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Estimated pulse wave velocity and incident heart failure and its subtypes: Findings from the multi-ethnic study of atherosclerosis

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Abstract

Age-associated increase in aortic stiffness, measured as carotid-femoral pulse wave velocity (PWV), is an important effector of cardiac damage and heart failure (HF). Pulse wave velocity estimated from age and blood pressure (ePWV) is emerging as a useful proxy of vascular aging and subsequent cardiovascular disease risk. We examined the association of ePWV with incident HF and its subtypes in a large community sample of 6814 middle-aged and older adults from the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods: Participants with an ejection fraction ≤40 % were classified as HF with reduced ejection fraction (HFrEF) while those with an ejection fraction ≥50 % were classified as HF with preserved ejection fraction (HFpEF). Cox proportional hazards regression models were used to calculate hazard ratios (HR) and 95 % confidence intervals (CI).

Results: Over a mean follow-up period of 12.5 years, incident HF was diagnosed in 339 participants: 165 were classified as HFrEF and 138 as HFpEF. In fully adjusted models, the highest quartile of ePWV was significantly associated with an increased risk of overall HF (HR 4.79, 95 % CI 2.43–9.45) compared with the lowest quartile (reference). When exploring HF subtypes, the highest quartile of ePWV was associated with HFrEF (HR 8.37, 95 % CI 4.24–16.52) and HFpEF (HR 3.94, 95 % CI 1.39–11.17).

Conclusions: Higher ePWV values were associated with higher rates of incident HF and its subtypes in a large, diverse cohort of men and women.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

Keywords

Vascular stiffness; MESA; Heart failure; Epidemiology; Pulse wave velocity

1. Introduction

Over 6 million adults in the U.S. are currently living with heart failure (HF), and prevalence is projected to rise by 46 % through the next decade [1-3]. As such, increasing the accuracy of cardiovascular disease (CVD) risk prediction remains imperative. Accurately detecting risk allows for better primordial prevention and management of disease progression. Complicating risk stratification for HF is the heterogeneous nature of its phenotype. HF can broadly be categorized into two sub-types: HF with reduced ejection fraction (i.e., systolic failure) or HF with preserved ejection fraction (i.e., diastolic failure), with less being known about the pathophysiology of HFpEF [4].

Measurement of aortic stiffness is a useful tool to assist with CVD risk prediction and subsequent risk stratification [5]. The aorta is an inherently elastic large artery, serving an important role not only as a conduit but as a hemodynamic buffer. Loss of elasticity with aging and subsequent increases in stiffness (i.e., vascular aging) serve to increase cardiac afterload and expose target organs to deleterious pulsatile blood pressure and flow [6,7]. As such, aortic stiffness is inextricably linked to HF pathophysiology [8]. However, the association between vascular aging and HF is not well established especially in relation to HF subtypes [9].

The referent standard method for the measurement of aortic stiffness is carotid-femoral pulse wave velocity (cfPWV) [5]. cfPWV offers insight into HF progression, severity, and response to therapy [10-12]. Moreover, cfPWV has been shown to predict incident HF [13-16]. Emerging evidence indicates that cfPWV can be reasonably estimated from two commonly measured clinical variables: age and blood pressure [17] with correlations between the two PWV measures ranging from 0.52 to 0.67 [18-20]. As such, estimated pulse wave velocity (ePWV) may be a useful proxy of vascular aging and offer insight into HF risk in settings where cfPWV is not measured. Indeed, ePWV is predictive of cardiovascular and cerebrovascular events and mortality, even after controlling for the constituent factors of age and blood pressure [21-24]. To date, many of the studies that have explored ePWV as a predictor of CVD outcomes have done so in White European cohorts and have not adequately taken biological sex, race, and ethnicity into account [22,23,25]. This is notable as HF disproportionally affects older women as well as Black and Hispanic adults in the U.S [26-28]. As the U.S. population continues to age and become more racially and ethnically diverse, further validation of ePWV as a predictor of CVD events in diverse cohorts is needed for its construct validity as an equitable proxy of vascular aging to be properly evaluated. To this end, we determined the association between ePWV as a measure of vascular aging and incident HF in a sample of middle-aged and older men and women from the Multi-Ethnic Study of Atherosclerosis (MESA).

