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# **Associations Between Carotid-Femoral and Heart Femoral Pulse Wave Velocity in Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study**

Running Title: Carotid-Femoral vs. Heart-Femoral Pulse Wave Velocity

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## **Abstract**

### **Background**

Carotid-femoral pulse wave velocity (cfPWV) is widely used in epidemiological studies to assess central arterial stiffness. However, despite being superior to traditional risk factors in predicting cardiovascular outcomes, cfPWV is not routinely used in clinical practice. cfPWV assessments require appplanation of the carotid artery, which can be cumbersome, and subject-level factors, including carotid artery plaque, may confound the measurements. Heart-femoral PWV (hfPWV) may be a suitable alternative measure of central arterial stiffness.

### **Objectives**

To estimate the strength of the agreement between hfPWV and cfPWV.

### **Methods**

We evaluated 4,133 older-aged (75.2 [5.0] years) African American and Caucasian adults in the community-based Atherosclerosis Risk in Communities (ARIC) Study. cfPWV and hfPWV were measured using an automated cardiovascular screening device. Agreement between the two measurements was determined using Pearson's correlation coefficient ( $r$ ), standard error of estimate (SEE), and Bland-Altman analysis.

### **Results**

There was strong ( $r > 0.7$ ) agreement between hfPWV and cfPWV ( $r = 0.83$ , 95%CI: 0.82, 0.84). While the mean cfPWV (11.5 m/s [SD: 3.0]) and hfPWV (11.5 m/s [SD: 2.3]) were comparable, the SEE was 1.7 m/s. Inspection of the Bland-Altman plot revealed greater variability and bias for higher PWV values, with higher PWV further away from the regression line.

### **Discussion**

Findings suggest good agreement between hfPWV and cfPWV. hfPWV is a simpler alternative to cfPWV which is less likely to be confounded by subject-level factors. Considering the greater variability for higher PWV values, further work is warranted to determine the importance of local artery mechanics to both measures.

### **Key Words**

Arterial stiffness; measurement; sex; vascular risk factors

## Introduction

Pulse wave velocity (PWV) is widely used in epidemiological studies to assess arterial stiffness and estimate cardiovascular disease (CVD) risk.[1] PWV is calculated by measuring the transit time (TT) of the arterial waveform between two points of a measured distance.[2] The mostly widely studied path is between the carotid and femoral arteries (the cfPWV), which represents the aorto-iliac pathway. International reference norms have been established for population, age, and risk factor strata [3] for cfPWV, a measure found to be strongly associated with the risk of CV events. [4]. However, cfPWV assessments typically require applanation of the carotid artery, which can be technically challenging in certain populations, including persons who are obese and those with advanced carotid artery atherosclerosis.[5] Further, cfPWV assessment is not consistent with the path of blood flow from the aortic arch to the carotid artery, which is not included in measurement of the distance between the carotid and femoral measurement points. In order to adjust for this, an assumption is made about the timing of the pressure wave travelling to the carotid artery and this is used to adjust the measure accordingly.[6] An alternative measure of central arterial stiffness is the heart-femoral PWV (hfPWV).

For cfPWV assessments, TT is recorded as the time between the foot of the carotid pressure waveform and the foot of the femoral pressure waveform. For hfPWV, TT can be calculated as the time between the ventricular ejection, determined from an electrocardiogram and/or a phonocardiogram, and the foot of the femoral pressure waveform. The hfPWV approach confers a number of potential advantages over cfPWV: (i) it is simpler to conduct, as the measurement is not dependent on applanation of the carotid artery; (ii) the measurement path is consistent with the blood flow path; and (iii) the presence of carotid plaque is unlikely to confound measurements. To date, of the few studies on hfPWV[7–14] only one directly compared hfPWV to cfPWV.[6] While the previous study reported a strong correlation ( $r = 0.81$ ) between the two measures, systemic bias was not explored, the study did not include women, and the age range of the population was narrow (40-49 years). Therefore, the primary aim of the current study was to determine the association between hfPWV and cfPWV using a well-characterized population of older men and women from the Atherosclerosis Risk in Communities (ARIC) Study cohort. The second aim was to compare the strength of associations of hfPWV and cfPWV with traditional vascular risk factors, such as age, smoking status, body mass index (BMI), blood pressure (BP), heart rate, glucose, and blood lipid levels.

## **Methodology**

This observational study is reported in accordance with STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines.[15] 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. Data availability and detailed policies for requesting Atherosclerosis Risk in Communities (ARIC) data can be found at <https://sites.csc.unc.edu/aric/pubs-policies-and-forms-pg>. ARIC data can be also obtained from the NHLBI BioLINCC repository (<https://biolincc.nhlbi.nih.gov/home/>).

## **Participants**

The ARIC Study is a population-based, longitudinal study of 15,792 participants 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.[16] Prior to exclusions, the current analysis includes 5,638 participants who attended visit 5 between 2011 and 2013 and had PWV measured.

## **Exclusions**

We excluded participants with the following conditions due to concerns over the quality of the PWV measures: 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 Caucasian 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.

## **Study Design**

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.

## **Measures**

### **Pulse Wave Velocity**

Technicians measured cfPWV and hfPWV following a standardized protocol with the automated cardiovascular screening device VP-1000 Plus (Omron, Kyoto, Japan)[17] after participants were supine for 5–10 minutes. The device simultaneously measured electrocardiogram, phonocardiogram, bilateral brachial and ankle blood pressures and carotid and femoral arterial pulse waves. A minimum of two measurements were taken per participant and the last 2 measurements were averaged. The validity and reliability of the automatic device for measuring PWV have been described previously.[18,19] 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.

**Carotid-Femoral Pulse Wave Velocity.** The cfPWV was calculated using the equation: distance / TT. 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. To calculate TT, 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.

**Heart-Femoral Pulse Wave Velocity.** The hfPWV was calculated from the equation: distance/ TT. The distance from the heart to the femoral artery was automatically calculated by the VP-1000 Plus using a height-based equation:  $0.5643 \times \text{height} - 18.381$ . [20] To calculate TT, the time interval between the S2 heart sound on phonocardiogram and the dicrotic notch of the brachial pulse wave, and time interval between the brachial and femoral artery pulse waves were recorded. The sum of these time intervals gives the time required for pulse waves to travel from the heart (aortic orifice) to the femoral artery.

### **Covariate Measurements**

**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 0.1kg, and height was recorded to the nearest centimeter. BMI was calculated using height and weight.

**BP.** Three seated 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 2 measurements was used.

**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 [21] 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,[22] and HDL concentrations were measured using the method of Warnick et al.[23]

**Medications.** Participants were asked to bring all prescription and nonprescription medications taken within 2 weeks. That information was transcribed and categorized using MediSPAN prescription codes and classified into medication categories.

