ORIGINAL RESEARCH

Gender Differences in Risk Factors Associated With Pulmonary Artery Systolic Pressure, Heart Failure, and Mortality in Blacks: Jackson Heart Study

Suvasini Lakshmanan, MD, MS; Matthew Jankowich, MD; Wen-Chih Wu, MD, MPH; Chad Blackshear, MS; Siddique Abbasi, MD, MS; Gaurav Choudhary, MD

***Background*—**Pulmonary hypertension is prevalent in black individuals, especially women. Elevated pulmonary artery systolic pressure (PASP) is associated with significant morbidity and mortality.

***Methods and Results*—**We developed linear and proportional hazards models to examine potential gender-related differences in risk factors for elevated PASP (estimated by transthoracic echocardiography) and PASP-associated clinical outcomes (incident heart failure admissions and mortality) in JHS (Jackson Heart Study) participants. JHS is a prospective observational cohort study of heart disease in blacks from the Jackson, Mississippi, metropolitan area. The study cohort included participants with measurable transtricuspid gradients (n=3286) at the time of first/baseline examination, 2000–2004. The median age (interquartile range) of patients at baseline was 57.8 years (18.6 years) with 67.5% being women. The median PASP at baseline was higher in women (men: 26 mm Hg [interquartile range 8], women: 27 mm Hg [interquartile range 9]. In multivariate linear regression analyses with PASP, significant gender interactions were noted for age, chronic lung disease, pulse pressure, and obstructive spirometry. In exploratory analyses stratified by gender, body mass index, and obstructive and restrictive spirometry patterns were associated with PASP in women, and chronic lung disease was associated with PASP in men. Age and pulse pressure had stronger associations with PASP in women compared with men. There was a significant interaction between gender and PASP for heart failure admissions but not mortality.

***Conclusions*—**Specific cardiopulmonary risk factors are associated with elevated PASP in women and men. Women with elevated PASP have a higher risk of incident heart failure admissions. Future research is needed to understand associated gender-specific mechanisms that can help identify targeted prevention and management strategies for patients with elevated PASP. **(*J Am Heart Assoc*. 2020;9:e013034. DOI: 10.1161/JAHA.119.013034.)**

Key Words: blacks • gender • pulmonary hypertension

Pulmonary hypertension (PH) is an important chronic illness in the black community,[1,2] with higher prevalence in women.[1] PH is a known complication of left heart disease, diseases of the lung, metabolic diseases, and thromboembolic disease,[3] and is associated with significant morbidity and mortality in black women.[4–7] Surveillance studies in the United States report a steady increase in PH-related deaths and hospitalizations particularly in women and blacks.[6] Despite these relevant clinical and epidemiological observations, reasons for high prevalence of PH, specifically nongroup 1 PH in black women, are poorly understood. Many comorbid risk factors for PH, including systemic hypertension, obesity, and diabetes mellitus, are prevalent in blacks.[8–11] Whether these clinical comorbidities may disproportionately affect the risk for elevated pulmonary artery (PA) systolic pressure (PASP) and associated clinical outcomes in women compared with men is unknown.

Echocardiography with measurement of tricuspid regurgitant jet for estimation of PASP allows for further studies of factors associated with elevated PASP in large epidemiologic cohorts.[1,2] We sought to examine whether there are gender-related differences in risk factors and clinical outcomes associated with elevated PASP in a large community-based cohort of black patients. We hypothesized that the relationship between PASP and associated clinical characteristics and outcomes, namely

From the Divisions of Cardiology (S.L., W.-C.W., S.A., G.C.) and Pulmonary, Critical Care and Sleep Medicine (M.J.), Providence VA Medical Center, Providence, RI; Alpert Medical School of Brown University, Providence, RI (S.L., M.J., W.-C.W., S.A., G.C.); Department of Data Science, University of Mississippi, Jackson, MS (C.B.).

Accompanying Data S1 through S4 and Tables S1 through S4 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013034

Correspondence to: Gaurav Choudhary, MD, Providence Veterans Affairs Medical Center, 830 Chalkstone Avenue, Providence, RI 02908. E-mail: gaurav_choudhary@brown.edu

Received April 18, 2019; accepted November 25, 2019.

Clinical Perspective

What Is New?

- Specific cardiopulmonary risk factors are associated with elevated pulmonary artery systolic pressure (PASP) in black women and men.
- Body mass index and obstructive and restrictive spirometry patterns are associated with elevated PASP in women and chronic lung disease is associated with PASP in men.
- Women with elevated PASP have a higher risk of incident heart failure admissions, compared with men.

What Are the Clinical Implications?

- Elevated PASP is associated with gender-specific risk factors in blacks, highlighting the need for guidelines and resource mobilization to enable early screening, increased surveillance, and target risk factor modification.

future heart failure (HF) admissions and mortality, would be significantly different between black men and women.

Methods

Study Design and Population

We conducted post hoc analyses using data from JHS (Jackson Heart Study). The conduct of the JHS was approved by the University of Mississippi Medical Center Institutional Review Board. The participants gave written informed consent to participate in the research study. Requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to JHS at https://www.jacksonheartstudy.org/Research/Study-Data. JHS is a longitudinal, population-based cohort study of cardiovascular disease that recruited noninstitutionalized black adult participants (N=5306) residing in the Jackson, Mississippi, metropolitan area.[12] The conduct of the study was approved by the institutional review board of the University of Mississippi Medical Center. Participants answered predefined questionnaires, underwent venipuncture, echocardiography, and spirometry at the first examination between 2000 and 2004. The study cohort included participants who had echocardiography data available (n=5076), of whom those with a measureable tricuspid regurgitant jet velocity on echocardiography (allowing for estimation of the PASP, as described in the Outcome section) (n=3286) were included for final analysis (Figure 1). Additional details of the study population are included in Data S1.

The characteristics of 2020 excluded participants with no tricuspid regurgitant jet measurements were comparable with the included study participants and are detailed in Table S1.

Exposure

The main exposure was participant gender, self-identified by participants as male or female in the predefined questionnaire.

Outcome

The main outcome for linear regression analyses was PASP, estimated by echocardiography in units of millimeters of mercury. PASP was calculated by addition of 5 mm Hg (to account for the typical right atrial pressure [RAP]) to the transtricuspid gradient, derived by the modified Bernoulli equation.[2,13]

For Cox proportional hazards analyses, the main outcome was all-cause mortality, with time to death calculated from the time of the index echocardiographic examination; the mortality cutoff date was December 31, 2012. We also conducted a Cox proportional hazards analysis in which outcome was the time to incident HF requiring hospital admission, after adjudication based on available data on history, physical examination, laboratory analysis, and medication use as per procedures used in the ARIC (Atherosclerosis Risk in Communities) study. Event adjudication began on January 1, 2005, and HF admission data were available for a median of 8 years (35–2921 days). More details regarding adjudication procedures in JHS have been outlined elsewhere.[14] Participants with a self-reported HF hospitalization history before January 1, 2005, (n=112) were excluded for analysis of incident HF admissions.[14]

Clinical Covariates

Data on clinical covariates were collected at the time of the first/baseline examination, when echocardiographic measurements were also performed. Covariates for linear regression analyses with PASP included age, body mass index (BMI), coronary heart disease (CHD), diabetes mellitus, hypertension, brachial pulse pressure measurement, presence of severe mitral or aortic valvular heart disease on baseline echocardiography, history of chronic lung disease, and pattern on baseline spirometry measurement (normal, obstructive, restrictive). For Cox proportional hazards model for mortality, covariates included age, sex, BMI, American Heart Association (AHA) physical activity category, smoking status, total cholesterol measured at first examination, diabetes mellitus, history of HF, history of CHD, presence of hypertension, history of stroke, and estimated glomerular filtration rate. For Cox proportional hazards model of incident HF hospitalization, covariates included age, sex, diabetes mellitus, CHD, systolic blood pressure, BMI, heart rate on ECG at time of first examination, use of antihypertensive agents, and smoking status. Definitions for the clinical covariates used in this study are outlined in Data S2.