2. Methods

MESA is designed to prospectively explore the correlates, predictors, and progression of subclinical CVD in a diverse (38 % White, 28 % Black, 22 % Hispanic, and 12 % Asian American primarily of Chinese descent) population-based cohort of middle-aged men and women [29]. Participants between the ages of 45–84 years (n = 6814), with no history of clinical CVD at baseline, were recruited from six field centers across the USA (Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore City and Baltimore County, MD; St. Paul, MN; Chicago, IL; and Los Angeles County, CA) between July 2000 and August 2002. There have been six subsequent examinations completed since 2000. Details on the MESA protocol have been described elsewhere [30,31], and additional information can be found at https://www.mesa-nhlbi.org/. All participants provided written informed consent prior to their inclusion in the study. All study protocols were approved by the institutional review boards of each participating research field center. The study was conducted in accordance with the 1964 Declaration of Helsinki. The use of MESA data for this analysis, which consisted of deidentified data files, was approved by the Institutional Review Board of the University of North Florida.

2.1. Heart failure

Heart failure, classified as either definite or probable, was an adjudicated event in MESA determined by a panel of physicians following review of patient medical records. Probable HF was defined as HF diagnosed by a physician and the patient receiving medical treatment for HF. Definite HF determination required additional evidence from the medical record of pulmonary edema or congestion, dilated ventricle, poor left ventricular function, or left ventricular diastolic dysfunction. Data on EF, determined via echocardiography at the time of diagnosis, were also recorded by MESA from the review of medical records. In the present study, those with an EF ≤40 % at the time of diagnosis were classified as HFrEF, and those with an EF ≥50 % were classified as HFpEF. Those with an intermediate phenotype (EF > 40 % but <50 %) were included in the HF overall analyses but were excluded from the subtype analyses.

2.2. ePWV

Participants reported for a morning clinic examination after an 8–12 h overnight fast. Blood pressure was measured in the right arm with participants in the seated position using a Dinamap Pro 100® automated sphygmomanometer (Critikon, Tampa, FL). The average of the 2nd and 3rd blood pressure readings were used for subsequent analyses. ePWV was determined from the following algorithm used in the Systolic Blood Pressure Intervention Trial (SPRINT) [32]:

$$9.587 - (0.402 \times \text{age}) + \left(4.560 \times 0.001^{\star}\left(\text{age}^2\right)\right) - \left(2.621 \times 0.00001^{\star}\left(\text{age}^2\right) \times \text{MAP}\right) + (3.176 \times 0.001 \times \text{age} \times \text{MAP}) - (1.832 \times 0.01 \times \text{MAP})$$

In this algorithm, age was expressed in years and mean arterial pressure (MAP) was calculated as: [(DBP) + (0.4*(SBP-DBP))] where DBP is diastolic blood pressure and SBP is systolic blood pressure. Different equations are available to estimate PWV based on CVD

risk status [18]. As participants in MESA are generally a higher CVD risk group by design, we chose an equation derived from a reference cohort with moderate-high CVD risk. ePWV estimated with this specific equation has been shown to predict survival in the SPRINT, which includes hypertensive adults [32], and in the NHANES, which is based on the general population of U.S. adults [21].

2.3. Covariates

Age, sex, race, ethnicity, smoking status, and medical history were self-reported during the baseline MESA examination. The smoking status classified participants as never smokers, former smokers, or current smokers (smoking cigarettes in the last 30 days). Anthropometric measures included height, body weight, and waist circumference (WC). WC was categorized into 'normal' and 'increased' based on sex. Body mass index (BMI) was calculated as body weight (kg)/height (m^2) and categorized into 'normal' (<25), 'overweight' [25-30], 'obese' [30-40], and 'extreme obese' (>40). Blood pressure was categorized into three groups: normal (SBP < 120 mmHg and DBP < 80 mmHg and no BP medication use), elevated (SBP 120–129 mmHg and DBP < 80 mmHg and no BP medication use), and hypertensive (SBP ≥ 130 mmHg or DBP ≥ 80 mmHg or use of BP medication). Blood samples from the fasting venipuncture were analyzed at the University of Vermont and the University of Minnesota for glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides, standardized according to the Centers for Disease Control and Prevention. Low-density lipoprotein (LDL) cholesterol was calculated according to the Friedewald equation. The presence of diabetes mellitus was based on self-reported physician diagnosis, use of insulin or oral hypoglycemic medication, or a fasting glucose value ≥ 126 mg/dL. Physical activity (PA) was measured according to a formula defined by MESA. The formula used the sum of seven questions from the typical week PA survey (TWPAS), including those regarding walking for exercise, participation in sports or dance activities, and moderate to heavy effort conditioning reported in MET-minutes per day. PA was categorized into two groups: meeting the recommendations of 150 min-week of moderate-vigorous physical activity and not meeting the recommendations.

