year age groups from  $<70$  to  $>85$  years, whilst

Table 1 Descriptive characteristics of ARIC visit 5 participants, overall and stratified by aortic-femoral arterial stiffness gradient (af-SG) quartiles.

	Overall n = 4183	Q1 n = 1057	Q2 n = 1038	Q3 n = 1041	Q4 n = 1047	P Value
<b>Continuous Variables (Mean, SD)</b>						
Age (years)	75.2 (5.0)	76.7 (5.2)	75.4 (5.0)	74.7 (4.8)	74 (4.7)	<0.001*
Body Mass Index (kg/m <sup>2</sup> )	27.9 (4.4)	28.2 (4.6) <sup>†</sup>	28.1 (4.54) <sup>†</sup>	27.8 (4.3)	27.3 (4.2)	<0.001
Diastolic blood pressure (mm Hg)	66 (10)	65 (10.5) <sup>†,‡</sup>	66 (10)	67 (10)	67 (10)	<0.001
Systolic blood pressure (mm Hg)	130 (17)	134 (18)	131 (17)	128 (16)	126 (17)	<0.001*
Heart rate (bpm)	65 (11)	66 (11) <sup>†</sup>	65 (11) <sup>†</sup>	65 (11) <sup>†</sup>	63 (10)	<0.001
Fasting glucose (mg/dL)	6.2 (1.5)	6.5 (1.7) <sup>†,‡,§</sup>	6.3 (1.6) <sup>†,‡</sup>	6.1 (1.3)	6.0 (1.1)	<0.001
LDL (mg/dL)	2.7 (0.9)	2.7 (0.9) <sup>†,‡</sup>	2.7 (0.9)	2.8 (0.9)	2.8 (0.9)	0.013
HDL (mg/dL)	1.4 (0.4)	1.3 (0.4) <sup>†,‡</sup>	1.4 (0.4) <sup>†</sup>	1.4 (0.4) <sup>†</sup>	1.4 (0.4)	<0.001
Triglycerides (mg/dL)	1.4 (0.6)	1.4 (0.7) <sup>†</sup>	1.4 (0.6) <sup>†</sup>	1.4 (0.6) <sup>†</sup>	1.3 (0.6)	<0.001
cfPWV (m/s)	11.6 (3.0)	15.1 (2.6)	12.1 (1.7)	10.6 (1.4)	8.7 (1.6)	<0.001*
faPWV (m/s)	10.8 (1.7)	9.7 (1.5)	10.5 (1.4)	11.2 (1.5)	11.9 (1.7)	<0.001*
af-SG	0.998 (0.3)	0.653 (0.1)	0.873 (0.1)	1.050 (0.1)	1.410 (0.3)	<0.001*
<b>Categorical Variables (No., %)</b>						
<b>Sex</b>		<sup>†,‡</sup>	<sup>‡</sup>			
Men	1692 (40)	591 (56)	449 (43)	388 (37)	399 (38)	0.002
Women	2491 (60)	456 (44)	592 (57)	650 (63)	658 (62)	
<b>Race</b>		<sup>†,‡,§</sup>	<sup>†</sup>			
African American	934 (22)	362 (35)	215 (21)	183 (18)	174 (16)	<0.001
White	3249 (78)	685 (65)	826 (79)	855 (82)	883 (84)	
<b>Prevalent Cardiovascular Disease</b>						
Hypertension	3012 (72)	867 (83) <sup>†,‡,§</sup>	745 (71.6) <sup>†</sup>	731 (70) <sup>†</sup>	687 (65)	<0.001
Coronary heart disease	586 (14)	204 (20) <sup>†,‡,§</sup>	152 (14.6) <sup>†</sup>	117 (11)	113 (11)	<0.001
Heart failure	432 (10)	175 (17) <sup>†,‡,§</sup>	86 (8)	85 (8)	86 (8)	<0.001