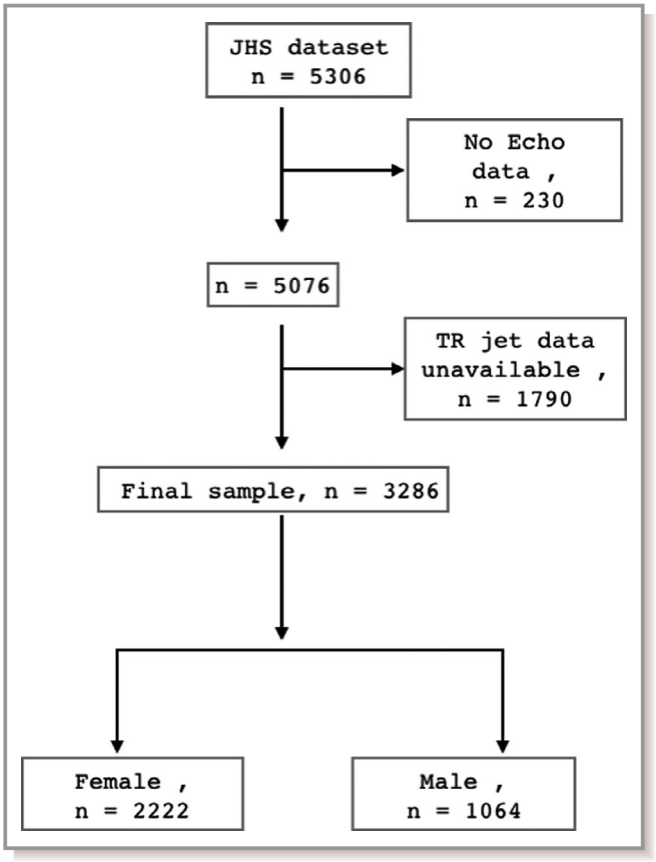

Figure 1. A schematic depiction of our study cohort. JHS indicates Jackson Heart Study; TR, tricuspid regurgitant.

Echocardiographic Parameters

Details regarding echocardiographic data and procedures are outlined in Data S3.

Statistical Analysis

Baseline characteristics between men and women were compared using the Wilcoxon–Mann–Whitney test for continuous variables and χ^2 analysis for categorical variables. Continuous variables were described as median with interquartile range. Linear regression analyses were conducted to assess for gender interactions for clinical covariates associated with PASP to assess possible effect modification by gender on associations of covariates with PASP. The PASP models were adjusted for age, BMI (kg/m^2), brachial pulse pressure (mm Hg), hypertension, diabetes mellitus, CHD, severe mitral/aortic valvular heart disease, history of chronic lung disease, and spirometry profile (normal, obstructive, and restrictive)—a model adapted from Choudhary et al.[1] Interaction terms with gender were developed for each of the covariates outlined above and added individually to the models. Exploratory analyses stratified by gender were performed if variables with significant multiplicative interaction testing were present.

Cox proportional hazards modeling was used for analyses of mortality and incident HF hospitalization. The hazard ratio (HR) for all-cause mortality associated with PASP was determined with an adjusted model for mortality adapted from Gu et al,[15] adjusting for age, sex, BMI, physical activity, smoking status, high cholesterol, diabetes mellitus, history of HF, history of CHD, hypertension, estimated glomerular filtration rate, and history of stroke. To assess for effect modification of gender on PASP association with these outcomes, a gender×PASP interaction term was then added to the model. Next, the association of PASP with decompensated incident HF events requiring hospital admission was assessed. Cox proportional hazards modeling was used to determine the HR for HF events associated with PASP in an adjusted model of HF (ARIC model) from Agarwal et al,[16] adjusting for age, sex, CHD, diabetes mellitus, systolic blood pressure, blood pressure medication use, heart rate, smoking status, and BMI. Participants who died before an HF event were censored. Similar to the mortality models, a gender×PASP interaction term was then added to the model.

If there was evidence of a significant gender interaction with PASP in the Cox proportional hazards models, exploratory analyses stratified by gender were then performed. Competing risk analysis for incident HF was also performed with all-cause mortality as a competing event. Finally, to assess for potential differences in incidence of HF hospitalization by level of PASP in women and men, the incident rate of HF was plotted against groupings of PASP in men and women.

In the regression analyses with PASP as the outcome, we included all participants (N=3286). However, to ensure that incident HF episodes were identified, patients who self-reported HF history (n=112) in their questionnaire were excluded from proportional hazards analyses that had incident HF as the outcome.

Missing data for clinical covariates were handled using multiple imputation, as outlined in Data S4. Distributions of missing covariates are listed in Table S2.

All analysis was performed using Stata/SE, version 15.1 software (StataCorp LP). A 2-sided *P* value of <0.05 was considered significant.

Results

Baseline Characteristics

Table 1 shows the baseline clinical characteristics of the cohort by gender. The median (interquartile range) age of the study population was 57.8 years (18.6 years), with 67.5% of participants being women. The overall prevalence of obesity was 51.1%, hypertension was 56.1%, and diabetes mellitus was 19.4%. Women were more likely to

Table 1. Baseline Characteristics by Gender

Characteristic	Total	Women, No. (%)	Men, No. (%)	*P* Value
Total	3286 (100)	2222 (67.6)	1064 (32.4)	
Age, y				
<45	666 (20.27)	445 (20.03)	221 (20.77)	0.560
45 to <55	784 (23.86)	517 (23.27)	267 (25.09)	
55 to <65	950 (28.91)	651 (29.30)	299 (28.10)	
≥65	886 (26.96)	609 (27.41)	277 (26.03)	
AHA BMI categories				
Obese	1674 (51.05)	1279 (57.69)	395 (37.19)	<0.001
Overweight	1106 (33.73)	646 (29.14)	460 (43.31)	
Normal	499 (15.22)	292 (13.17)	207 (19.49)	
Hypertension	1842 (56.06)	1305 (58.73)	537 (50.47)	<0.001
Diabetes mellitus	630 (19.40)	444 (20.25)	186 (17.65)	0.079
Severe left-sided valvular heart disease	7 (0.22)	4 (0.18)	3 (0.29)	0.544
History of CHD	334 (10.69)	214 (10.08)	120 (11.98)	0.110
Reduced EF (EF <40%)	31 (0.95)	13 (0.6)	18 (1.69)	
Mid-range EF (EF 40–55%)	191 (5.84)	101 (4.59)	90 (8.48)	
Preserved EF (EF >55%)	3045 (93.2)	2092 (94.83)	953 (89.82)	<0.001
Lung disease history	229 (6.98)	165 (7.44)	64 (6.03)	0.137
Smoker	639 (19.62)	347 (15.75)	292 (27.70)	<0.001
AHA physical activity categorization				
Poor health	1634 (49.82)	1115 (50.27)	519 (48.87)	<0.001
Intermediate health	1039 (31.68)	742 (33.45)	297 (27.97)	
Ideal health	607 (18.51)	361 (16.28)	246 (23.16)	
Stroke history	146 (4.44)	89 (4.01)	57 (5.36)	0.08
BP medication use	1573 (51.9)	1161 (56.2)	412 (42.74)	<0.001
History of HF	112 (4.19)	72 (3.89)	40 (4.85)	0.25
Spirometry profile				
Normal	2209 (71.05)	1530 (72.93)	679 (67.16)	0.004
Obstructive	278 (8.94)	172 (8.20)	106 (10.48)	
Restrictive	622 (20.01)	396 (18.88)	226 (22.35)	
	Median (Quartile 1–Quartile 3)	Median (Quartile 1–Quartile 3)	Median (Quartile 1– Quartile 3)	*P*-value
Systolic BP, mm Hg	125.66 (115.58–135.75)	124.75 (114.66–135.75)	125.66 (116.49–135.75)	0.49
Diastolic BP, mm Hg	75.05 (69.24–80.86)	77.54 (71.73–83.35)	74.22 (68.41–79.20)	<0.001
Pulse pressure, mm Hg	49.3 (41.88–59.13)	47.66 (40.75–56.78)	50.1 (42.50–60.17)	<0.001
Estimated glomerular filtration rate, mL/min per 1.73 m^2	94.76 (80.47–108.37)	92.70 (79.57–105.71)	95.91 (80.84–109.58)	0.001

Data are presented as number (percentage) or median (interquartile range). AHA indicates American Heart Association; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; EF, ejection fraction; HF, heart failure.

be obese, exhibit poor to intermediate levels of physical activity per AHA categorization, and have hypertension and normal spirometry profiles. However, men were more likely to be smokers, to have a reduced left ventricular ejection fraction (EF), and to have obstructive or restrictive spirometry profiles. Men also had higher brachial pulse pressures than women. Median PASP was higher in women (men: 26 mm Hg [quartile 1–quartile 3: 22–30], women: 27 mm Hg [quartile 1–quartile 3: 23–32], $P<0.05$). The overall prevalence of PH (PASP ≥40 mm Hg) was 5.6%, with

a higher prevalence in women (men: 4.04%, women: 6.35%; $P<0.05$).

