Circulation

ORIGINAL RESEARCH ARTICLE

Cigarette Smoking and Incident Heart Failure

Insights From the Jackson Heart Study

BACKGROUND: Cigarette smoking has been linked with several factors associated with cardiac dysfunction. We hypothesized that cigarette smoking is associated with left ventricular (LV) structure and function, and incident heart failure (HF) hospitalization.

METHODS: We investigated 4129 (never smoker n=2884, current smoker n=503, and former smoker n=742) black participants (mean age, 54 years; 63% women) without a history of HF or coronary heart disease at baseline in the Jackson Heart Study. We examined the relationships between cigarette smoking and LV structure and function by using cardiac magnetic resonance imaging among 1092 participants, cigarette smoking and brain natriuretic peptide levels among 3325 participants, and incident HF hospitalization among 3633 participants with complete data.

RESULTS: After adjustment for confounding factors, current smoking was associated with higher mean LV mass index and lower mean LV circumferential strain (P<0.05, for both) in comparison with never smoking. Smoking status, intensity, and burden were associated with higher mean brain natriuretic peptide levels (all P<0.05). Over 8.0 years (7.7–8.0) median follow-up, there were 147 incident HF hospitalizations. After adjustment for traditional risk factors and incident coronary heart disease, current smoking (hazard ratio, 2.82; 95% confidence interval, 1.71–4.64), smoking intensity among current smokers (≥20 cigarettes/d: hazard ratio, 3.48; 95% confidence interval, 1.65–7.32), and smoking burden among ever smokers (≥15 pack-years: hazard ratio, 2.06; 95% confidence interval, 1.29–3.3) were significantly associated with incident HF hospitalization in comparison with never smoking.

CONCLUSIONS: In blacks, cigarette smoking is an important risk factor for LV hypertrophy, systolic dysfunction, and incident HF hospitalization even after adjusting for effects on coronary heart disease.

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Clinical Perspective

What Is New?

- Cigarette smoking is a well-known risk factor for atherosclerotic cardiovascular disease; however, less is known about the risk for heart failure (particularly in blacks).
- We found that current cigarette smoking status, smoking intensity (cigarettes per day), and smoking burden (pack-years) were independently associated with higher left ventricular mass, lower left ventricular strain, higher brain natriuretic peptide levels, and higher risk of incident heart failure hospitalization in blacks.
- These relationships were significant after adjustment for coronary heart disease, suggesting mechanisms beyond atherosclerosis probably contribute to myocardial dysfunction and increased risk of heart failure in smokers.

What Are the Clinical Implications?

- Blacks are disproportionately affected by cardiovascular diseases including heart failure and they are more likely to die of smoking-related diseases than whites.
- Our findings suggest that smoking is associated with structural and functional left ventricular abnormalities that lead to heart failure in blacks and that smoking cessation should be encouraged in those with risk factors for heart failure.

Cigarette smoking is a risk factor for heart failure (HF) independent of traditional risk factors.[1–5] Whereas cigarette smoking increases the risk of coronary heart disease (CHD), a major cause of HF, there may be other effects of smoking that result in cardiac dysfunction and HF.[6] For example, smoking acutely increases systolic and diastolic blood pressure, total systemic vascular resistance, pulmonary artery pressure, and pulmonary vascular resistance, all known risk factors for HF.[7] Furthermore, smoking is associated with carbon monoxide exposure, which has been reported to increase oxidative stress and lead to impaired mitochondrial function, inflammation, impaired endothelial function, and worsening renal function, all of which have been implicated in the pathophysiology of HF.[8–13]

Blacks have a doubling in the incidence of HF in comparison with other races.[14] The prevalence of current cigarette smoking among blacks has declined in recent years, but remains ≈18% among adults.[15] Although some epidemiological studies have demonstrated a significant association of current cigarette smoking with risk of developing HF, there are limited data specific to blacks who are substantially affected by cardiovascular diseases.