2.4. Statistical analyses

Data were managed and analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC). Variables are presented as means and standard deviation (SD) if continuous and as percentages if categorical. The levels of ePWV were categorized according to quartiles as <8.1 m/s, 8.1–9.6 m/s, >9.6–11.2 m/s, and >11.2 m/s. Cox proportional hazards regression models were used to calculate multivariable-adjusted hazard ratios (HRs) and 95 % confidence intervals (CI) to determine the risk of HF overall, HFrEF, and HFpEF according to ePWV quartiles. Heart failure participants without EF data or an intermediate phenotype (EF >40 % but <50 %, n = 36) were excluded from the subtype analyses. Those with an intermediate phenotype were included in the HF overall analyses. Three different models were created controlling for known HF risk factors, including age, biological sex, race and ethnicity, BMI, WC, PA, diabetes status, anti-hypertensive medication use, smoking status, and total cholesterol. Model 1 was unadjusted, model 2 was age-adjusted, and model 3 fully adjusted. For model 3, using proportional hazards regression and a stepwise backward elimination process, covariates that did not contribute significantly based on p-value = 0.05 were removed and

excluded from the final analysis. A final parsimonious model was included to elucidate the relationship between the independent variable (ePWV) and dependent variables (HF and HF subtypes). The level of significance was set at $p = 0.05$ for all tests. Kaplan–Meier survival curves were plotted by quartiles of ePWV and compared statistically using the log-rank test.

3. Results

Over a mean follow-up period of 12.5 years, incident HF was diagnosed in 339 participants: 165 were classified as HFrEF, 138 as HFpEF, and 36 as having an intermediate phenotype (EF >40 but <50). Sample characteristics by ePWV quartile are shown in Table 1. Compared to the reference quartile, those in the highest ePWV quartile (Q4) tended to be older with a greater number of men and Black adults as well as adults with hypertension, and diabetes. Cumulative hazard curves demonstrated a higher incidence of HF in the top quartile of ePWV compared to the bottom quartile ($P < 0.0001$ for the log-rank test; Fig. 1).

The results of the crude (unadjusted) and age-adjusted models using the proportional hazard regression procedure are shown in Table 2. Crude analyses revealed that those in the highest quartile of ePWV had a significantly higher risk of HF, HFrEF, and HFpEF compared to those with the referent group. Results were similar in age-adjusted models, such that those within the highest ePWV quartile had a significantly higher risk of HF, HFrEF, and HFpEF compared to those with the referent group. Furthermore, positive dose-response relationships were seen for overall HF and both sub-types across all three models. Table 3 shows the multivariable-adjusted HRs and 95 % CI in the parsimonious models for HF, HFrEF, and HFpEF, respectively. Those with the highest ePWV quartile had a significantly higher risk of HF in fully adjusted models compared to the referent group. Finally, when exploring HF subtypes, compared to the referent group, the highest quartile of ePWV was associated with both HFrEF and HFpEF.

4. Discussion

In this population-based study that includes a sample of racially and ethnically diverse adults, elevated ePWV values were associated with higher rates of incident HF and HF subtypes (both HFrEF and HfpEF). These findings support a role for arterial stiffness in HF pathogenesis and add to the evidence demonstrating that ePWV might be a useful and convenient marker of vascular aging when exploring CVD risk in large cohort studies.