	Overall n = 4183	Q1 n = 1057	Q2 n = 1038	Q3 n = 1041	Q4 n = 1047	P Value
Stroke	114 (3)	50 (5) <sup>†,‡,§</sup>	25 (2)	18 (2)	21 (2)	<0.001
Diabetes	1230 (29)	437 (42) <sup>†,‡,§</sup>	318 (31) <sup>‡</sup>	261 (25)	214 (20)	<0.001
<b>Medication use</b>						
β-Blocker	1172 (28)	346 (33) <sup>†,‡</sup>	310 (30) <sup>†,‡</sup>	269 (26)	247 (23)	<0.001
α-Blocker	135 (3)	52 (5) <sup>†,‡</sup>	40 (4) <sup>†</sup>	22 (2)	21 (2)	<0.001
Diuretic	1611 (39)	488 (47) <sup>†,‡,§</sup>	387 (37)	387 (37)	349 (33)	<0.001
ACE Inhibitor	1274 (31)	369 (35) <sup>†,‡</sup>	298 (29)	301 (29)	307 (29)	0.012
ANG II receptor blocker	687 (16)	211 (20) <sup>†</sup>	174 (17) <sup>†</sup>	166 (16)	136 (13)	<0.001
Calcium channel blocker	1032 (25)	388 (37) <sup>†,‡,§</sup>	257 (25) <sup>†</sup>	215 (21) <sup>†</sup>	172 (16)	<0.001
<b>Current smoker</b>	239 (6)	64 (6)	52 (5)	55 (5)	68 (6)	0.448

**Abbreviations:** HDL, high-density lipoprotein cholesterol; LDL, Low-density lipoprotein cholesterol; cfPWV, carotid-femoral pulse-wave velocity; faPWV, femoral-ankle pulse-wave velocity. **af-SG quartiles** Q1, <0.784; Q2, 0.784 to 0.956; Q3, 0.957 to 1.160, Q4 >1.160. **Comparisons:** \*All groups significantly different; † vs. Q4; ‡ vs. Q3; § vs. Q2.

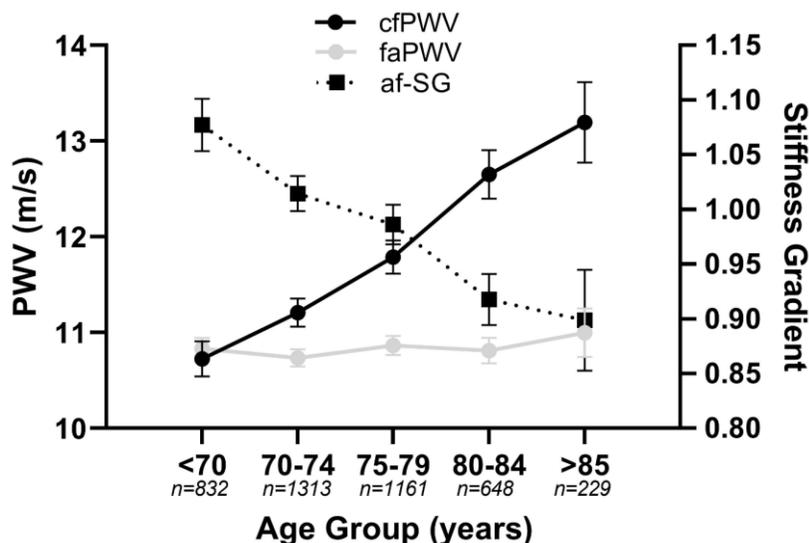


Figure 1 Mean carotid-femoral pulse-wave velocity (cfPWV), femoral-ankle pulse-wave velocity (faPWV) and aortic-femoral arterial stiffness gradient (af-SG) in 5-year age groups, with 95% confidence intervals.  $n = 4,183$ .

faPWV did not differ across age groups. Age was positively correlated (Spearman) with cfPWV ( $r = 0.22$ , 95% CI: 0.19, 0.25,  $P < 0.01$ ) and negatively correlated with af-SG ( $r = -0.18$ , 95% CI: -0.21, -0.15,  $P < 0.01$ ), but not correlated with faPWV ( $r = 0.03$ , 95% CI: 0.00, 0.06,  $P = 0.09$ ).

Backwards stepwise regression analysis was used to identify CVD risk factors that were associated with af-SG and cfPWV (**Table 2**). For cfPWV, there was a positive association with age, SBP, HR, and fasting glucose, and a negative association with BMI, DBP, and HDL. With the exception of BMI, CVD risk factor associations for af-SG were consistent, albeit in opposing directions due to the nature of the measure, with cfPWV. The highest standardized regression coefficients were observed for the same CVD risk factors (SBP, HR, age, DBP). For faPWV, there was a positive association with age, DBP and fasting glucose, and a negative association with BMI.