We hypothesized that cigarette smoking is associated with cardiac remodeling, left ventricular dysfunction, and incident HF hospitalization in blacks. To test this hypothesis, we examined the association of cigarette smoking status, intensity, and burden with cardiac structure and function and incident HF hospitalization in the JHS (Jackson Heart Study).

METHODS

The data, analytic methods, and study materials can be made available to other researchers for purposes of reproducing the results or replicating the procedure by following the Jackson Heart Study publications procedures and data use agreements.

Study Participants

The JHS is a large prospective community-based observational study designed to investigate risk factors for cardiovascular diseases in blacks. Details of the JHS study design, recruitment, and data collection have been described previously.[16] In brief, 5301 black participants residing in the Jackson, Mississippi, tricounty area (Hinds, Rankin, and Madison) were recruited for the baseline examination between 2000 and 2004 and completed 3 subsequent study follow-up visits (visit 1, 2000–2004; visit 2, 2005–2008; visit 3, 2009–2012). The JHS was approved by the institutional review boards of Jackson State University, Tougaloo College, and the University of Mississippi Medical Center in Jackson, Mississippi. All study participants provided written informed consent.

For the present analysis, we excluded all individuals with a history of CHD or HF (n=717), missing CHD/HF data (n=5), missing information on smoking status (n=33), or missing information on study covariates (n=422) at visit 1 (Figure 1).

Smoking Information

Smoking information was obtained via questionnaire at both visits 1 and 3. Participants who smoked >400 cigarettes in their lifetime were defined as ever smokers. Participants who gave a positive response to the question, "Do you now smoke cigarettes?" were classified as current smokers. Those who responded negatively to both of these questions were classified as never smokers.[12] Participants who smoked >400 cigarettes but no longer smoked at the time of the examination were classified as former smokers. Cigarettes per day (smoking intensity) and pack-years (smoking burden) were also collected. Smoking burden and data related to time since quitting in former smokers is available in Table I in the online-only Data Supplement.

Clinical Covariates

At each examination, systolic and diastolic blood pressures were measured in the right arm of participants twice using the random-0 blood pressure sphygmomanometer (Hawksley and Sons Limited). The first blood pressure was obtained after allowing the participant to rest for 5 minutes in a seated position, and the second blood pressure was obtained after waiting 1 additional minute. The average of the 2 measurements was used. Body mass index was calculated as body weight

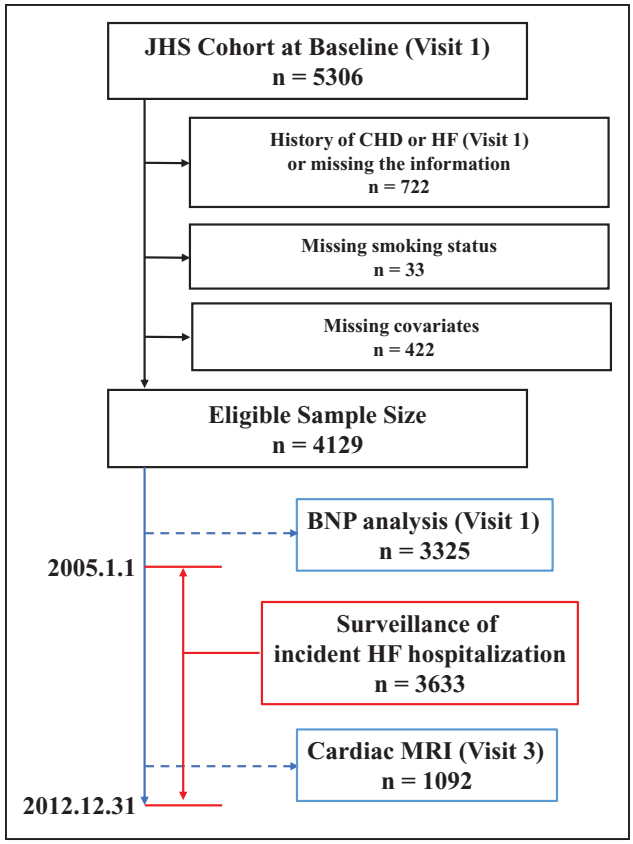

Figure 1. Exclusion criteria and the numbers of participants for each study.
BNP indicates brain natriuretic peptide; CHD, coronary heart disease; HF, heart failure; JHS, Jackson Heart Study; and MRI, magnetic resonance imaging.