Our findings support previous work of ePWV predicting incident HF in adults with hypertension in the SPRINT trial [32] as well as in a group of middle-aged White-European men [22]. Our findings importantly advance this area of research by including women and other racial and ethnic minorities in the U.S as well as exploring HF subtypes. HF disproportionally affects more women than men and this has been attributed to a number of sex-specific factors such as iron status, pregnancy, preeclampsia as well as pathophysiological factors linked to large artery stiffness and pulsatile central hemodynamics [33]. Sex differences in large artery stiffness and central hemodynamic burden contributes to greater afterload, detrimental LV remodeling and LV diastolic dysfunction in women compared to men [34-36]. HF also disproportionally affects Black

and Hispanic adults in the U.S [26-28]. Arterial stiffness is emerging as an important construct and risk factor that may contribute to racial and ethnic variation in CVD risk. Vascular aging is accelerated in Hispanic and non-Hispanic Black individuals compared to non-Hispanic White individuals [37]. Reasons for this are unknown, but likely reflect the complex interactions of social and economic hardship and cumulative inequality affecting access to resources that promote healthy vascular aging. More research will be needed to explore the impact of structural racism on arterial stiffness and subclinical CVD. Overall, our findings support construct validity of ePWV as a measure of vascular aging and risk factor for HF in a diverse group of men and women.

In the present study, the highest quartile of ePWV was associated with higher rates of incident HF and HF subtypes, even after adjustment for known HF risk factors. Previous work from Tsao et al. as part of the Framingham Heart Study reported similar stronger association of cfPWV with HFrEF risk as compared to HFpEF risk [16]. Moreover, we noted weaker, albeit still significant, associations between ePWV with HFpEF and this too supports previous work from Tsao et al. [16]. ePWV has been shown to be associated with CVD events and mortality in numerous studies, with the greater majority of these studies demonstrating value added above age and blood pressure [21-24]. Addition of ePWV to traditional CVD risk factors (including age and blood pressure) was able to improve area under the receiver operator characteristic curve and the net reclassification index for identification of LV hypertrophy [38], a known precursor and risk factor for HF. We are not proposing ePWV as a replacement for the referent standard cfPWV. In research environments where measurement of cfPWV is not feasible or when performing secondary analyses on large data sets where cfPWV is not measured but blood pressure is, ePWV may offer insight into vascular aging and CVD risk. ePWV findings may be viewed as hypothesis generating and can later be substantiated in prospective studies utilizing other valid measures of vascular aging.

Findings from MESA spanning the past decade reveal a complex association between arterial stiffness, central hemodynamic load, and CV events, including HF. While various components of arterial load differentially associate with LV hypertrophy and concentric remodeling [39], pulsatile load appears to be a more important effector of HF risk and CV events than resistive load [40]. In the first study to assess the relationship between central pulsatile hemodynamic load and cardiovascular events in MESA [41], arterial wave reflections as assessed by the reflection magnitude (a ratio of forward to backward travelling waves) was significantly associated with incident HF while other measures of central pulsatile hemodynamics (i.e., augmentation index and pulse pressure amplification) were not [41]. Similarly, the reflection magnitude as a measure of pulsatile LV afterload, was found to be an independent predictor of HF risk, even after considering resistive load appraised as systemic vascular resistance, pulsatile load measured as total arterial compliance and lumped parameters that capture both resistive and pulsatile load components such as effective arterial elastance [42]. The effect of wave reflections on LV afterload is likely mediated by loading sequence with mid-late systolic load having a more notable effect on LV mass and remodeling [39] and new onset HF [43]. Aortic stiffness is another factor that affects LV remodeling, but such association remain highly controversial in the MESA cohort. Ohyama et al. found that aortic arch PWV, measured via MRI, was significantly associated with LV

remodeling and reduced systolic and diastolic LV function [44]. Interestingly, subsequent work from the same authors found that aortic arch PWV was not a predictor of CV events or incident HF in the general MESA cohort [45], a finding observed earlier by Redheuil et al. noting that proximal aortic distensibility assessed by MRI was not associated with HF in fully adjusted models [46]. Our present findings complement and extend the MESA literature by noting that ePWV, a measure obtained from age and brachial blood pressure, is associated with incident HF and its subtypes. ePWV appears to offer comparable insight into future HF risk as sophisticated measures obtained from tonometry and echocardiography and may offer insight into HF risk not provided by MRI. ePWV may be capturing a complex interaction between age and blood pressure influenced by both intrinsic arterial wall stiffening (i.e., cfPWV) and other load-dependent factors (i. e., increased pressure from wave reflections). As such, our findings support the construct validity of ePWV as a measure of vascular aging as it relates to risk for HF and its subtypes.