**Prevalent Cardiovascular Diseases.** Hypertension was defined as systolic BP (SBP)  $\geq 140$  mm Hg, diastolic BP (DBP)  $\geq 90$  mm Hg, or antihypertensive medication use. Prevalent coronary heart disease and stroke were defined by ARIC cohort surveillance data at Visit 5. Prevalent heart failure was defined as physician reported heart failure or a hospitalization discharge with an ICD code 428.x.

### **Statistical Analyses**

Statistical analyses were performed using R Statistical Software. The  $\alpha$ -level was set a priori for all statistical procedures at  $\alpha = 0.05$ . Participant characteristics were estimated as means and SDs, or frequencies and percent, where appropriate. Cumulative frequency and Q-Q plots were used to compare the distributions of cfPWV and hfPWV.

Initially, linear regression models included sex and race interaction terms to determine their importance to the agreement between hfPWV and cfPWV. If sex or race interaction term(s) were

significant, subsequent models were stratified by sex and/or race. Next, linearity was explored by specifying the hfPWV quadratic term. Subsequently, the association between the two measurements was determined by calculating the Pearson product-moment correlation ( $r$ ) and standard error of estimate (SEE). Although there is no universal criterion, in general,  $r$  value estimates of  $<0.2$ ,  $0.2-0.4$ ,  $0.4-0.70$ ,  $0.70-0.9$  and  $>0.9$  indicate negligible, weak, moderate, strong, and very strong agreement, respectively.[24] The SEE represents the average distance that the observed values fall from the regression line, with smaller values indicating that the observations are closer to the fitted line. The SEE was calculated using the equation:  $SD \times \sqrt{(1-r^2)}$ ,[25,26] whereby SD is the standard deviation of the criterion measure and  $r$  is the Pearson product-moment correlation between test and criterion devices. The relative standard error (RSE) was also calculated by expressing SEE relative to the mean of cfPWV. Bland–Altman plots were generated to permit visual analysis of the uniformity of error over the range of participant measurement values.[27]

Associations between risk factors with cfPWV and hfPWV were evaluated using multivariable linear regression. Independent variables included sex, age, BMI, current smoking, DBP, SBP, heart rate, glucose, HDL cholesterol, LDL cholesterol, and triglycerides. Models were adjusted for study center, prevalent diabetes, prevalent cardiovascular disease (hypertension, coronary heart disease, heart failure, stroke), and medication count ( $\beta$ -blockers,  $\alpha$ -blockers, calcium channel blockers, diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers). We retained variables significantly associated with cfPWV or hfPWV ( $P < 0.1$ ). We report  $\beta$  coefficient estimates, their precision, and the  $R^2$  values for the models.

## Results

### Participants

Descriptive characteristics are reported in **Table 1**. Following exclusions, the sample included 4,133 participants between the ages of 66 and 90 years, of which 60% were women and 22% were African American. Of the original 5,683 participants, 1550 were excluded because they had one or more of the exclusion conditions ( $n = 576$ ): PWV values were 3 SDs above or below the mean ( $n = 59$ ), missing PWV data ( $n = 572$ ), race other than Caucasian or African American ( $n=13$ ), missing risk factor data ( $n = 128$ ), and missing covariates ( $n=202$ ). Men had higher cfPWV ( $0.3$  m/s,  $P = 0.002$ ) and hfPWV ( $0.3$  m/s,  $P = <0.001$ ) values compared to women, though distributions were similar for each sex (**Suppl. Figure 1**).

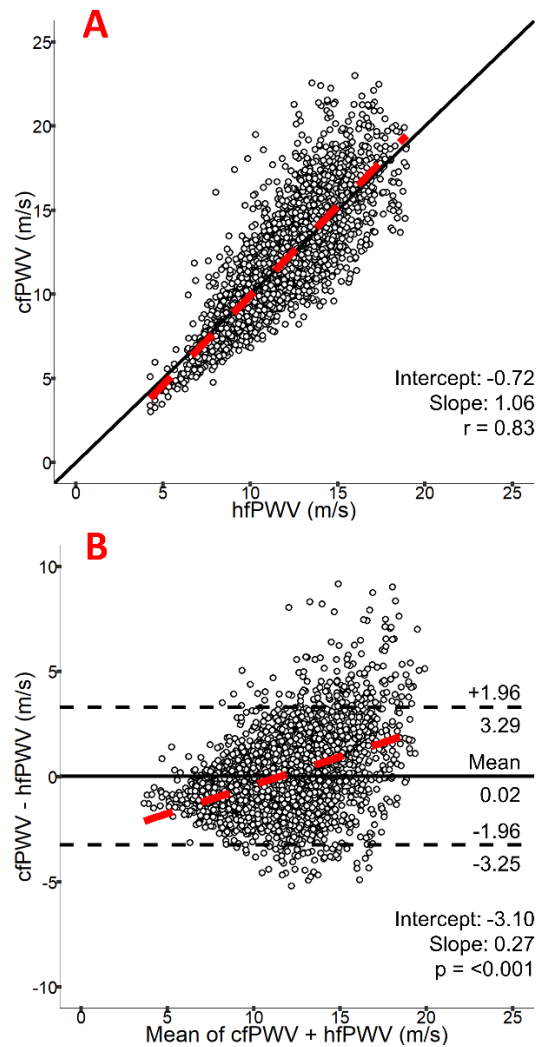


**Table S1.** Linear and non-linear regression estimates for pulse-wave velocity (hfPWV) versus carotid-femoral pulse wave velocity (cfPWV), stratified by sex

	Total n = 4,133			Women n = 2,489			Men n = 1,644		
	$\beta$	LCI	UCI	$\beta$	LCI	UCI	$\beta$	LCI	UCI
<b>Linear</b>									
$R^2$	0.69			0.72			0.67		
hfPWV	1.06	1.04	1.09	1.14	1.11	1.17	1.02	0.99	1.06
Intercept	-0.72	-0.97	-0.46	-1.29	-1.61	-0.97	-0.59	-1.01	-0.16
<b>Non-Linear</b>									
$R^2$	0.69			0.72			0.67		
hfPWV	1.40	1.24	1.55	1.41	1.22	1.60	1.19	0.93	1.45
hfPWV*hfPWV	-0.01	-0.02	-0.01	0.00	0.00	0.01	-0.01	-0.02	0.00
Intercept	-2.62	-3.53	-1.71	-2.82	-3.92	-1.72	-1.58	-3.16	0.01

**Abbreviations:**  $\beta$ , beta coefficient; LCI, lower 95% confidence interval; UCI, upper 95% confidence interval

**Figures 1A and 1B.**



### Agreement between cfPWV and hfPWV

In a model regressing hfPWV against cfPWV, the race interaction term was non-significant ( $P = 0.600$ ) but the sex interaction term was significant ( $P < 0.001$ ). Subsequently, linearity was explored by specifying the hfPWV quadratic term for each sex (**Suppl. Table 1**). For combined sexes, the quadratic term was significant ( $P = < 0.001$ ), but the change in  $R^2$  was marginal ( $\Delta R^2 = 0.001$ ). Similarly, for women the quadratic term was significant ( $P = < 0.005$ ), but the change in  $R^2$  was marginal ( $\Delta R^2 = < 0.001$ ). For men, the change in  $R^2$  was non-significant ( $\Delta R^2 = < 0.001$ ,  $P = 0.206$ ). Thus, we used linear models for subsequent analysis.