Table 2 Linear regression models for association of carotid-femoral pulse wave velocity (cfPWV), femoral-ankle pulse wave velocity (faPWV) and aortic-femoral arterial stiffness gradient (af-SG) with cardiovascular disease risk factors at visit 5.

	cfPWV						faPWV						af-SG					
	$\beta$	Std. $\beta$	95% CI		<i>P</i>	$\dagger R^2$	$\beta$	Std. $\beta$	95% CI		<i>P</i>	$\dagger R^2$	$\beta$	Std. $\beta$	95% CI		<i>P</i>	$\dagger R^2$
<b>Model 1</b>	$R^2 = 0.22$						$R^2 = 0.16$						$R^2 = 0.10$					
Age (years)	0.11	0.19	0.17	0.20	<0.001	0.030	0.02	0.05	0.04	0.06	<0.001	0.00	-0.01	-0.12	-0.12	-0.12	<0.001	0.012
BMI (kg/m <sup>2</sup> )	-0.04	-0.05	-0.07	-0.03	<0.001	0.002	-0.10	-0.25	-0.27	-0.24	<0.01	0.05	-0.01	-0.08	-0.08	-0.08	<0.001	0.006
DBP (mm Hg)	-0.03	-0.10	-0.11	-0.09	<0.001	0.005	0.05	0.30	0.29	0.31	<0.001	0.05	0.01	0.20	0.20	0.20	<0.001	0.022
SBP (mm Hg)	0.06	0.35	0.35	0.36	<0.001	0.074	0.00	0.02	0.02	0.03	0.22	0.00	0.00	-0.25	-0.25	-0.25	<0.001	0.037
HR (bpm)	0.06	0.22	0.21	0.23	<0.001	0.044	0.02	0.11	0.11	0.12	<0.001	0.01	0.00	-0.12	-0.12	-0.12	<0.001	0.013
FBG (mg/dL)	0.21	0.10	0.04	0.16	<0.001	0.009	0.03	0.03	-0.01	0.06	0.07	0.00	-0.01	-0.06	-0.07	-0.06	<0.001	0.003
LDL (mmol/l)	-0.04	-0.01	-0.11	0.09	0.382	0.000	-0.05	-0.03	-0.09	0.03	0.07	0.00	0.00	-0.01	-0.02	0.00	0.492	0.007
HDL (mmol/l)	-0.79	-0.10	-0.35	0.16	<0.001	0.007	0.11	0.02	-0.13	0.17	0.17	0.00	0.09	0.10	0.07	0.13	<0.001	0.000
TG (mmol/l)	0.09	0.02	-0.12	0.16	0.226	0.000	0.14	0.05	-0.03	0.14	<0.001	0.00	0.01	0.01	0.00	0.03	0.400	0.000
<b>Final Model*</b>	$R^2 = 0.24$						$R^2 = 0.18$						$R^2 = 0.13$					
Age (years)	0.11	0.18	0.16	0.20	<0.001	0.028	0.02	0.05	0.05	0.06	<0.001	0.00	-0.01	-0.11	-0.12	-0.11	<0.001	0.011
BMI (kg/m <sup>2</sup> )	-0.05	-0.08	-0.10	-0.06	<0.001	0.005	-0.08	-0.22	-0.23	-0.21	<0.001	-0.04	0.00	-0.05	-0.05	-0.04	0.004	0.002
DBP (mm Hg)	-0.03	-0.11	-0.12	-0.10	<0.001	0.007	0.05	0.33	0.32	0.33	<0.001	0.05	0.01	0.20	0.20	0.21	<0.001	0.022
SBP (mm Hg)	0.06	0.35	0.34	0.36	<0.001	0.069							0.00	-0.24	-0.24	-0.24	<0.001	0.032
HR (bpm)	0.07	0.24	0.23	0.24	<0.001	0.048	0.02	0.11	0.10	0.11	<0.001	0.01	0.00	-0.13	-0.13	-0.13	<0.001	0.016
FBG (mg/dL)	0.18	0.09	0.03	0.14	<0.001	0.005	0.06	0.05	0.02	0.08	<0.001	0.00	-0.01	-0.04	-0.05	-0.03	0.008	0.001
HDL (mmol/l)	-0.57	-0.07	-0.33	0.19	<0.001	0.001							0.06	0.06	0.03	0.09	<0.001	0.002
TG (mmol/l)							0.03	0.01	-0.07	0.09	0.52	0.00						

\***Final Model Adjustments:** race, field center, sex, current smoker, prevalent cardiovascular diseases (coronary heart disease, stroke, heart failure), and number of medications ( $\beta$ -blockers,  $\alpha$ -blockers, calcium channel blockers, diuretics). **Abbreviations:**  $\beta$ , beta coefficient; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate; FBG, fasting blood glucose; LDL, Low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, tryglycerides ; std.  $\beta$ , standardized beta coefficient; 95% CI, 95% confidence interval; †, partial  $R^2$ .