Our findings should be carefully interpreted within the confines of study limitations. We noted an overall modest number of HF cases, preventing adequate examination into HF subtypes. We selected a single time point to use as baseline. Given the time-varying nature of arterial stiffness and changes in rates of vascular aging over time, future studies that use ePWV to explore vascular aging trajectories may offer additional insight into cumulative vascular-hemodynamic burden and subsequent CVD risk. Studies that employ serial measures of BP can also be used to explore novel factors that promote healthy vascular aging and factors that accelerate vascular aging. Strengths of this study included the prospective study design and inclusion of a sample that is representative of the racial and ethnic diversity of the U. S. population.

In conclusion, the present study demonstrated that higher ePWV values are associated with higher rates of incident HF and HF subtypes, supporting a possible role of vascular stiffness in HF pathogenesis. ePWV holds promise as an easily obtained measure of vascular aging that may offer insight into future CVD risk.

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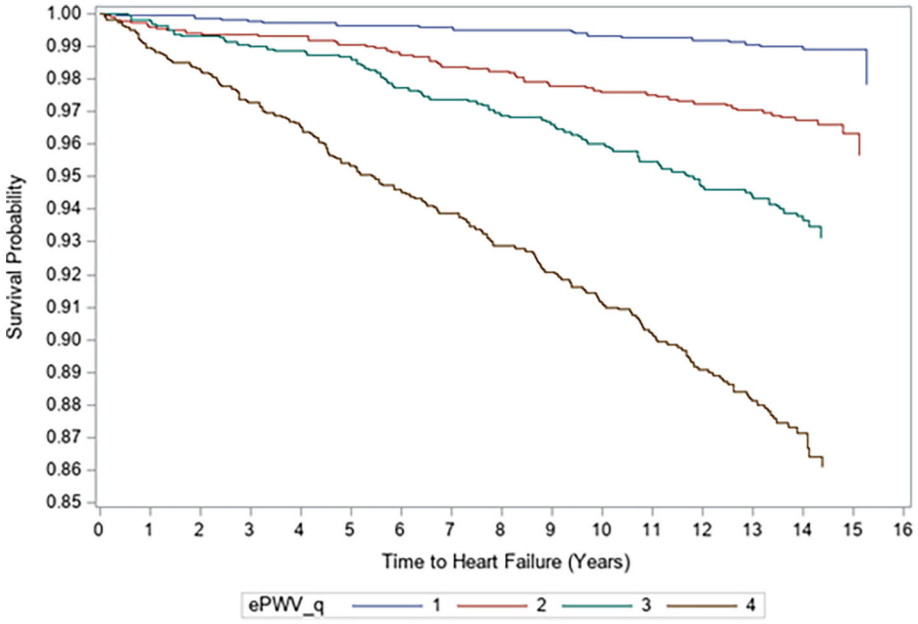

Fig. 1.

The Kaplan-Meier curves for incident heart failure (HF) by estimated pulse wave velocity (ePWV) quartiles.

Table 1

Descriptive characteristics by quartile of ePWV.

	ePWV Q1 (<8.1 m/s)	ePWV Q2 (8.1–9.6 m/s)	ePWV Q3 (>9.6–11.2 m/s)	ePWV Q4 (>11.2 m/s)	p-value
Age (years)	50.8 ± 4.3	58.1 ± 5.9	65.7 ± 5.6	74.1 ± 5.5	<0.0001
Male sex, n (%)	708 (41.4)	842 (48.3)	798 (49.0)	865 (50.0)	<0.0001
Race and ethnicity (n)					<0.0001
White	714	669	587	652	
Asian	207	194	196	207	
American					
Black	361	512	507	512	
Hispanic	430	370	338	358	
BMI (n)					<0.0001
Normal	578	454	415	507	
Overweight	622	641	665	739	
Obese	437	564	499	447	
Extreme obese	75	86	49	36	
Smoking (n)					<0.0001
Never	886	865	774	893	
Former	499	620	662	706	
Current	324	255	184	124	
Hypertension (n)					<0.0001
Normal	1298	567	245	97	
Elevated	106	198	150	88	
Hypertensive	306	980	1233	1544	
HTN Med, n (%)	251 (14.7)	561 (32.2)	786 (48.3)	938 (54.3)	<0.0001
Diabetes, n (%)	135 (7.9)	228 (13.1)	263 (16.2)	300 (17.4)	<0.0001
Waist (n)					<0.0001
Normal	928	759	686	753	
Increased	784	986	942	976	
Total cholesterol (n)					<0.0001
Normal	927	817	692	786	
Elevated	785	928	936	942	
PA (MET-min/day)	1044 ± 61	1059 ± 61	1014 ± 62	1055 ± 61	0.7875
HF	18	49	81	155	<0.0001
HFrEF	10	29	47	79	
HFpEF	8	20	34	76	
ePWV (m/s)	7.2 ± 0.6	8.9 ± 0.4	10.4 ± 0.5	12.5 ± 1.0	<0.0001