Demographic and Clinical Characteristics Associated With PASP and Interaction of PASP With Gender

After adjusting for relevant clinical characteristics in linear multivariate regression analyses, significant gender interactions with PASP were seen with age, BMI, diagnosis of hypertension, pulse pressure, history of chronic lung disease, and obstructive spirometry pattern. The results of interaction testing for each of the covariates are outlined in Table 2.

Stratified Analysis in Men and Women

In exploratory analyses stratified by gender (Table 3), higher BMI and obstructive and restrictive spirometry patterns were associated with PASP in women, while no evidence of an association of these factors with PASP was found in men. Also, age and pulse pressure, while associated with PASP in both men and women, demonstrated a stronger association with PASP in women compared with men (adjusted β coefficient [SE] for age 0.18 [0.01] in women versus 0.14 [0.02] in men; adjusted β coefficient [SE] for pulse pressure 0.07 [0.01] in women versus 0.05 [0.02] in men). A history of chronic lung disease was associated with PASP in men, but no evidence of an association of chronic lung disease with PASP was found in women. In a supplementary analysis of spirometry values (forced expiratory volume in the first second of expiration [FEV_1], forced vital capacity), there was a significant gender interaction with FEV_1 and forced vital capacity (Table S3). In stratified analyses, FEV_1 was significantly associated with PASP in both men and women, with a stronger association in women (adjusted β coefficient [SE] for FEV_1 in women −2.63 [0.58] versus men −1.23 [0.62]) (Table S4). However, there was no evidence of an association of PASP with forced vital capacity in men or women (Table S4).

Table 2. Adjusted β Coefficients for Association of Gender Interaction Terms With PASP

Variable	Adjusted β Coefficient for Interaction Term (95% CI)*	*P* Value for Interaction Term
Age × gender	−0.06 (−0.09 to −0.02)	0.005
Male	NA	NA
BMI (kg/m^2) × gender	−0.09 (−0.17 to −0.01)	0.029
Diabetes mellitus × gender	−0.21 (−1.04 to +1.46	0.745
Hypertension × gender	−1.21 (−2.18 to −0.24)	0.015
Pulse pressure (mm Hg) × gender	−0.04 (−0.08 to −0.01)	0.014
Severe left-sided valve disease × gender	9.09 (−0.84 to +19.0)	0.073
CHD × gender	1.23 (−0.33 to +2.80)	0.122
Normal spirometry	1.00 (Ref)	
Obstructive spirometry × gender	−1.98 (−3.67 to −0.30)	0.021
Restrictive spirometry × gender	−0.45 (−1.68 to +0.78)	0.47
Chronic lung disease × gender	2.79 (0.82–4.76)	0.005

*Each individual regression model was adjusted for age, gender, body mass index (BMI), coronary heart disease (CHD), diabetes mellitus, hypertension, pulse pressure, severe mitral or aortic valvular disease, history of chronic lung disease, and spirometry category, as well as the designated gender interaction term. PASP indicates pulmonary artery systolic pressure.

Relationship of PASP With Mortality and Interaction With Gender

The median (range) follow-up time for the mortality analysis was 10.1 years (0–12.3 years). During the follow-up period, 363 deaths occurred, including 216 deaths in women and 147 deaths in men. After adjustment for potential confounders, PASP was significantly associated with mortality (adjusted HR per 1 mm Hg of PASP, 1.03; CI, 1.01–1.04). No evidence of a gender interaction with PASP and mortality was seen in the adjusted analysis when an interaction term for PASP and gender was included (*P* interaction >0.05).

Relationship of PASP With Incident HF Admissions and Interaction With Gender

The median (range) follow-up time for incident HF analysis was 8.0 years (0–8.0 years).

During the follow-up period, 141 patients were admitted with decompensated HF, including 104 women and 37 men.

For HF events, there was evidence of a significant interaction between gender and PASP (*P* interaction <0.05). In analyses stratified by gender, elevated PASP increased the hazards of incident HF in women, while no evidence of a relationship was found between PASP and hazards of HF in men (adjusted HR per 1 mm Hg of PASP, 1.05; 95% CI, 1.02–1.07 in women versus HR per 1 mm Hg of PASP, 0.99; 95% CI, 0.95–1.05 in men) (Table 4). No evidence of a gender interaction was observed in competing risk analysis for incident HF, when death was treated as a competing risk.

Differences in incidence rates of HF in men and women by groupings of PASP is displayed in Figure 2, showing an increase in the incident rate of HF with increasing PASP grouping in women but not in men.

Table 3. Association of Clinical Characteristics With PASP Stratified by Gender

Variable	Men		Women	
	Adjusted β Coefficient (95% CI)*	*P* Value	Adjusted β Coefficient (95% CI)*	*P* Value
Age, y	0.14 (0.10–0.17)	<0.001	0.18 (0.15–0.21)	<0.001
BMI, kg/m^2	0.06 (−0.01 to 0.13)	0.092	0.17 (0.13–0.21)	<0.001
Hypertension	−0.23 (−0.48 to 1.70)	0.616	0.48 (−0.18 to 1.14)	0.157
Pulse pressure, mm Hg	0.05 (0.02–0.08)	0.004	0.07 (0.05–0.09)	<0.001
Obstructive spirometry	0.48 (−0.89 to 1.85)	0.494	2.72 (1.65–3.79)	<0.001
Restrictive spirometry	0.49 (−0.56 to 1.54)	0.360	1.05 (0.31–1.79)	0.006
Chronic lung disease	2.94 (1.27–4.62)	0.001	0.13 (−0.92 to 1.18)	0.813

*Adjusted for age, body mass index (BMI), pulse pressure, hypertension, diabetes mellitus, coronary heart disease, severe valvular disease, history of chronic lung disease, spirometry categories. PASP indicates pulmonary artery systolic pressure.

Discussion

To the best of our knowledge, our study is the first to examine gender-specific differences in pathogenesis and prognosis of elevated PASP in a vulnerable black cohort. While female predominance has been observed in group 1 PH,[7,17] epidemiological data from population-based studies and nongroup 1 PH is limited. We report that there was evidence of a significant gender interaction with a number of clinical risk factors for elevated PASP in blacks. Gender-stratified exploratory analyses found that black women with specific risk factors, namely higher BMI and obstructive or restrictive spirometry profile, are likely to have higher mean PASP compared with men with similar risk factor profiles. Furthermore, age and brachial pulse pressure were more strongly associated with PASP in women than in men in these exploratory analyses. Finally, elevated PASP was noted to be related to subsequent incident HF admissions in women, but there was no evidence of such a relationship in men, while there was no evidence of a gender-interaction with PASP with regards to overall mortality. The relationship between PASP and incident HF events in women was independent of important clinical comorbidities, suggesting that elevated PASP can serve as an important marker to identify women who are at risk for subsequent HF admission. Given the known higher prevalence of PH and associated poor prognosis in black women, our study findings can potentially help identify relevant patients to be targeted for the study of prevention and management strategies.