(kg)/height (m^2). Self-reported antihypertensive medication use was collected at the time of each examination. Venous blood samples were drawn from each participant after >12 hours of fasting. Fasting plasma glucose, hemoglobin A1c, and serum creatinine levels were assessed by using standard laboratory techniques. Diabetes mellitus was defined as the use of diabetes medications, a hemoglobin A1c ≥6.5%, or a fasting blood glucose ≥126 mg/dL at baseline. Estimated glomerular filtration rate was calculated by using the Modification of Diet in Renal Disease Study equation.[17]

Cardiac and Aortic Magnetic Resonance Imaging

Cardiac magnetic resonance (CMR) images were obtained with 1.5T MR Siemens Espree scanner (Siemens Medical Solutions) at visit 3 (Figure 1) in a randomly selected subset of 1092 participants without incident CHD between visits 1 and 3. Cine and tagged imaging were performed to assess LV mass, volumes, and deformation parameters. LV mass and volumes were indexed to body surface area measured at visit 3. LV peak midwall circumferential strain was assessed at the apex, middle, and base of the LV, and these 3 variables were averaged to determine total LV circumferential strain. All strain variables are negative values; more negative values indicate greater circumferential shortening. The coefficients of variation of each LV strain variable are as follows: base strain, 19.0%; mid strain, 20.2%; apex strain, 18.3%; and total strain, 15.5%. CMR aortic pulse wave velocity was calculated as follows: pulse wave velocity (m/s) = distance (mm)/transit time between ascending to the diaphragm level of descending aorta (ms). Transit time was calculated as the average time difference using the least-squares estimate between all data points on the systolic upslope of the ascending and descending aortic flow curves after peak flow normalization, and distance from ascending to descending aorta was measured using the oblique sagittal image through the thoracic aorta.

Brain Natriuretic Peptide Measurements

Plasma brain natriuretic peptide (BNP) levels were measured at visit 1 using a chemiluminescent immunoassay performed on the Siemens Advia Centaur (Siemens Medical Solutions) (Figure 1).[18] The coefficient of variation of the assay was previously described.[18] We included the histogram of raw BNP data in the Figure in the online-only Data Supplement.

Outcomes of the Longitudinal Study

The primary outcome was time to HF hospitalization. In the JHS cohort, HF hospitalization surveillance began January 1, 2005. Among participants who survived to January 1, 2005, we assessed the cumulative incidence of HF hospitalization from January 1, 2005, through December 31, 2012 (Figure 1). Potential HF hospitalizations were identified and adjudicated as previously described.[19] In brief, hospitalization data were obtained from the hospital discharge index from all catchment area hospitals and annual follow-up information. Hospitalization data from noncatchment area hospitals were obtained after participant consent. The self-reported data from annual follow-up were confirmed with the hospital discharge index data. The primary diagnoses based on *International Classification of Diseases, Ninth Revision, Clinical Modification* codes were reviewed by trained medical personnel and adjudicated by trained adjudicators based on signs and symptoms, clinical documentation, laboratory tests, chest x-ray films, and other imaging modalities including echocardiography, multiple gated acquisition scans, and magnetic resonance imaging.[20] Incident CHD was ascertained through directed patient queries during an annual telephone follow-up and ongoing surveillance of hospitalizations, and subsequently confirmed through the review of hospital records.

Statistical Analysis

Data are presented as mean with SDs for normally distributed continuous variables, median with interquartile ranges for nonnormally distributed continuous variables, and frequencies and proportions for categorical variables. ANOVA with post hoc Bonferroni test, Mann-Whitney *U* test, and χ^2 test were used for comparison of variables between smoking status groups if applicable. Relationships between smoking variables and BNP levels and cardiac structure and function were examined as cross-sectional analyses at visit 1 and visit 3, respectively. Relationships between smoking variables and incident HF hospitalization were assessed as prospective longitudinal analyses.