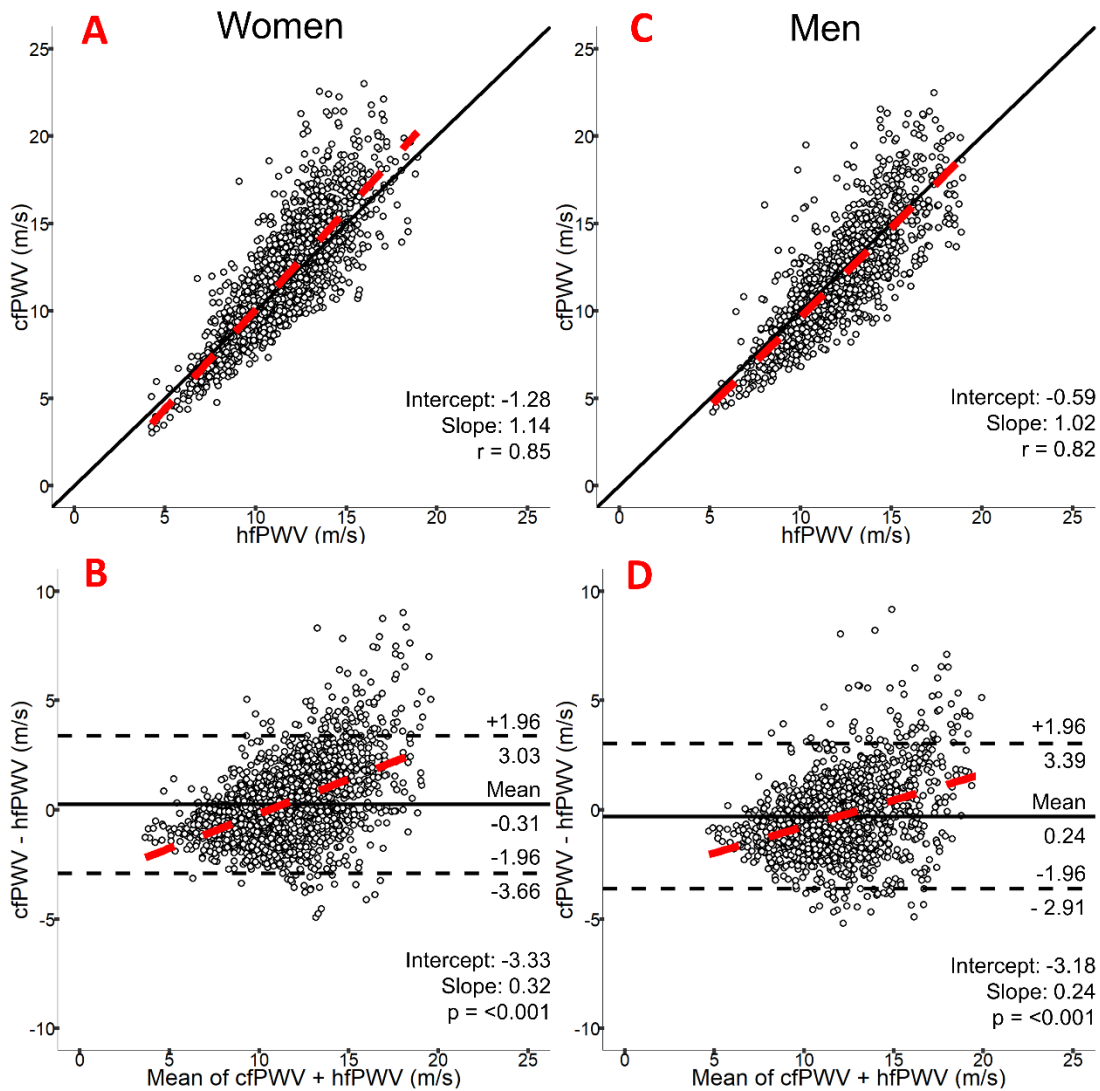
Correlations between cfPWV and hfPWV are reported in **Table 2**. There was strong ( $r > 0.7$ ) agreement between hfPWV and cfPWV for the combined sexes ( $r = 0.83$ , 95%CI: 0.82 to 0.84, **Figure 1A**), in women ( $r = 0.85$ , 95%CI: 0.84 to 0.86 **Figure 2A**), and in men ( $r = 0.82$ , 95%CI: 0.81 to 0.84, **Figure 2C**). For the combined sexes, inspection of the regression (**Figure 1A**) and Bland-Altman (**Figure 1B** and **Suppl. Table 2**) plots indicate greater variability and bias for higher PWV values. Similarly, inspection of the regression and Bland-Altman plots for women (**Figures 1A-B** and **Suppl. Table 2**) and men (**Figures 1C-D**) indicate greater variability and bias for higher PWV values. This greater variability for higher PWV values explains why the SEE ranged from 1.6 to 1.7 m/s (**Table 2**) even though the mean bias from Bland-Altman analysis was 0.02 m/s (95%CI: 0.03 to 0.07) for the combined sexes, -0.31 m/s (95%CI: -0.39 – 0.23) for men, and 0.24 m/s (95%CI: 0.18 to 0.30) for women.

**Table S2.** Bland-Altman estimates for heart-femoral pulse velocity (hfPWV) versus carotid-femoral pulse wave velocity (cfPWV), stratified by sex. Women=2,489, Men=1,644

	Bias			Lower LoA			Upper LoA			Mean
	$\beta$	LCI	UCI	$\beta$	LCI	UCI	$\beta$	LCI	UCI	Diff.
Total	0.02	-0.03	0.07	-3.25	-3.34	-3.16	3.29	3.21	3.38	-1.09
Women	-0.31	-0.39	-0.23	-3.66	-3.80	-3.51	3.03	2.89	3.17	-3.83
Men	0.24	0.18	0.30	-2.91	-3.02	-2.80	3.39	3.28	3.50	0.72

**Abbreviations:**  $\beta$ , beta coefficient; LCI, lower 95% confidence interval; UCI, upper 95% confidence interval

Figures 2A, 2B, 2C and 2D.