Table 4. Gender-Stratified Cox Proportional Hazards Analysis of Association of PASP With Incident Decompensated HF

	Men		Women	
	Adjusted HR (95% CI)*	*P* Value	Adjusted HR (95% CI)*	*P* Value
PASP, mm Hg	0.99 (0.95–1.05)	0.87	1.05 (1.02–1.07)	<0.001

Patients who self-reported heart failure (HF) history (n=112) in their questionnaire were excluded from analyses that had incident HF as the outcome.
*Adjusted for age, gender, diabetes mellitus, coronary heart disease, systolic blood pressure, body mass index, heart rate, use of antihypertensive agents, and smoking status. HR indicates hazard ratio; PASP, pulmonary artery systolic pressure.

Gender Differences in Risk Factors Associated With PASP

We report that obese women are more likely to have elevated PASP compared with men with similar risk factors. Our observation is particularly relevant given the high prevalence of obesity in women participants in JHS (57% in our cohort), and in the overall US population with higher age-adjusted prevalence of obesity in women (40.4%) compared with men (35.0%).[18] Obesity is a major global health and economic challenge[19] with significant associated morbidity and mortality.[20] Obesity is a well-known risk factor for global microvascular dysfunction including in the pulmonary circulation and has been linked with PH through common physiologic syndromes such as obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS) causing group 3 PH and cardiomyopathy of obesity causing group 2 PH. Although previous studies have reported strong correlations between obesity and elevated PASP,[21,22] data on gender-based differences are limited. In the background of high obesity burden in women, our study results can also potentially be attributed to significantly higher leptin/adiponectin ratio in obese women compared with men,[23] and subsequent effects on leptin-mediated proinflammatory pathways,[24,25] structural modeling, and endothelial dysfunction.[26,27] Women with OSA are reported to have higher waist-hip ratio and elevated BMI,[28,29] causing differential hormonal regulation of ventilatory responses,[30] also likely contributing to PH.

We also observed that obstructive and restrictive spirometry patterns appear to be associated with elevated PA pressures in women but not in men, while a history of chronic lung disease was associated with higher PASP in men but not women. Furthermore,

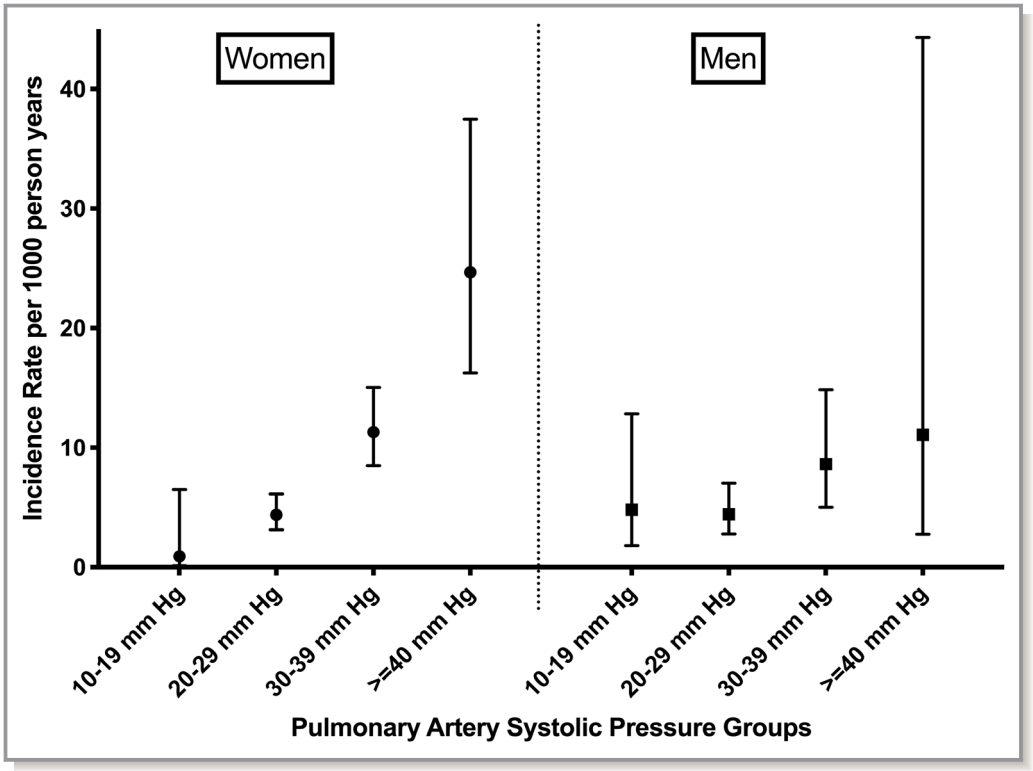

Figure 2. Incidence rates of heart failure in men and women according to pulmonary artery systolic pressure (PASP) groupings. Vertical lines represent 95% CIs of incidence rates of heart failure.

decreased FEV_1 values were more strongly associated with elevated PASP in women than men. These gender-related differences have not been extensively studied previously but are significant given the higher prevalence of obstructive airway disorders in women[31] and associated increased rates of hospitalizations[32] and mortality.[33] Some potential mechanisms that can explain this association include exaggerated vascular inflammation related to increased secretion of interleukin 4 and interleukin 13 in women,[34] role of estrogen in hypoxia-related vascular remodeling,[35] and estrogen receptor–mediated expression of CYP1A1 that promotes susceptibility to oxidant damage.[36] Restrictive spirometry patterns have also been shown to be associated with increased arterial stiffness in men and women.[37] The exact mechanisms mediating the association of PASP and restrictive spirometry especially in women remains unclear but can be linked to similar hormone-related activation of inflammatory pathways.[38,39] The association of a prior diagnosis of chronic lung disease being associated with higher PASP values in men but not women may relate to differences in presentation and the likelihood of accurate diagnosis of lung disease in men versus women.[40] However, these intriguing gender differences in the association of lung disease with PASP require confirmation and further study in diverse populations.

In our study, elevated PASP in women is more strongly influenced by age compared with men. PH is being increasingly diagnosed in the elderly and associated with poor prognosis[41]; however, studies on differences in gender distribution are sparse. Redfield et al[42] evaluated age- and gender-related interaction effects on vascular and cardiac parameters and reported that advancing age in women was associated with an increase in vascular and ventricular systolic/diastolic stiffness even in the absence of cardiovascular disease. Previous studies have reported other vascular indices such as central large artery stiffness, pulse pressures, and systemic pressures to be increased in older women compared with men.[43,44] These effects on cardiac and vascular indices likely contribute to the development of PH through a decrease in PA compliance,[45,46] increased pulmonary vascular resistance,[46] associated ventricular diastolic dysfunction, and left atrial enlargement.[47,48] Animal studies have attributed this age-dependent gender-related vascular heterogeneity to the effect of menopause-related hormonal changes on vascular remodeling[49] and differential modulation of the renin-angiotensin aldosterone system and sympathetic systems.[50,51]

Gender Differences With PASP and Associated Clinical Outcomes

Finally, we found that in blacks, elevated PASP was a risk factor for poorer prognosis, including HF admissions and mortality. Our study specifically suggests that women with elevated PASP have a higher risk of incident/new

decompensated HF admissions requiring hospitalization. The result was consistent after adjustment for relevant risk factors, suggesting that pulmonary pressures could be an independent predictor for decompensated HF admissions in women. Many studies have previously reported increased risk of HF admissions (mainly HF with preserved EF phenotype) in women compared with men.[52,53] Although elevated PASP has been identified as a possible risk factor for HF admissions in multiple studies,[54,55] including an analysis of the JHS cohort,[2] to the best of our knowledge, this is the first study to report elevated PASP as a distinct gender-specific risk factor for HF admissions in black women. Mechanisms underlying this observation could be related to aforementioned direct hormonal influences on increased vascular stiffness and risk of diastolic dysfunction in women that manifests as clinical HF. HF is a major public health problem[56,57] with significant morbidity and mortality burden; hence, future research in understanding the exact mechanisms outlining the role and mechanisms of PASP in HF risk is needed.