## AIM 2: ASSOCIATIONS WITH CVD STATUS

**Table 3** presents associations for cfPWV, faPWV and af-SG with CVD status following multivariable logistic regression analyses. For final model logistic regression analyses, when specified as a continuous variable, cfPWV was positively associated with CHD, stroke and diabetes, but a high cfPWV was only associated with diabetes. For af-SG as a continuous variable, there were negative associations with CHD, HF, stroke and diabetes, and a low af-SG was also associated with CHD, HF, stroke and diabetes. For faPWV as a continuous variable, there were positive associations with hypertension but negative associations with CHD and HF, but a high faPWV was not associated with any disease.

## SENSITIVITY AND ANCILLARY ANALYSIS

Data analysis conducted with the exclusion of peripheral arterial disease (PAD) patients, as identified by an ankle-brachial index (ABI) below 0.9, revealed no notable differences. Further, analysis of af-SG derived using left and right faPWV measures separately had no impact on findings when compared to those determined using a mean of left and right faPWV measures. The associations between cfPWV and faPWV (**Figure S1**) are reported using standard Pearson product moment correlation and are provided in the supplement.

## DISCUSSION

The primary aims of the current study were to compare the associations of af-SG and cfPWV with, 1) age and traditional CVD risk factors, and, (2) CVD status. Our findings suggest that the af-SG

Table 3 Logistic regression models for association of carotid-femoral pulse wave velocity (cfPWV), femoral-ankle pulse wave velocity (faPWV) and aortic-femoral stiffness gradient (afSG) with CVD status at visit 5.

<i>Continuous</i>	CHD			Heart Failure			Stroke			Hypertension			Diabetes							
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P					
<b>Model 1</b>																				
cfPWV	1.07	1.04	1.10	<0.001	1.08	1.05	1.11	<0.001	1.12	1.06	1.19	<0.001	1.15	1.12	1.18	<0.001	1.12	1.10	1.15	<0.001
faPWV	0.87	0.83	0.92	<0.001	0.81	0.77	0.87	<0.001	0.90	0.81	1.01	0.079	0.99	0.95	1.03	0.648	0.90	0.87	0.94	<0.001
af-SG	0.38	0.28	0.52	<0.001	0.31	0.22	0.46	<0.001	0.27	0.13	0.55	<0.001	0.41	0.33	0.50	<0.001	0.29	0.23	0.37	<0.001
<b>Final Model*</b>																				
cfPWV	1.04	1.01	1.07	0.014	1.03	0.99	1.06	0.139	1.08	1.02	1.15	0.014	1.03	0.99	1.06	0.206	1.12	1.09	1.15	<0.001
faPWV	0.92	0.87	0.98	0.008	0.90	0.84	0.96	0.002	0.93	0.83	1.05	0.245	1.02	0.96	1.09	0.457	0.99	0.95	1.04	0.710
af-SG	0.57	0.41	0.80	0.000	0.44	0.21	0.90	0.024	0.57	0.41	0.80	0.001	0.89	0.65	1.21	0.457	0.41	0.32	0.54	0.000
<b>Model 1</b>																				
cfPWV	1.36	1.12	1.65	0.002	1.69	1.36	2.09	0.059	1.81	1.23	2.67	0.003	1.94	1.63	2.31	<0.001	1.93	1.67	2.24	<0.001
faPWV	0.76	0.62	0.94	0.011	0.61	0.47	0.79	<0.001	0.72	0.45	1.14	0.156	1.06	0.91	1.24	0.432	0.78	0.67	0.92	0.002
af-SG	0.57	0.48	0.69	<0.001	0.44	0.36	0.55	<0.001	0.40	0.27	0.58	<0.001	0.46	0.39	0.55	<0.001	0.47	0.41	0.55	<0.001
<b>Final Model*</b>																				
cfPWV	1.15	0.93	1.43	0.200	1.26	1.00	1.59	0.053	1.42	0.94	2.13	0.098	1.03	0.79	1.34	0.829	1.85	1.57	2.18	<0.001
faPWV	0.89	0.70	1.12	0.301	0.80	0.61	1.05	0.111	0.75	0.46	1.22	0.254	1.10	0.87	1.39	0.439	1.03	0.87	1.22	0.714
af-SG	0.72	0.58	0.88	0.002	0.67	0.53	0.83	<0.001	0.51	0.34	0.76	0.001	0.97	0.74	1.27	0.815	0.58	0.49	0.68	<0.001