### Correlations between cfPWV and hfPWV with traditional vascular risk

Stepwise regression analysis was used to identify which covariates associated with cfPWV and hfPWV (see **Suppl. Table 3** for full, unadjusted models). For the combined sexes and for women, cfPWV was positively associated with age, SBP, heart rate, and fasting glucose, and negatively associated with BMI, DBP and HDL-cholesterol. For men, cfPWV did not significantly associate with fasting glucose or HDL-cholesterol levels. Across sexes, the highest standardized regression coefficients were between cfPWV and SBP, heart rate and then age. Except for DBP, covariate

associations were consistent between cfPWV and hfPWV, and the highest standardized regression coefficients were observed for the same covariates (SBP, heart rate and age).

Table S3. Multivariable

**TABLE S3.** Multivariable linear regression associations with pulse-wave velocity (hfPWV) and carotid-femoral pulse wave velocity (cfPWV)

	Total n = 4,133				Women n= 2,489				Men n= 1,644			
	$\beta$	Std. $\beta$	SE	P	$\beta$	Std. $\beta$	SE	P	$\beta$	Std. $\beta$	SE	P
cfPWV		$R^2 =$	0.21			$R^2 =$	0.22			$R^2 =$	0.19	
Age (years)	0.10	0.17	0.01	<.001	0.11	0.18	0.01	<.001	0.09	0.15	0.01	<.001
Smoker Status (1=yes)	-0.06	0.00	0.18	0.755	0.09	0.01	0.23	0.692	-0.27	-0.02	0.29	0.347
Body Mass Index (kg/m <sup>2</sup> )	-0.04	-0.06	0.01	<.001	-0.03	-0.04	0.01	0.028	-0.05	-0.06	0.02	0.008
Diastolic blood pressure (mm Hg)	-0.03	-0.09	0.01	<.001	-0.03	-0.10	0.01	<.001	-0.03	-0.12	0.01	<.001
Systolic blood pressure (mm Hg)	0.06	0.34	0.00	<.001	0.06	0.36	0.00	<.001	0.06	0.35	0.01	<.001
Heart rate (bpm)	0.06	0.22	0.00	<.001	0.06	0.22	0.01	<.001	0.07	0.25	0.01	<.001
Fasting glucose (mmol/l)	0.20	0.10	0.03	<.001	0.21	0.10	0.04	<.001	0.15	0.08	0.04	<.001
LDL (mmol/l)	-0.07	-0.02	0.05	0.140	-0.01	0.00	0.06	0.906	-0.15	-0.04	0.08	0.073
HDL (mmol/l)	-0.76	-0.09	0.13	<.001	-0.61	-0.07	0.17	<.001	-0.18	-0.02	0.26	0.485
Triglycerides (mmol/l)	0.07	0.02	0.07	0.303	0.05	0.01	0.10	0.598	0.25	0.05	0.11	0.027
hfPWV		$R^2 =$	0.19			$R^2 =$	0.22			$R^2 =$	0.17	
Age (years)	0.08	0.18	0.01	<.001	0.08	0.18	0.01	<.001	0.08	0.16	0.01	<.001
Smoker Status (1=yes)	-0.07	-0.01	0.14	0.616	-0.01	0.00	0.17	0.971	-0.14	-0.01	0.24	0.545
Body Mass Index (kg/m <sup>2</sup> )	-0.06	-0.12	0.01	<.001	-0.05	-0.11	0.01	<.001	-0.05	-0.09	0.01	<.001
Diastolic blood pressure (mm Hg)	0.00	0.02	0.00	0.268	-0.01	-0.02	0.01	0.297	0.00	-0.02	0.01	0.549
Systolic blood pressure (mm Hg)	0.04	0.29	0.00	<.001	0.04	0.35	0.00	<.001	0.04	0.30	0.00	<.001
Heart rate (bpm)	0.03	0.15	0.00	<.001	0.04	0.18	0.00	<.001	0.04	0.19	0.01	<.001
Fasting glucose (mmol/l)	0.15	0.09	0.02	<.001	0.15	0.09	0.03	<.001	0.08	0.05	0.04	0.034
LDL (mmol/l)	-0.02	-0.01	0.04	0.565	0.04	0.02	0.05	0.379	-0.04	-0.02	0.07	0.512
HDL (mmol/l)	-0.83	-0.13	0.10	<.001	-0.41	-0.07	0.13	0.001	0.06	0.01	0.21	0.794
Triglycerides (mmol/l)	-0.09	-0.03	0.06	0.107	-0.05	-0.01	0.07	0.462	0.12	0.03	0.09	0.178

**Abbreviations:**  $\beta$ , beta coefficient; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SE, standard error; std.  $\beta$ , standardized beta coefficient

## Discussion

This study investigated the agreement between hfPWV and cfPWV and compared which traditional vascular risk factors correlated with hfPWV and cfPWV. Our findings show strong ( $r > 0.7$ ) agreement between hfPWV and cfPWV. Additionally, both hfPWV and cfPWV positively correlated with age, SBP, heart rate, and fasting glucose and negatively correlated with BMI and HDL-cholesterol. The findings suggest that hfPWV may be a suitable alternative to cfPWV. However, in interpreting the findings, the following should be considered: (i) while the strength of the association between hfPWV and cfPWV was equitable across sexes, the sex interaction term was significant; and (ii) for both sexes, there was greater variability for higher PWV values – suggesting that hfPWV and cfPWV are less comparable at higher PWV values.

## **Limitations and Strengths**

The strengths and limitations of this study need to be addressed to best contextualize the findings. First, our population consisted of older adults, limiting the generalizability of our findings to younger populations. Additionally, since the African American members of the ARIC cohort predominantly reside in Jackson, MS, the observed associations may not generalize to African Americans as a demographic group. Second, the study population may be biased through predominate inclusion of participants who have survived from baseline (1987-1989) to the time of the Visit 5 examination (2011-2013) and are healthier as compared to those who did not participate in the visit. Last, as with any observational study, we cannot rule out the possibility of residual confounding - though we did include several important confounders in our models. A major strength is that this is the largest study to directly and simultaneous compare hfPWV and cfPWV assessments.