Elevated PASP in this cohort of black patients was associated with decreased survival with no evidence of gender interaction. Our observation is consistent with surveillance studies that have reported highest mortality rates in blacks with PH compared with other ethnicities.[7] Multiple studies have established black race as an independent risk factor for mortality in patients with PH.[58,59] These observations have significant public health and clinical implications given the known background of under-recognition and delayed diagnoses of PH[7] in this at-risk population. Our results further emphasize the need for guidelines and resource mobilization to enable early screening and increased surveillance and target risk factor modification in this vulnerable population. While interaction analysis in our study did not suggest gender-based differences in mortality risk, multiple epidemiological studies have reported trends of higher mortality rates in women with PH,[4,7,60] but the mechanisms driving differential mortality risk remain unclear. A few earlier studies had observed that women with connective tissue disease–related PAH, namely systemic sclerosis, had higher risk of death, even after accounting for demographic and hemodynamic characteristics.[4,61] The risk factor profile and distribution of PH groups of the women participants in our study is likely different from these studies, which could explain our equivocal results.

Limitations

Our study has some limitations. Our study design is observational and hence these results cannot be used to determine causality. Residual confounding may also be present despite attempts to account for known confounding variables. A few of the clinical covariates were self-reported through questionnaires and subject to recall bias. Our main outcome, PASP, has been estimated by echocardiography and is likely prone to measurement bias. There were no inferior vena cava measurements, so we used an assumed right atrial pressure of 5 mm Hg as in a previous population-based cohort study.[13] This may have led to underestimation of PA pressure in participants with more elevated right atrial pressures. Presence of obesity, which was prevalent in this cohort, can also make echocardiography measurements technically difficult.[62] Although an invasive right heart catheterization–derived PA pressure measurement is considered the gold standard, this is not practical to perform in population-based studies. There may be a lack of precision in measured PASP that may have slightly affected the associations identified in the study. However, many cohort studies have demonstrated good sensitivity, specificity, and reliability of echocardiographic pulmonary hemodynamic measurements in comparison with right heart catheterization measurements.[63,64] We do not have detailed phenotyping data to adjudicate for PH classification (World Health Organization groups 1–5); however, ongoing studies such as PVDOMICS (Redefining Pulmonary Hypertension Through Pulmonary Vascular Disease Phenomics) that are performing detailed phenotypic assessment of patients may be able to explore these in the future.[65]

While the study enrollment started between 2000 and 2004, adjudication of HF events started in 2005. Thus, we may be underestimating the association between PASP and HF hospitalization assuming that the HF event rates remained constant throughout the study period. We are unable to comment on temporal trends in relation to HF events or mortality, since we are using PASP measurements from the baseline visit only. We do not have data regarding EF at the time of admission for decompensated HF and therefore cannot differentiate between the nature of HF (HF with preserved EF, HF with reduced EF, or HF with midrange EF) leading to hospitalization. Finally, given the multiple tests performed to assess gender interaction with covariates in the models, type 1 errors may have been made in concluding significant gender interactions were present.

Conclusions

Distinct cardiopulmonary risk factors are associated with elevated PASP in black women and men. This knowledge may assist in screening and early diagnosis of PH in at-risk members of the black population. Women with elevated PASP appear predisposed to a higher risk of incident HF admissions compared with men. These findings warrant future research to identify specific genetic and hormonal mechanisms to enable targeted prevention and management of PH.

Acknowledgments

The authors wish to thank the staff and participants of JHS. Disclaimer: The views expressed in this article are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute (NHLBI); the National Institutes of Health (NIH); the US Department of Health and Human Services; the Department of Veterans Affairs; or the US government.

Sources of Funding

JHS is supported and conducted in collaboration with Jackson State University (HHSN268201800013I), Tougaloo College (HHSN268201800014I), the Mississippi State Department of Health (HHSN268201800015I/HHSN26800001), and the University of Mississippi Medical Center (HHSN268201800010I, HHSN268201800011I, and HHSN268201800012I) contracts from the NHLBI and the National Institute for Minority Health and Health Disparities. G.C. is supported by a Department of Veterans Affairs MERIT award I01CX001892, NIH/NHLBI R01HL128661, and NIH/NHLBI R01HL148727.

Disclosures

None.