\***Final Model Adjustments:** age, race, field center, sex, mean arterial pressure, current smoker, and number of medications ( $\beta$ -blockers,  $\alpha$ -blockers, calcium channel blockers, diuretics). **Abbreviations:** CHD, coronary heart disease;  $\beta$ , beta coefficient; 95% CI, 95% confidence interval; OR, odds ratio. **af-SG quartile comparisons:** Q1: <0.784 vs. Q2-Q4: >0.784; **cfPWV quartile comparisons:** Q1-Q3: <13.3 m/s vs. Q4: >13.3 m/s; **faPWV quartile comparisons:** Q1-Q3: <11.8 m/s vs. Q4: >11.8 m/s.

and cfPWV demonstrate similar associations with age and traditional cardiovascular risk factors including DBP, SBP, HR, fasting glucose, and HDL, but do contrast in their associations with BMI. However, the af-SG demonstrates a unique association with CVD status; specifically, a low af-SG was associated with coronary heart disease, heart failure and stroke, but a high cfPWV was not. Accordingly, the af-SG may be a clinically useful marker of arterial stiffness and confer a unique picture of hemodynamic integration, vascular pathophysiology, and the identification of CVD risk

#### **LIMITATIONS AND STRENGTHS**

The strengths and limitations of this study need to be addressed to best contextualize the findings. Firstly, the generalizability of our findings is limited to older populations and cannot be extended to younger, healthier cohorts. Further, the predominate inclusion of participants who had survived from baseline (1987-1989) and attended the Visit 5 examination (2011-2013), and were thus likely healthier compared to those who did not participate in the visit, may have generated a bias within the study population. Secondly, the use of height-based formulas to calculate faPWV were validated in a Japanese population and may not be applicable to other racial or ethnic groups. Finally, we did not exclude patients based upon peripheral arterial disease (PAD) diagnosis which has the potential to impact measures of faPWV. However, our sensitivity analysis excluding PAD patients (ABI < 0.9) and using af-SG derived from left and right faPWV measures independently did not impact findings. A major strength is that this is the first study to explore af-SG, an index of central to peripheral arterial stiffness gradient, derived using the lower extremity, and does so using a large community-dwelling population.

#### **COMPARISON TO THE LITERATURE: AGE AND CVD RISK FACTORS**

Both af-SG and cfPWV were significantly associated with age, whilst faPWV was stable across age-groups. This finding supports the previous assertion that age-related changes in the SG are chiefly driven by cfPWV[11,18], and therefore the af-SG may confer limited prognostic value over cfPWV. However, stratification of participants into af-SG quartiles revealed that both cfPWV and faPWV contribute towards af-SG measures, with a decrease in the af-SG (Table 1) appearing to be a consequence of decreased faPWV as well as increased cfPWV. Indeed, faPWV was significantly different between af-SG quartiles, with individuals in Q1 (an af-SG of <0.784) displaying the lowest faPWV and most adverse CVD risk factor profile. Although the cross-sectional nature of the present study limits inference, collectively these findings suggest that reductions in the af-SG are likely to be pathological and are impacted by the central and peripheral vasculature. Although femorotibial arterial stiffness is thought to change little with age [32,33], faPWV has been shown to regress in the presence of CVD risk factors and disease, including diabetes[20] and in hemodialysis patients [34], respectively. A low peripheral arterial stiffness has been presented as a novel consequence of increased aortic arterial stiffness[6,34,35]. This reduction in peripheral muscular artery stiffness is thought to shift the site of pressure wave reflection distally, attenuating wave reflection and its influence on central BP and cardiac workload[15]. Although preserving cardiac function and aortic pressure, this could lead to greater transmission of the forward pressure wave to the microcirculation and cause end-organ damage[16,17,36]. Accordingly, variations in faPWV may have clinically important consequences and integration of faPWV in the af-SG may be a relevant complimentary approach to cfPWV, providing an alternative picture of hemodynamic integration and prognostic information beyond aortic stiffness.