## **Comparison to Literature**

A study by Choo *et al.*, [6] which included 784 Korean men and is the only other study to directly compare hfPWV to cfPWV, reported a comparable association ( $r = 0.81$ ) to that reported in the current study ( $r = 0.83$ ). The current study extends these previous findings through the recruitment of participants with a greater age range (66 to 90 years), and participants with a greater range of hfPWV (4.3 to 18.9 m/s) and cfPWV (3.0 to 23.0 m/s) values. Further, the previous study [6] did not include women, nor was systemic bias explored. For the current study, sex did interact with the agreement between hfPWV and cfPWV. By way of explanation, vascular structural and functional properties differ between the sexes, [28,29] as does the relationship between HR and cfPWV. [30] These differences could affect the relationship between central PWV measures. However, it should be considered that the differences in the hfPWV vs. cfPWV slopes between women and men were small (1.14 vs 1.02 m/s, respectively, Figure 2A-B). Additionally, the faster slope for the women was likely driven by greater error variance at higher PWV values, as evident from the greater Bland-Altman slope for the women compared to men (-3.3 vs. -3.18 m/s).

The bias at higher PWV values may have been driven by several sources, including measurement of distance between the two pulse waveform sites, and the likelihood of carotid plaque in participants with high PWV values. The distance for calculating hfPWV was estimated using a height-based formula, which could have introduced error. Further error may have been introduced by the measurement of the distance between carotid and femoral sites, which was measured over the body and may not reflect the actual length of the aorta. However, neither of these sources of

error likely explain the greater variability for higher PWV values. It is conceivable that carotid plaque was more prevalent in participants with a higher PWV value. The presence of atherosclerotic plaques, commonly found in carotid arteries, influences local mechanics and vessel elasticity.[31] The effect of plaque on local mechanics may explain why the lowest quartile of cfPWV - and not the highest quartile as may be expected - has been reported to most strongly associate with stroke,[11] and why local carotid arterial stiffness is associated with stroke independent of cfPWV.[32]

Both hfPWV and cfPWV positively correlated with age, SBP, heart rate, and fasting glucose and negatively correlated with BMI and HDL-cholesterol. However, glucose and HDL-cholesterol were significantly associated with both PWV measures for women, but not men. In particular, there was a stronger association between HDL-cholesterol and both PWV measures for women, which may indicate that HDL-cholesterol has a greater protective effect in women. [33] The finding of a negative association between BMI and both PWV measures across sexes is consistent with cross-sectional studies examining associations between BMI with hfPWV [6] or cfPWV.[6,34] Obesity is associated with higher cardiac output and lower peripheral vascular resistance [35,36] that could contribute to a lower PWV. It is important to note that longitudinal studies consistently report a positive relationship between adiposity and central PWV progression.[37–40] Collectively, these findings suggest that elevated adiposity may be associated with a lower central PWV at baseline, but that the change over time is accelerated in participants with greater adiposity.

Besides the study by Choo *et al.*, [6] seven other studies have reported on hfPWV and cardiovascular-related outcomes,[7–13] of which three also included cfPWV.[10–12] Collectively, these studies report that hfPWV is positively associated with age,[7] N-terminal pro b-type natriuretic peptide (NT-proBNP),[12] blood pressure,[7] diabetes,[7] albumin-creatinine ratio (ACR)[10] and aldosterone,[9] and negatively associated with either estimated glomerular filtration rate (eGFR).[8,10,12] The comparative studies report that both cfPWV and hfPWV are positively associated with proBNP[12] and ACR,[10] and negatively associated with eGFR,[10] but that the highest quartile of cfPWV was most strongly associated with CVD, especially heart failure.[11] It should be acknowledged that the later study[11] and the current study utilized ARIC participants, and we do report greater variability between hfPWV and cfPWV at higher PWV values. As reasoned above, these findings may suggest that higher cfPWV values indicate the presence of carotid artery plaque and/or altered carotid mechanics, which is robustly associated

with heart failure.[42,43] Further work is required to determine the importance of local artery mechanics to both cfPWV and hfPWV.

### **Implications**

To date, despite being superior to traditional risk factors in predicting CVD outcomes,[4] cfPWV is not routinely used in clinical practice. One likely reason for low clinical uptake is the requirement of carotid artery applanation, which can be cumbersome to both technicians and participants. hfPWV is a simpler alternative which is also less likely to be confounded by subject-level factors, including the presence of plaque. The current study extends the scant hfPWV literature by reporting good agreement between hfPWV and cfPWV, and a similar relationship between the two measures with traditional vascular risk factors. In addition to hfPWV, emerging PWV measures should be considered. One study recently compared cfPWV to heart-thigh PWV,[14] using an oscillometric cuff placed around the thigh, and previous studies have compared cfPWV to brachial-thigh PWV, [44,45] using oscillometric cuffs placed around both sites. For both of these techniques there was moderate to strong ( $R = 0.59 - 0.75$ ) agreement with cfPWV. Further work is required to compare these PWV measures in terms of predicting and tracking CVD, and to identifying strategies for implementing into clinical practice.

### **Conclusions**

Findings suggest that hfPWV may be a suitable alternative to cfPWV due to high agreement. Considering there was greater variability for higher PWV values, and the presence of plaque is more likely for high PWV values, further work is warranted to determine the importance of local artery mechanics to both cfPWV and hfPWV.

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**Conflicts of interest**

The authors declare that they have no conflict of interest. KM received research funding and personal fee from Fukuda Denshi outside of the work.



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## Figures and Tables

**TABLE 1.** Descriptive characteristics of ARIC visit 5 participants, stratified by sex.

	<b>Total n = 4133</b>	<b>Women n = 2489</b>	<b>Men n = 1644</b>
<b>Continuous Variables</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>
Age (years)	75.2 (5.0)	75.0 (5.0)	75.4 (5.0)
Body Mass Index (kg/m <sup>2</sup> )	27.9 (4.5)	27.7 (4.8)	28.1 (3.9)
Diastolic blood pressure (mm Hg)	66.1 (10.3)	65.9 (10.2)	66.5 (10.5)
Systolic blood pressure (mm Hg)	130.0 (17.3)	131.2 (17.8)	128.3 (16.3)
Heart rate (bpm)	64.5 (10.5)	65.9 (10.4)	62.3 (10.2)
Fasting glucose (mmol/l)	6.2 (1.5)	6.1 (1.4)	6.4 (1.6)
LDL (mmol/l)	2.7 (0.9)	2.9 (0.9)	2.5 (0.9)
HDL (mmol/l)	1.4 (0.4)	1.5 (0.4)	1.2 (0.3)
Triglycerides (mmol/l)	1.4 (0.6)	1.4 (0.6)	1.4 (0.7)
<b>Categorical Variables</b>	<b>No. (%)</b>	<b>No. (%)</b>	<b>No. (%)</b>
<b>Race</b>			
African American	917 (22.2)	619 (24.9)	298 (18.1)
White	3216 (77.8)	1870 (75.1)	1346 (81.9)
<b>Current smoker</b>	229 (5.5)	137 (5.5)	92 (5.6)
<b>Prevalent Cardiovascular Disease</b>			
# Prevalent CVD (Median, Q1, Q3)	(1) (1, 1)	(1) (1, 1)	(1) (1, 2)
Hypertension	2991 (72.4)	1823 (73.2)	1168 (71.1)
Coronary heart disease	567 (13.7)	198 (8.0)	369 (22.5)
Heart failure	425 (10.3)	226 (9.1)	199 (12.1)
Stroke	118 (2.9)	65 (2.6)	53 (3.2)
<b>Medication use</b>			
# Medications (Median, Q1, Q3)	(1) (0, 2)	(1) (0, 2)	(1) (0, 2)
β-Blocker	1154 (27.9)	675 (27.1)	479 (29.1)
α-Blocker	136 (3.3)	79 (3.2)	57 (3.5)
Diuretic	1588 (38.4)	1043 (41.9)	545 (33.2)
ACE Inhibitor	1246 (30.2)	645 (25.9)	601 (36.6)
ANG II receptor blocker	675 (16.3)	452 (18.2)	223 (13.6)
Calcium channel blocker	1006 (24.3)	626 (25.2)	380 (23.1)