References

1. Choudhary G, Jankowich M, Wu WC. Prevalence and clinical characteristics associated with pulmonary hypertension in African-Americans. *PLoS One*. 2013;8:e84264.
2. Choudhary G, Jankowich M, Wu WC. Elevated pulmonary artery systolic pressure predicts heart failure admissions in African Americans: Jackson Heart Study. *Circ Heart Fail*. 2014;7:558–564.
3. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H, Robbins IM, Souza R. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62:D34–D41.
4. Frost AE, Badesch DB, Barst RJ, Benza RL, Elliott CG, Farber HW, Krichman A, Liou TG, Raskob GE, Wason P, Feldkircher K, Turner M, McGoon MD. The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US Contemporary Registries. *Chest*. 2011;139:128–137.
5. Kjaergaard J, Akkan D, Iversen KK, Kjoller E, Kober L, Torp-Pedersen C, Hassager C. Prognostic importance of pulmonary hypertension in patients with heart failure. *Am J Cardiol*. 2007;99:1146–1150.
6. Mehari A, Valle O, Gillum RF. Trends in pulmonary hypertension mortality and morbidity. *Pulm Med*. 2014;2014:105864.
7. George MG, Schieb LJ, Ayala C, Talwalkar A, Levant S. Pulmonary hypertension surveillance: United States, 2001 to 2010. *Chest*. 2014;146:476–495.
8. Beckles GL, Chou CF. Disparities in the prevalence of diagnosed diabetes—United States, 1999–2002 and 2011–2014. *MMWR Morb Mortal Wkly Rep*. 2016;65:1265–1269.
9. Robbins IM, Newman JH, Johnson RF, Hemnes AR, Fremont RD, Piana RN, Zhao DX, Byrne DW. Association of the metabolic syndrome with pulmonary venous hypertension. *Chest*. 2009;136:31–36.
10. Russo C, Jin Z, Homma S, Rundek T, Elkind MS, Sacco RL, Di Tullio MR. Effect of obesity and overweight on left ventricular diastolic function: a community-based study in an elderly cohort. *J Am Coll Cardiol*. 2011;57:1368–1374.
11. Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG. Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. *Diabetes Care*. 2001;24:5–10.
12. Taylor HA Jr, Wilson JG, Jones DW, Sarpong DF, Srinivasan A, Garrison RJ, Nelson C, Wyatt SB. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. *Ethn Dis*. 2005;15:S6-4-17.
13. Lam CS, Borlaug BA, Kane GC, Enders FT, Rodeheffer RJ, Redfield MM. Age-associated increases in pulmonary artery systolic pressure in the general population. *Circulation*. 2009;119:2663–2670.
14. Jankowich MD, Wu WC, Choudhary G. Association of elevated plasma endothelin-1 levels with pulmonary hypertension, mortality, and heart failure in African American individuals: the Jackson Heart Study. *JAMA Cardiol*. 2016;1:461–469.
15. Gu Q, Burt VL, Paulose-Ram R, Yoon S, Gillum RF. High blood pressure and cardiovascular disease mortality risk among U.S. adults: the third National Health and Nutrition Examination Survey mortality follow-up study. *Ann Epidemiol*. 2008;18:302–309.
16. Agarwal SK, Chambless LE, Ballantyne CM, Astor B, Bertoni AG, Chang PP, Folsom AR, He M, Hoogeveen RC, Ni H, Quibrera PM, Rosamond WD, Russell SD, Shahar E, Heiss G. Prediction of incident heart failure in general practice: the Atherosclerosis Risk in Communities (ARIC) study. *Circ Heart Fail*. 2012;5:422–429.
17. Foderaro A, Ventetuolo CE. Pulmonary arterial hypertension and the sex hormone paradox. *Curr Hypertens Rep*. 2016;18:84.
18. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. *JAMA*. 2016;315:2284–2291.
19. Tremmel M, Gerdtham UG, Nilsson PM, Saha S. Economic burden of obesity: a systematic literature review. *Int J Environ Res Public Health*. 2017;14:E435.
20. Kushner RF, Kahan S. Introduction: the state of obesity in 2017. *Med Clin North Am*. 2018;102:1–11.
21. Weatherald J, Huertas A, Boucly A, Guignabert C, Taniguchi Y, Adir Y, Jevnikar M, Savale L, Jais X, Peng M, Simonneau G, Montani D, Humbert M, Sitbon O. Association between BMI and obesity with survival in pulmonary arterial hypertension. *Chest*. 2018;154:872–881.
22. McQuillan BM, Picard MH, Leavitt M, Weyman AE. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. *Circulation*. 2001;104:2797–2802.
23. Selthofer-Relatic K, Radic R, Stupin A, Sisljagic V, Bosnjak I, Bulj N, Selthofer R, Delic Brkljacic D. Leptin/adiponectin ratio in overweight patients—gender differences. *Diab Vasc Dis Res*. 2018;15:260–262.
24. Sorop O, Olver TD, van de Wouw J, Heinonen I, van Duin RW, Duncker DJ, Merkus D. The microcirculation: a key player in obesity-associated cardiovascular disease. *Cardiovasc Res*. 2017;113:1035–1045.
25. Mancuso P. Obesity and lung inflammation. *J Appl Physiol (1985)*. 2010;108:722–728.
26. Szmitko PE, Teoh H, Stewart DJ, Verma S. Adiponectin and cardiovascular disease: state of the art?. *Am J Physiol Heart Circ Physiol*. 2007;292:H1655–H1663.
27. van Rooy MJ, Pretorius E. Obesity, hypertension and hypercholesterolemia as risk factors for atherosclerosis leading to ischemic events. *Curr Med Chem*. 2014;21:2121–2129.
28. BaHammam AS, Pandi-Perumal SR, Piper A, Bahammam SA, Almeneessier AS, Olaish AH, Javaheri S. Gender differences in patients with obesity hypoventilation syndrome. *J Sleep Res*. 2016;25:445–453.
29. Sin DD, Jones RL, Man GC. Hypercapnic ventilatory response in patients with and without obstructive sleep apnea: do age, gender, obesity, and daytime PaCO(2) matter? *Chest*. 2000;117:454–459.
30. Regensteiner JG, Woodard WD, Hagerman DD, Weil JV, Pickett CK, Bender PR, Moore LG. Combined effects of female hormones and metabolic rate on ventilatory drives in women. *J Appl Physiol (1985)*. 1989;66:808–813.
31. Akinbami LJ, Liu X. Chronic obstructive pulmonary disease among adults aged 18 and over in the United States, 1998–2009. *NCHS Data Brief*. 2011:1–8.
32. Rosenberg SR, Kalhan R, Mannino DM. Epidemiology of chronic obstructive pulmonary disease: prevalence, morbidity, mortality, and risk factors. *Semin Respir Crit Care Med*. 2015;36:457–469.
33. Grabicki M, Kuznar-Kaminska B, Rubinsztajn R, Brajer-Luftmann B, Kosacka M, Nowicka A, Piorunek T, Kostrzewska M, Chazan R, Batura-Gabryel H. COPD course and comorbidities: are there gender differences? *Adv Exp Med Biol*. 2019;1113:43–51.
34. Straub RH. The complex role of estrogens in inflammation. *Endocr Rev*. 2007;28:521–574.
35. Mollerup S, Ryberg D, Hewer A, Phillips DH, Haugen A. Sex differences in lung CYP1A1 expression and DNA adduct levels among lung cancer patients. *Cancer Res*. 1999;59:3317–3320.

36. Berge G, Mollerup S, ØVrebø S, Hewer A, Phillips DH, Eilertsen E, Haugen A. Role of estrogen receptor in regulation of polycyclic aromatic hydrocarbon metabolic activation in lung. *Lung Cancer*. 2004;45:289–297.
37. Wu IH, Sun ZJ, Lu FH, Yang YC, Chou CY, Chang CJ, Wu JS. Restrictive spirometry pattern is associated with increased arterial stiffness in men and women. *Chest*. 2017;152:394–401.
38. Chang SS, Vaz Fragoso CA, Van Ness PH, Fried LP, Tinetti ME. Association between combined interleukin-6 and C-reactive protein levels and pulmonary function in older women: results from the Women's Health and Aging Studies I and II. *J Am Geriatr Soc*. 2011;59:113–119.
39. Gimeno D, Delclos GL, Ferrie JE, De Vogli R, Elovainio M, Marmot MG, Kivimaki M. Association of CRP and IL-6 with lung function in a middle-aged population initially free from self-reported respiratory problems: the Whitehall II study. *Eur J Epidemiol*. 2011;26:135–144.
40. Roberts NJ, Patel IS, Partridge MR. The diagnosis of COPD in primary care; gender differences and the role of spirometry. *Respir Med*. 2016;111:60–63.
41. Pugh ME, Sivarajan L, Wang L, Robbins IM, Newman JH, Hemnes AR. Causes of pulmonary hypertension in the elderly. *Chest*. 2014;146:159–166.
42. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: a community-based study. *Circulation*. 2005;112:2254–2262.
43. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension*. 2004;43:1239–1245.
44. Smulyan H, Asmar RG, Rudnicki A, London GM, Safar ME. Comparative effects of aging in men and women on the properties of the arterial tree. *J Am Coll Cardiol*. 2001;37:1374–1380.
45. Thenappan T, Prins KW, Pritzker MR, Scandurra J, Volmers K, Weir EK. The critical role of pulmonary arterial compliance in pulmonary hypertension. *Ann Am Thorac Soc*. 2016;13:276–284.
46. Olivari MT, Fiorentini C, Polese A, Guazzi MD. Pulmonary hemodynamics and right ventricular function in hypertension. *Circulation*. 1978;57:1185–1190.
47. Marcus R, Krause L, Weder AB, Dominguez-Meja A, Schork NJ, Julius S. Sex-specific determinants of increased left ventricular mass in the Tecumseh Blood Pressure Study. *Circulation*. 1994;90:928–936.
48. Mukherjee M, Mehta NK, Connolly JJ, Dusaj RS, Choi BG, Katz RJ, Lewis JF. Pulmonary hypertension in hypertensive patients: association with diastolic dysfunction and increased pulmonary vascular resistance. *Echocardiography*. 2014;31:442–448.
49. Di Giosia P, Giorgini P, Stamerra CA, Petrarca M, Ferri C, Sahebkar A. Gender differences in epidemiology, pathophysiology, and treatment of hypertension. *Curr Atheroscler Rep*. 2018;20:13.
50. Fischer M, Baessler A, Schunkert H. Renin angiotensin system and gender differences in the cardiovascular system. *Cardiovasc Res*. 2002;53:672–677.
51. Sullivan JC. Sex and the renin-angiotensin system: inequality between the sexes in response to RAS stimulation and inhibition. *Am J Physiol Regul Integr Comp Physiol*. 2008;294:R1220–R1226.
52. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, Hernandez AF, Fonarow GC. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. *Circulation*. 2012;126:65–75.
53. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *J Am Coll Cardiol*. 2007;50:768–777.
54. Mutlak D, Lessick J, Carasso S, Kapeliovich M, Dragu R, Hammerman H, Agmon Y, Aronson D. Utility of pulmonary hypertension for the prediction of heart failure following acute myocardial infarction. *Am J Cardiol*. 2012;109:1254–1259.
55. Ristow B, Ali S, Ren X, Whooley MA, Schiller NB. Elevated pulmonary artery pressure by Doppler echocardiography predicts hospitalization for heart failure and mortality in ambulatory stable coronary artery disease: the Heart and Soul Study. *J Am Coll Cardiol*. 2007;49:43–49.
56. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Card Fail*. 2017;23:628–651.
57. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Mackey JS, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey A, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation*. 2018;137:e67–e492.
58. Davis KK, Lilienfeld DE, Doyle RL. Increased mortality in African Americans with idiopathic pulmonary arterial hypertension. *J Natl Med Assoc*. 2008;100:69–72.
59. Yang BQ, Assad TR, O'Leary JM, Xu M, Halliday SJ, D'Amico RW, Farber-Eger EH, Wells QS, Hemnes AR, Brittain EL. Racial differences in patients referred for right heart catheterization and risk of pulmonary hypertension. *Pulm Circ*. 2018;8:2045894018764273.
60. Hyduk A, Croft JB, Ayala C, Zheng K, Zheng ZJ, Mensah GA. Pulmonary hypertension surveillance—United States, 1980–2002. *MMWR Surveill Summ*. 2005;54:1–28.
61. Kawut SM, Taichman DB, Archer-Chicko CL, Palevsky HI, Kimmel SE. Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. *Chest*. 2003;123:344–350.
62. Trullas JC, Casado J, Morales-Rull JL. Difficulties in the diagnosis of heart failure in patients with comorbidities. *Rev Clin Esp*. 2016;216:276–285.
63. Greiner S, Jud A, Aurich M, Hess A, Hilbel T, Hardt S, Katus HA, Mereles D. Reliability of noninvasive assessment of systolic pulmonary artery pressure by Doppler echocardiography compared to right heart catheterization: analysis in a large patient population. *J Am Heart Assoc*. 2014;3:e001103. DOI: 10.1161/JAHA.114.001103
64. D'Alto M, Romeo E, Argiento P, D'Andrea A, Vanderpool R, Correra A, Bossone E, Sarubbi B, Calabro R, Russo MG, Naeije R. Accuracy and precision of echocardiography versus right heart catheterization for the assessment of pulmonary hypertension. *Int J Cardiol*. 2013;168:4058–4062.
65. Hemnes AR, Beck GJ, Newman JH, Abidov A, Aldred MA, Barnard J, Berman Rosenzweig E, Borlaug BA, Chung WK, Comhair SAA, Erzurum SC, Frantz RP, Gray MP, Grunig G, Hassoun PM, Hill NS, Horn EM, Hu B, Lempel JK, Maron BA, Mathai SC, Olman MA, Rischard FP, Systrom DM, Tang WHW, Waxman AB, Xiao L, Yuan JX, Leopold JA. PVDOMICS: a multi-center study to improve understanding of pulmonary vascular disease through phenomics. *Circ Res*. 2017;121:1136–1139.