Body mass index, BMI; Med, Hypertension Medication Usage; Physical Activity, PA; Heart Failure, HF; Reduced Ejection Fraction, rEF; Preserved Ejection Fraction, pEF; estimated pulse wave velocity, ePWV; m/s, meters-per-second.

Table 2

Hazard ratios (HR) and 95 % confidence intervals (CI) associated with ePWV and risk of incident heart failure (HF) and its subtypes in unadjusted, age-adjusted and fully specified models (reference level: ePWV Q1).

HF	Model 1	Model 2	Model 3
	Unadjusted	**Age-adjusted**	**Fully specified**
ePWV Q2 (8.1–9.6 m/s)	3.12 (1.83–5.33)	2.66 (1.53–4.63)	2.02 (1.16–3.53)
ePWV Q3 (>9.6–11.2 m/s)	5.94 (3.58–9.86)	4.30 (2.39–7.34)	2.81 (1.55–5.09)
ePWV Q4 (>11.2 m/s)	12.93 (7.96–21.02)	7.83 (4.01–15.27)	4.79 (2.43–9.45)
HFrEF			
ePWV Q2 (8.1–9.6 m/s)	3.06 (1.49–6.28)	3.05 (1.45–6.43)	2.50 (1.22–5.16)
ePWV Q3 (>9.6–11.2 m/s)	5.74 (2.90–11.36)	5.69 (2.57–12.61)	4.35 (2.17–8.73)
ePWV Q4 (>11.2 m/s)	10.89 (5.63–21.07)	10.77 (4.31–26.89)	8.37 (4.24–16.52)
HFpEF			
ePWV Q2 (8.1–9.6 m/s)	2.61 (1.15–5.92)	1.89 (0.80–4.43)	1.67 (0.71–3.93)
ePWV Q3 (>9.6–11.2 m/s)	5.07 (2.35–10.96)	2.66 (1.07–6.61)	2.21 (0.89–5.48)
ePWV Q4 (>11.2 m/s)	12.71 (6.13–26.36)	4.67 (1.64–13.27)	3.94 (1.39–11.17)

Model 1 unadjusted,

Model 2 adjusted by age,

Model 3 (Fully Specified) adjusted by age, sex, BMI, diabetes, smoking status, HTN medication usage, and waist circumference.

HF heart failure, HFrEF heart failure with reduced ejection fraction, HFpEF heart failure with preserved ejection fraction.

Bold font signifies $p < 0.001$.

Table 3

Hazard ratios (HR) and 95 % confidence intervals (CI) of covariates associated with risk of incident heart failure (HF) and its subtypes for the respective parsimonious models.

	HF	**HFrEF**	**HFpEF**
Age	1.04 (1.01–1.06)	–	1.05 (1.02–1.09)
BMI (ref: normal)			
Overweight	1.07 (0.77–1.48)	–	–
Obese	1.14 (0.77–1.70)	–	–
Extreme obese	2.32 (1.32–4.07)	–	–
Smoking (ref: never)			
Former	1.23 (0.97–1.56)	1.18 (0.84–1.66)	1.54 (1.07–2.20)
Current	1.91 (1.36–2.69)	2.06 (1.30–3.26)	2.06 (1.18–3.58)
HTN Med (ref: No)			
Yes	1.47 (1.17–1.86)	1.51 (1.09, 2.10)	- -
Diabetes (ref: No)	2.11 (1.66–2.69)	2.00 (1.41–2.85)	2.35 (1.62–3.41)
Sex (ref: female)	1.83 (1.44–2.33)	2.79 (1.96–3.97)	–
WC (ref: normal)	1.56 (1.14–2.12)	1.89 (1.34–2.65)	1.86 (1.28–2.68)

Body mass index, BMI; Hypertension medication usage, HTN Med; Waist Circumference, WC. Empty cells signify variables that did not enter into parsimonious models for the respective dependent variable (HFrEF or HFpEF). Bold font signifies $p < 0.001$.