**Abbreviations:** Q1, 25<sup>th</sup> quartile; Q3, 75<sup>th</sup> quartile

**TABLE 2.** Comparison of heart-femoral pulse-wave velocity (hfPWV) and carotid-femoral pulse wave velocity (cfPWV), stratified by sex.

	n =	cfPWV		hfPWV		r		SEE (m/s)		RSE (%)	
		Mean (SD)		Mean (SD)		(95% CI)		(95% CI)		(95% CI)	
Total	4133	11.5 (3.0)		11.5 (2.3)		0.83 (0.82 - 0.84)		1.7 (1.6 - 1.7)		14.4 (14.0 - 14.8)	
Women	2489	11.4 (3.0)		11.2 (2.2)		0.85 (0.84 - 0.86)		1.6 (1.5 - 1.6)		13.8 (13.3 - 14.1)	
Men	1644	11.7 (3.0)		12.0 (2.4)		0.82 (0.81 - 0.84)		1.7 (1.6 - 1.7)		14.5 (13.8 - 14.9)	

**Abbreviations:** CI, confidence interval; SEE, standard error of estimate; r, Pearson's correlation coefficient; RSE, relative standard error

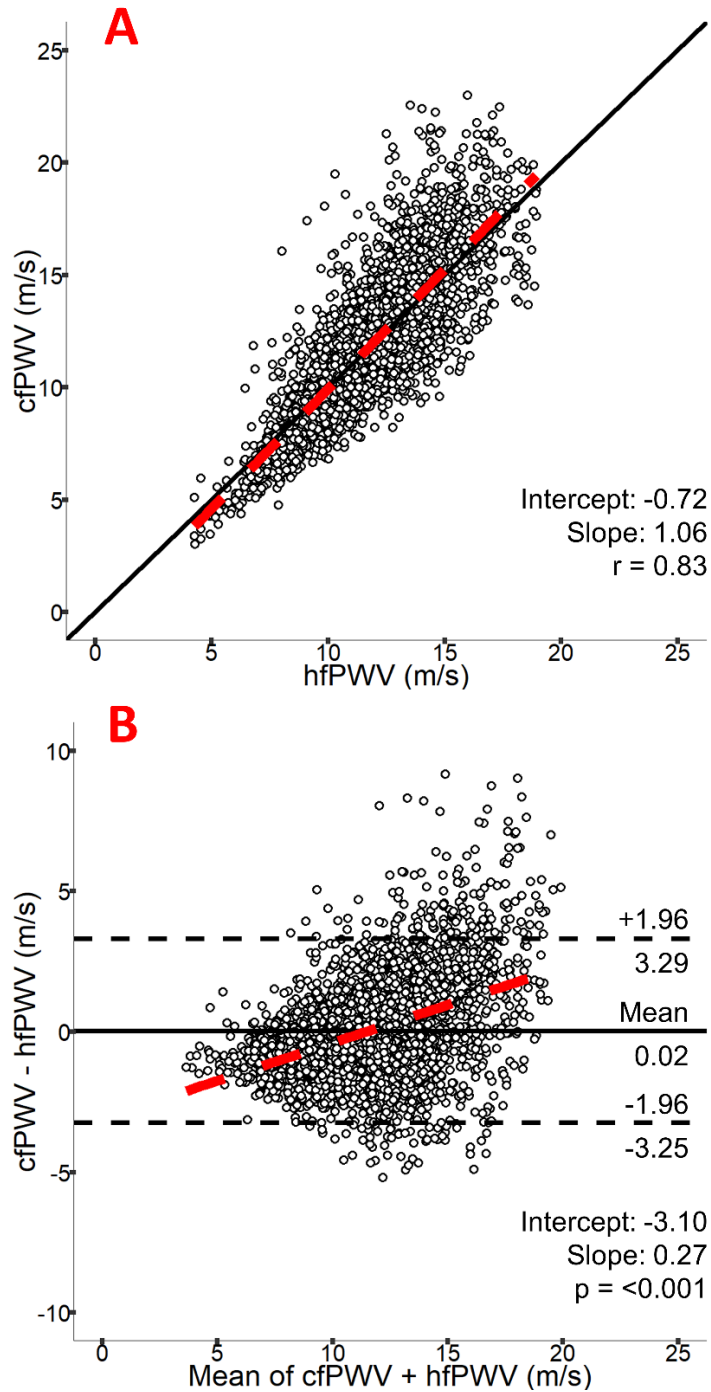
**TABLE 3.** Multivariable linear regression associations with pulse-wave velocity (hfPWV) and carotid-femoral pulse wave velocity (cfPWV)