SUPPLEMENTAL MATERIAL

Data S1. Study Design and Population

JHS is a longitudinal, population-based cohort study of cardiovascular disease that recruited noninstitutionalized AA adult participants (N = 5,306) residing in Jackson, Mississippi.[1] This included 4 recruitment pools: random, 17%; volunteer, 22%; secondary family members, 31% and those currently enrolled in Atherosclerosis Risk in Communities (ARIC) Study, 30%. Recruitment was limited to adult AAs 35-84 years old, except in family cohort where subjects 21-34 years of age were eligible. Written informed consent was obtained from participants to participate in the study. Final study cohort included 3,286 participants as depicted in Figure 1. The characteristics of 2,020 excluded participants with no TR jet measurements (excluded from primary analysis owing to inability to estimate PASP in absence of TR jet) compared to the 3,286 study participants are detailed in Table S1. Subjects with no TR jet were significantly younger (53.4 +/- 13.0 years vs 56.5 +/- 12.5 years) and were more likely to be male, to be active smokers, to have higher BMI , to have diabetes and have a reduced Left ventricle ejection fraction than study subjects, but had comparable spirometry patterns and AHA categories of physical activity.

Data S2. Clinical Covariates.

We initially investigated important demographic, clinical, and cardiopulmonary function variables related to the two most common forms of PH [2, 3] (World Health Organization (WHO) Group 2 , secondary to left heart disease and WHO Group 3, secondary to lung disease) as potential risk factors in men and women separately. To evaluate association with Group 2 PH , we included variables related to increased left atrial pressure : coronary heart disease, diabetes, hypertension, higher brachial artery (i.e., systemic) pulse pressure, body mass index, and presence of severe mitral or aortic valvular heart disease. For Group 3 PH we included history of chronic lung disease, smoking status, and spirometry measurements.[4]

Coronary heart disease was considered as present when the participant reported a history of myocardial infarction, abnormal stress test, prior coronary artery bypass graft surgery or prior coronary angioplasty or if there was EKG evidence of a prior myocardial infarction (per Minnesota code). Diabetes was considered as present when the participant reported a history of diabetes, use of diabetes medications, HgbA1c ≥ 6.5, or a fasting blood glucose ≥ 126 mg/dL. Presence of systemic hypertension was defined as subject having a systolic BP ≥ 140 mm Hg, or a diastolic BP ≥ 90 mm Hg, or taking anti-hypertensive medications. Pulse pressure was calculated as the difference between systolic and diastolic BP measurement. High cholesterol was considered present for participants with a total cholesterol ≥240mg/dl or who had use of statin medication. Severe mitral or aortic valve disease was considered as present if the qualitative assessment by echocardiography showed presence of severe mitral regurgitation, mitral stenosis, aortic regurgitation, or aortic stenosis. BMI (Body Mass Index) was calculated as weight in kilograms divided by height in meters squared. BMI was categorized by AHA ideal

cardiovascular health categorization (poor health : BMI >/= 30 kg/m^2 , intermediate health : BMI >/= 25 but < 30 kg/m^2 ; ideal health : BMI < 25 kg/m^2)[5]

Heart rate was measured on a baseline EKG. History of stroke was considered present if the subjects responded to the question "Have you been told by a physician you had a stroke?" in the affirmative at baseline study visit.

Chronic lung disease was considered present if the subjects responded to the question "Has your doctor or health professional ever said you have chronic lung disease, such as bronchitis or emphysema?" in the affirmative. Cigarette smoking status was categorized as never smoker (one who reported having smoked less than 400 cigarettes in one's life), former smoker (smoked >400 cigarettes but not currently smoking), and current smoker.

Obstructive spirometry pattern was considered present if the FEV1/FVC ratio was less than 0.70. This is a standard and widely-used definition for airflow obstruction, based on Global Obstructive Lung Disease task force guidelines [6] Restrictive spirometry pattern was considered present if the FEV1/FVC ratio was ≥ 0.70, but the FVC % predicted was less than 80%. Subjects not having either obstruction or restriction were considered to have normal spirometry pattern. Percent predicted values for FVC were derived from NHANES III data.[7,8] Detailed spirometry procedures for the Jackson Heart Study, including quality control procedures, are available online[9] . A history of heart failure was considered present if the participants responded to the question "Has a doctor ever said you had heart failure or congestive heart failure?" in the affirmative at the time of first annual telephone follow-up. Serum creatinine values in mg/dL were calibrated to the Cleveland Clinic equivalent. The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease formula. JHS Physical

activity (PAC) survey instrument was administered by interview and implementation of a validated JHS Physical activity cohort (JPAC) questionnaire.[10, 11]

Physical activity was categorized according to AHA ideal cardiovascular health guidelines [5]: poor physical activity: 0 minutes of moderate or vigorous physical activity per week; intermediate physical activity: less than 150 minutes of moderate physical activity, less than 75 minutes of vigorous physical activity, or less than 150 minutes of combined moderate and vigorous physical activity per week; and recommended physical activity: ≥ 150minutes of moderate, ≥ 75minutes of vigorous, or ≥ 150 minutes of combined moderate and vigorous physical activity per week[10]. Medications taken at the first study were classified using the Medispan Therapeutic system [9]. Subjects were categorized as taking antihypertensive medication if a beta blocker, calcium channel blocker, antihypertensive or diuretic was taken during the past two weeks.