The af-SG and cfPWV were associated with similar CVD risk factors, albeit in opposing directions due to the nature of measures, with an increase in age and a worsening of risk factors (DBP,

SBP, HR, fasting glucose, and HDL) associated with a worsening of af-SG and cfPWV. However, cfPWV and af-SG did contrast in their association with BMI. In the Framingham Heart Study of 2,114 older adults[11], the upper extremity ab-SG demonstrated equitable prognostic value when compared to cfPWV and was significantly associated with age, BMI, HDL, BP, and HR, all recognized correlates of cfPWV. These risk factors were all found to be correlated with both af-SG and cfPWV in the present study. The finding of a negative association with BMI and cfPWV is consistent with existing literature[33,37]. In cross-sectional studies, a lower aortic PWV in obese individuals has been attributed to higher cardiac output and lower peripheral vascular resistance[38,39]. However, longitudinal studies report a robust positive relationship between adiposity and central PWV progression[40,41]. This is consistent with the association between af-SG and BMI in the present study. These findings suggest that elevated adiposity may be associated with a lower central PWV at baseline, but normal age changes in central PWV are accelerated with greater adiposity. The af-SG may permit the identification of a novel association between adiposity and arterial stiffness.

#### **COMPARISON TO THE LITERATURE: CVD STATUS**

The af-SG and cfPWV demonstrated unique associations with CVD status. Consistent with previous literature, cfPWV was associated with CHD[42], stroke[10], and diabetes[20] but in contrast to previous findings, was not associated with heart failure[43] or hypertension[44]. Further, a high cfPWV was only associated with diabetes. Comparatively, the af-SG was associated with CHD, HF, stroke and diabetes, and a low af-SG was also associated with diabetes, CHD, HF and stroke. A high af-SG reduced the odds of having diabetes by 42% and similarly a high cfPWV increased the odds of having diabetes by 85% reflecting the significant impact diabetes has on systemic arterial stiffness. Although there are multiple pathways, diabetes can accelerate arterial remodeling by augmenting production of advanced glycation end products that cross-link with collagen and elastin[45]. Interestingly, diabetes has been associated with both

a higher cfPWV[7,20] and a lower faPWV[20], which would contribute to a low af-SG. A high af-SG reduced the odds of having CHD, HF and stroke by 28%, 33% and 49%, respectively, but none were significant for cfPWV when arterial stiffness measures were entered as categorical predictors. This suggests that the af-SG may demonstrate greater sensitivity with certain disease pathologies than segmental PWV alone.

In contrast to those mechanisms previously described, a reduced af-SG may actually *augment* wave reflection amplitude and increase pulse and central systolic pressure[18]. Systolic pressure elevation increases myocardial oxygen demand and induces left ventricular hypertrophy, a marker of HF, elevating CVD risk[14]. Pulse pressure elevation induces arterial remodeling, increasing arterial wall stiffness and thickness, and promoting atherosclerotic plaque development[46], characteristics of CHD. In this scenario, reversal of the SG and the concomitant increase in distance to wave reflection sites is still expected to increase the transmission of pulsatile flow to the periphery and lead to tissue and target organ damage[47], perhaps explaining the association between low af-SG and stroke. However, these contrasting theories highlight that the mechanism(s) for how a low af-SG (i.e. worsening) may contribute to both myocardial and end-organ pathology, and whether or not cfPWV is the sole determinant[11,18], is still unclear.

## IMPLICATIONS

A low central to peripheral SG may augment the transmission of excessive forward pressure into the microcirculation, a pathophysiological basis for cardiovascular events and target organ damage[4,14,15]. To date, the literature has focused on the upper-extremity derived ab-SG. The ab-SG has been reported to be a *better* prognostic indicator of CVD outcome than classical cfPWV in diseased populations[6,7,9,10] and comparable in healthy populations[11]. But it has been argued that the prognostic value, and therefore clinical utility, of the ab-SG is principally attributable to increases in cfPWV[11]. However, the upper extremities represent only a small

portion of the arterial tree and the absolute hemodynamic load is likely to be limited. In contrast, the lower extremities make up a considerable portion of the arterial tree and contribute significantly to wave reflection morphology and myocardial workload[22]. The current study extends the scant SG literature by being the first to report that the lower-extremity derived af-SG demonstrates comparable association with CVD risk factors when compared to cfPWV, but importantly, a unique association with CVD status, specifically coronary heart disease, heart failure and stroke. Collectively, these findings indicate that the af-SG may be clinically useful for the non-invasive assessment of arterial health and CVD risk. However, to confirm utility, future studies should seek to: i) identify the association of af-SG with CVD outcomes and end-organ damage, and ii) identify the mechanisms by which low af-SG contributes to disease progression.

## **CONCLUSIONS**

Future studies are necessary to confirm the clinical utility of the af-SG, including whether the af-SG can predict CVD outcomes. However, the present findings indicate that the af-SG is a promising tool that may provide a unique picture of hemodynamic integration, vascular pathophysiology, and the identification of CVD risk.

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