	Total				Women				Men			
	n = 4,133				n = 2,489				n = 1,644			
	$\beta$	Std. $\beta$	SE	P	$\beta$	Std. $\beta$	SE	P	$\beta$	Std. $\beta$	SE	P
<b>cfPWV</b>		$R^2 =$	0.22		$R^2 =$	0.25			$R^2 =$	0.20		
Age (years)	0.11	0.18	0.01	<0.001	0.10	0.17	0.01	<0.001	0.10	0.17	0.01	<0.001
Body Mass Index (kg/m <sup>2</sup> )	-0.06	-0.09	0.01	<0.001	-0.06	-0.10	0.01	<0.001	-0.06	-0.07	0.02	0.002
Diastolic blood pressure (mm Hg)	-0.02	-0.08	0.01	<0.001	-0.03	-0.09	0.01	<0.001	-0.03	-0.10	0.01	0.001
Systolic blood pressure (mm Hg)	0.05	0.32	0.00	<0.001	0.06	0.33	0.00	<0.001	0.06	0.33	0.01	<0.001
Heart rate (bpm)	0.06	0.22	0.00	<0.001	0.07	0.23	0.01	0.040	0.07	0.24	0.01	<0.001
Fasting glucose (mmol/l)	0.11	0.05	0.03	0.002	0.10	0.04	0.05	<0.001	0.09	0.05	0.05	0.080
HDL (mmol/l)	-0.81	-0.10	0.12	<0.001	-0.60	-0.07	0.15	<0.001	-0.40	-0.04	0.24	0.098
<b>hfPWV</b>		$R^2 =$	0.20		$R^2 =$	0.24			$R^2 =$	0.18		
Age (years)	0.08	0.18	0.01	<0.001	0.08	0.18	0.01	<0.001	0.08	0.17	0.01	<0.001
Body Mass Index (kg/m <sup>2</sup> )	-0.08	-0.15	0.01	<0.001	-0.08	-0.17	0.01	<0.001	-0.06	-0.10	0.02	<0.001
Systolic blood pressure (mm Hg)	0.04	0.29	0.00	<0.001	0.04	0.32	0.00	<0.001	0.04	0.29	0.00	<0.001
Heart rate (bpm)	0.03	0.14	0.00	<0.001	0.04	0.18	0.00	<0.001	0.04	0.18	0.01	<0.001
Fasting glucose (mmol/l)	0.11	0.07	0.03	<0.001	0.10	0.06	0.04	0.006	0.07	0.04	0.04	0.109
HDL (mmol/l)	-0.84	-0.13	0.10	<0.001	-0.39	-0.06	0.12	<0.001	-0.11	-0.01	0.20	0.563

**Adjustments:** race, field center, prevalent cardiovascular diseases (hypertension, coronary heart disease, stroke, heart failure), and medications ( $\beta$ -blockers,  $\alpha$ -blockers, calcium channel, blockers, diuretics).

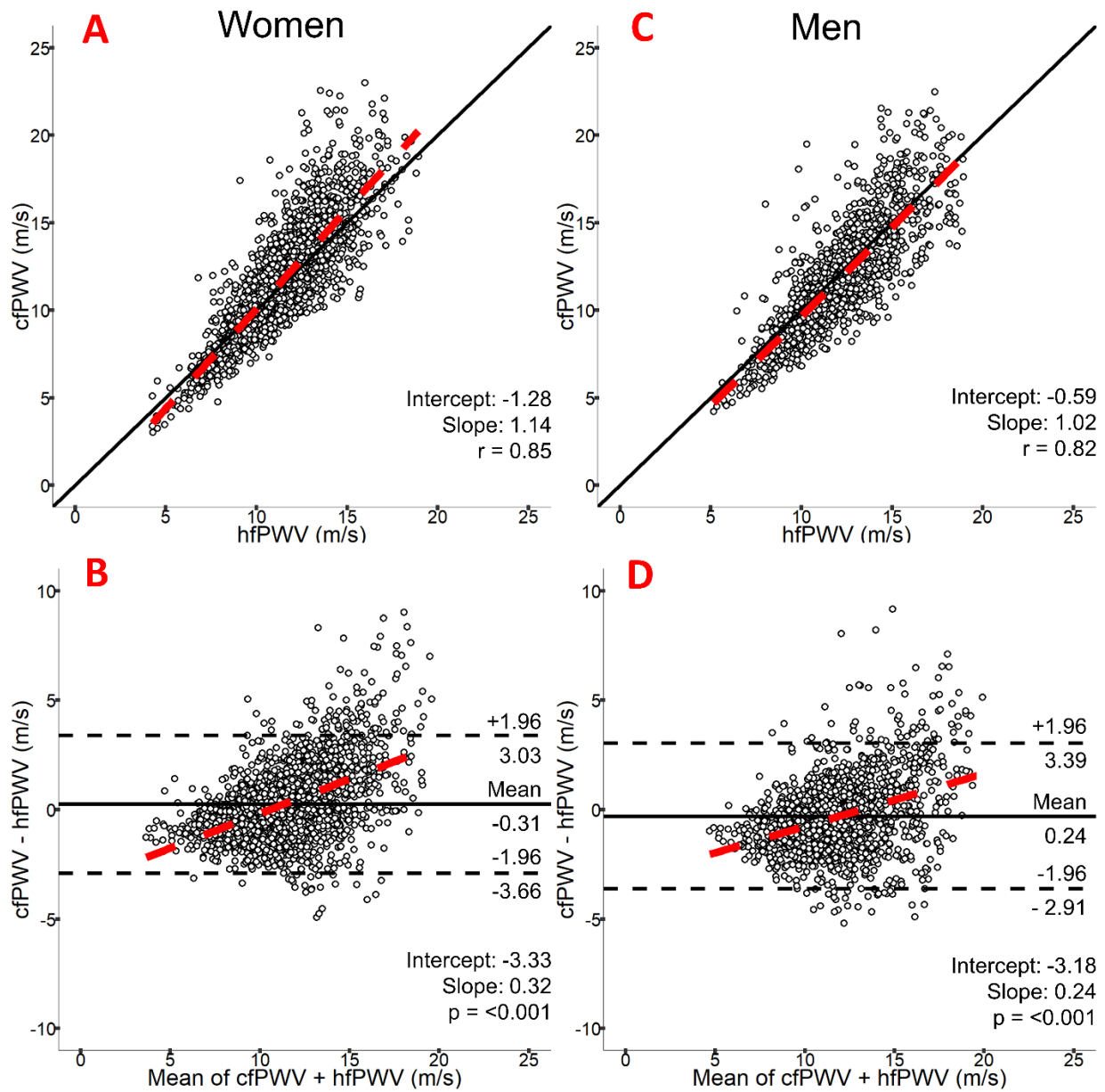
**Abbreviations:**  $\beta$ , beta coefficient; HDL, high-density lipoprotein cholesterol; SE, standard error; std.  $\beta$ , standardized beta coefficient

**FIGURE 1.** (A) regression and (B) Bland-Altman plots for heart-femoral pulse velocity (hfPWV) versus carotid-femoral pulse wave velocity (cfPWV). n = 4,133





**FIGURE 2.** (A+C) regression and (B+D) Bland-Altman plots for heart-femoral pulse velocity (hfPWV) versus carotid-femoral pulse wave velocity (cfPWV), stratified by sex. Women n = 2,489, men n =1,644.