Data S3. Echocardiographic parameters. Detailed echocardiography procedures are available online (Jackson Heart Study Echocardiography Manual). Briefly, echocardiograms were recorded by trained sonographers and interpreted by experienced cardiologists in the Echocardiography Reading Center located at the University of Mississippi Medical Center. Standard echocardiographic views were obtained and measurements performed by the interpreting physician who was blinded to the participants' clinical data[12] No tissue Doppler measurements were performed. All measurements used were performed in 2-dimensional images. The echocardiography data used for this current study included peak tricuspid regurgitant (TR) jet gradient (trans-tricuspid gradient), pulmonary acceleration time , in

milliseconds ; left atrial diameter index , in mm/m^2 ; unitless ratio of mitral valve peak E wave velocity (in m/sec) to mitral valve peak A valve velocity (in m/sec) and semi-quantitative left ventricular ejection fraction , to nearest 5% . Valvular disease was qualitatively graded. Left ventricular hypertrophy was defined as a left ventricular mass index greater than 51g / (height in meters/100)^2

Data S4. Statistical Analysis:

Missing Data

Missing data for clinical covariates were handled using multiple imputation. Missing data were imputed based on 5 sets of simulated values generated from nonmissing variables using the multiple imputation method in STATA (StataCorp, College Station, TX). Analyses were performed on each of the 5 data sets completed with imputed values and then combined using Rubin's combination rules[13] to consolidate the individual estimates into a single set of estimates using the MI estimate command in STATA.

Table S1. Comparison of baseline characteristics in study participants vs excluded participants.

	Excluded Participants without TR N(%)	Study Participants with TR N(%)	P value
Characteristics	2020	3286	
Male	871 (43.1)	1064 (32.4)	<0.001
Body Mass Index Categories			
Poor Health	1148 (57.0)	1674 (51.1)	<0.001
Intermediate Health	595 (29.6)	1106 (33.7)	
Ideal Health	270 (13.4)	499 (15.2)	
Hypertension	1154 (57.2)	1842 (56.1)	0.42
Diabetes	515 (25.8)	630 (19.4)	<0.001
Hyperlipidemia	794 (45.3)	1266 (44.1)	0.42
History of Coronary Heart Disease	206 (10.7)	334 (10.7)	0.98
Stroke History	88 (4.4)	146 (4.4)	0.88

Heart Failure History	69 (4.7)	112 (4.2)	0.48
Lung Disease History	152 (7.6)	229 (7.0)	0.44
Smoker			
Never	1355 (67.7)	2224 (68.3)	0.004
Former	347 (17.3)	639 (19.6)	
Current	299 (15.0)	394 (12.1)	
Spirometry			
Normal	1279 (68.7)	2209 (71.1)	0.06
Obstructive	159 (8.5)	278 (8.9)	
Restrictive	425 (22.8)	622 (20.0)	
AHA Physical Activity categorization			
Poor Health	978 (48.5)	1634 (49.8)	0.37
Intermediate Health	634 (31.5)	1039 (31.7)	
Ideal health	404 (20.0)	607 (18.5)	
Blood pressure meds Use	935 (50.1)	1573 (51.9)	0.21

Left Ventricular EF < 50%	69 (3.9)	92 (2.8)	0.04
Valvular Heart disease	3 (0.2)	7 (0.2)	0.71
	Median (Q1-Q3)	Median (Q1-Q3)	
Systolic Blood Pressure (mm Hg)	125.66 (116.5-138.0)	125.66 (115.6 – 135.75)	0.02
Pulse Pressure (mm Hg)	51.78 (41.25 – 59.39)	51.78 (41.88 – 59.13)	0.66
Estimated glomerular filtration rate (mL/min/1.73m^2)	97.6 (81.75 -111.72)	94.8 (80.47 -108.37)	<0.001

Table S2. Distribution of Missing Covariates in Analytic Sample.

Characteristic	Missing Values	Percentage
Body Mass Index	7	0.002
Diabetes	39	0.01
Hyperlipidemia	416	0.15
History of Coronary Heart Disease	162	0.05

Table S3. Adjusted beta coefficients for PASP and interaction analysis with gender.

Variable	Adjusted* beta coefficient for gender interaction term (95% CI)	P value for gender interaction term
FEV1	1.62 (0.80 - 2.43)	<0.001
FVC	1.28 (0.58 – 1.98)	<0.001

* Adjusted for age, gender, BMI, pulse pressure, hypertension, diabetes, coronary heart disease, severe mitral or aortic valvular disease, history of chronic lung disease, FEV1, FVC, and gender interaction term for FEV1 or FVC.

Table S4. Association of Clinical Characteristics with PASP stratified by gender.

	Men		**Women**	
Variable	**Adjusted beta-coefficient (95% CI)**	**P value**	**Adjusted beta-coefficient (95% CI)**	**P value**
FEV1	-1.23 (-2.46 - -.01)	0.048	-2.63 (-3.78 - -1.48)	<0.001
FVC	0.45 (-.61 - 1.50)	0.41	0.30 (-.58 - 1.17)	0.50

* Adjusted for age, gender, BMI, pulse pressure, hypertension, diabetes, coronary heart disease, severe mitral or aortic valvular disease, history of chronic lung disease, FEV1, FVC

Supplemental References:

1. Taylor HA, Jr., Wilson JG, Jones DW, Sarpong DF, Srinivasan A, Garrison RJ, Nelson C, Wyatt SB. Toward resolution of cardiovascular health disparities in african americans: Design and methods of the jackson heart study. *Ethnicity & disease*. 2005;15:S6-4-17.
2. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Kumar RK, Landzberg M, Machado RF, Olschewski H, Robbins IM, Souza R. [updated clinical classification of pulmonary hypertension]. *Turk Kardiyoloji Dernegi arsivi : Turk Kardiyoloji Derneginin yayin organidir*. 2014;42 Suppl 1:45-54.
3. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H, Robbins IM, Souza R. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62:D34-41.
4. Choudhary G, Jankowich M, Wu WC. Prevalence and clinical characteristics associated with pulmonary hypertension in african-americans. *PloS one*. 2013;8:e84264.
5. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD. Defining and setting national goals for cardiovascular health promotion and disease reduction: The american heart association's strategic impact goal through 2020 and beyond. *Circulation*. 2010;121:586-613.
6. GOLD. Executive committee, global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. 2019.
7. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J. Interpretative strategies for lung function tests. *Eur Respir J*. 2005;26:948-968.
8. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general u.S. Population. *American journal of respiratory and critical care medicine*. 1999;159:179-187.
9. Jankowich MD, Wu WC, Choudhary G. Association of elevated plasma endothelin-1 levels with pulmonary hypertension, mortality, and heart failure in african american individuals: The jackson heart study. *JAMA cardiology*. 2016;1:461-469.
10. Dubbert PM, Carithers T, Ainsworth BE, Taylor HA, Jr., Wilson G, Wyatt SB. Physical activity assessment methods in the jackson heart study. *Ethnicity & disease*. 2005;15:S6-56-61.
11. Smitherman TA, Dubbert PM, Grothe KB, Sung JH, Kendzor DE, Reis JP, Ainsworth BE, Newton RL, Jr., Lesniak KT, Taylor HA, Jr. Validation of the jackson heart study physical activity survey in african americans. *Journal of physical activity & health*. 2009;6 Suppl 1:S124-132.
12. Samdarshi TE, Taylor HA, Edwards DQ, Liebson PR, Sarpong DF, Shreenivas SS, Howard G, Garrison RJ, Fox ER. Distribution and determinants of doppler-derived diastolic flow indices in african americans: The jackson heart study (jhs). *American heart journal*. 2009;158:209-216.
13. Rubin DB, Schenker N. Multiple imputation in health-care databases: An overview and some applications. *Statistics in medicine*. 1991;10:585-598.