**Supplement**

**TABLE S1.** Linear and non-linear regression estimates for pulse-wave velocity (hfPWV) versus carotid-femoral pulse wave velocity (cfPWV) and pulse-wave velocity (hfPWV), stratified by sex

**Abbreviations:** Q1, 25<sup>th</sup> quartile; Q3, 75<sup>th</sup> quartile

	Total n = 4,133			Women n= 2,489			Men n= 1,644		
	$\beta$	LCI	UCI	$\beta$	LCI	UCI	$\beta$	LCI	UCI
<b>Linear</b>									
$R^2$	0.69			0.72			0.67		
hfPWV	1.06	1.04	1.09	1.14	1.11	1.17	1.02	0.99	1.06
Intercept	-0.72	-0.97	-0.46	-1.29	-1.61	-0.97	-0.59	-1.01	-0.16
<b>Non-Linear</b>									
$R^2$	0.69			0.72			0.67		
hfPWV	1.40	1.24	1.55	1.41	1.22	1.60	1.19	0.93	1.45
hfPWV*hfPWV	-0.01	-0.02	-0.01	0.00	0.00	0.01	-0.01	-0.02	0.00
Intercept	-2.62	-3.53	-1.71	-2.82	-3.92	-1.72	-1.58	-3.16	0.01

**Abbreviations:**  $\beta$ , beta coefficient; LCI, lower 95% confidence interval; UCI, upper 95% confidence interval

**TABLE S2.** Bland-Altman estimates for heart-femoral pulse velocity (hfPWV) versus carotid-femoral pulse wave velocity (cfPWV), stratified by sex. **Women**=2,489, **men**=1,644.

**Abbreviations:**  $\beta$ , beta coefficient; LCI, lower 95% confidence interval; UCI, upper 95% confidence interval

0

	Bias			Lower LoA			Upper LoA			Mean Diff.
	$\beta$	LCI	UCI	$\beta$	LCI	UCI	$\beta$	LCI	UCI	
Total	0.02	-0.03	0.07	-3.25	-3.34	-3.16	3.29	3.21	3.38	-1.09
Women	-0.31	-0.39	-0.23	-3.66	-3.80	-3.51	3.03	2.89	3.17	-3.83
Men	0.24	0.18	0.30	-2.91	-3.02	-2.80	3.39	3.28	3.50	0.72

**Abbreviations:**  $\beta$ , beta coefficient; LCI, lower 95% confidence interval; UCI, upper 95% confidence interval

**TABLE S3.** Multivariable linear regression associations with pulse-wave velocity (hfPWV) and carotid-femoral pulse wave velocity (cfPWV)

**Abbreviations:**  $\beta$ , beta coefficient; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SE, standard error; std.  $\beta$ , standardized beta coefficient

	Total n = 4,133				Women n= 2,489				Men n= 1,644			
	$\beta$	Std. $\beta$	SE	P	$\beta$	Std. $\beta$	SE	P	$\beta$	Std. $\beta$	SE	P
<b>cfPWV</b>		$R^2 =$	0.21			$R^2 =$	0.22			$R^2 =$	0.19	
Age (years)	0.10	0.17	0.01	<.001	0.11	0.18	0.01	<.001	0.09	0.15	0.01	<.001
Smoker Status (1=yes)	-0.06	0.00	0.18	0.755	0.09	0.01	0.23	0.692	-0.27	-0.02	0.29	0.347
Body Mass Index (kg/m <sup>2</sup> )	-0.04	-0.06	0.01	<.001	-0.03	-0.04	0.01	0.028	-0.05	-0.06	0.02	0.008
Diastolic blood pressure (mm Hg)	-0.03	-0.09	0.01	<.001	-0.03	-0.10	0.01	<.001	-0.03	-0.12	0.01	<.001
Systolic blood pressure (mm Hg)	0.06	0.34	0.00	<.001	0.06	0.36	0.00	<.001	0.06	0.35	0.01	<.001
Heart rate (bpm)	0.06	0.22	0.00	<.001	0.06	0.22	0.01	<.001	0.07	0.25	0.01	<.001
Fasting glucose (mmol/l)	0.20	0.10	0.03	<.001	0.21	0.10	0.04	<.001	0.15	0.08	0.04	<.001
LDL (mmol/l)	-0.07	-0.02	0.05	0.140	-0.01	0.00	0.06	0.906	-0.15	-0.04	0.08	0.073
HDL (mmol/l)	-0.76	-0.09	0.13	<.001	-0.61	-0.07	0.17	<.001	-0.18	-0.02	0.26	0.485
Triglycerides (mmol/l)	0.07	0.02	0.07	0.303	0.05	0.01	0.10	0.598	0.25	0.05	0.11	0.027
<b>hfPWV</b>		$R^2 =$	0.19			$R^2 =$	0.22			$R^2 =$	0.17	
Age (years)	0.08	0.18	0.01	<.001	0.08	0.18	0.01	<.001	0.08	0.16	0.01	<.001
Smoker Status (1=yes)	-0.07	-0.01	0.14	0.616	-0.01	0.00	0.17	0.971	-0.14	-0.01	0.24	0.545
Body Mass Index (kg/m <sup>2</sup> )	-0.06	-0.12	0.01	<.001	-0.05	-0.11	0.01	<.001	-0.05	-0.09	0.01	<.001
Diastolic blood pressure (mm Hg)	0.00	0.02	0.00	0.268	-0.01	-0.02	0.01	0.297	0.00	-0.02	0.01	0.549
Systolic blood pressure (mm Hg)	0.04	0.29	0.00	<.001	0.04	0.35	0.00	<.001	0.04	0.30	0.00	<.001
Heart rate (bpm)	0.03	0.15	0.00	<.001	0.04	0.18	0.00	<.001	0.04	0.19	0.01	<.001
Fasting glucose (mmol/l)	0.15	0.09	0.02	<.001	0.15	0.09	0.03	<.001	0.08	0.05	0.04	0.034
LDL (mmol/l)	-0.02	-0.01	0.04	0.565	0.04	0.02	0.05	0.379	-0.04	-0.02	0.07	0.512
HDL (mmol/l)	-0.83	-0.13	0.10	<.001	-0.41	-0.07	0.13	0.001	0.06	0.01	0.21	0.794
Triglycerides (mmol/l)	-0.09	-0.03	0.06	0.107	-0.05	-0.01	0.07	0.462	0.12	0.03	0.09	0.178

**Abbreviations:**  $\beta$ , beta coefficient; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SE, standard error; std.  $\beta$ , standardized beta coefficient

**FIGURE S1.** Distribution of carotid-femoral pulse wave velocity (cfPWV) for women (A) and men, and distribution of heart-femoral pulse wave velocity (hfPWV) for women (C) and men (D).