Cross-Sectional Study

Relationships between smoking status (current, former, never), intensity among current smokers (cigarettes/d), and burden among ever smokers (pack-years), and cardiac structure and function measured using CMR (LV volume variables, LV ejection fraction, LV mass index, LV mass/volume, and LV systolic strain variables) and BNP levels were assessed by using linear regression analysis. Two models, minimally and further adjusted models, were constructed to evaluate the associations of smoking and cardiac structure and function. Model 1 included adjustment for age and sex, whereas model 2, in addition, included body mass index, systolic blood pressure, use of antihypertension medication, and history of diabetes based on a previous meta-analysis, and we additionally included estimated glomerular filtration rate to determine if the effect of smoking is independent of its effect on renal function.[12,21] Medication use may affect the relationship between smoking status and LV structure and function. Thus, we created another model to examine the relationship between smoking status and LV structure and function assessed by cardiac magnetic resonance imaging with additional adjustment for classes of medications (calcium channel blocker use, β-blocker use, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, and diuretics use; Table II in the online-only Data Supplement) instead of antihypertensive medication use. To examine the possibility of unmeasured differences in blood pressure that may affect the associations, we additionally included average ambulatory systolic blood pressure instead of office systolic blood pressure (model 3). Ambulatory systolic blood pressure monitoring was performed as previously described.[22] Ambulatory systolic blood pressure was evaluated only at visit 1, and the number of included participants who underwent ambulatory systolic blood pressure monitoring was small (n=711). Therefore, we were only able to examine the relationship between smoking status and BNP levels (model 3). Aortic valve stenosis and mitral valve regurgitation can increase LV load and promote LV hypertrophy. Thus, we additionally adjusted for aortic valve stenosis and mitral valve regurgitation severity evaluated by echocardiography at visit 1. Analyses of smoking status and BNP levels (Table III in the online-only Data Supplement, model 4), and smoking status and incident HF hospitalization (Table IV in the online-only Data Supplement, model 5) were additionally performed with adjustment for the grade of aortic valve stenosis and mitral valve regurgitation. Detailed information on the echocardiographic methods is described in the online-only Data Supplement. BNP levels were natural log transformed because they were not normally distributed. To visualize the relationship between smoking intensity and burden and BNP levels, restricted cubic spline curves were used. The analysis was adjusted using multiple covariates (model 2), and we used 3 knots. Knots were located at 10 (half-pack), 20 (pack), and 40 cigarettes (2 packs)/d for intensity, and 7.5, 15, and 30 pack-years for burden. For this analysis, the y axes were expressed as adjusted geometric mean ratios with 95% confidence interval (CI).

Longitudinal Study

We constructed Kaplan-Meier curves for cumulative survival free from incident HF for smoking status (current, former, never), intensity among current smokers (cigarettes/d), and burden among ever smokers (pack-years), and compared by using log-rank tests. Cox proportional hazards models were used to estimate the hazard ratios (HRs) of incident HF by using smoking status, intensity, and burden category groups. Censoring was applied to both loss to follow-up and deaths. The assumption of proportionality was tested by using Schoenfeld residuals. No significant deviations from proportionality were observed. Several models were constructed to evaluate associations of smoking information with outcomes. The same models that were used in the cross-sectional analyses were used, with the exception of model 2, in which incident CHD was additionally included as a time-dependent variable to evaluate the influence of incident CHD on incident HF. All statistical analyses were performed with STATA version 14 (STATA Corp). A 2-sided *P* value of <0.05 was considered significant.

RESULTS

Baseline Characteristics

Among the study participants (n=4129), 503 (12%) were current smokers, 742 (18%) were former smok-

Table 1. Baseline Characteristics

Variable	Overall (n=4129)	Never Smoker (n=2884)	Former Smoker (n=742)	Current Smoker (n=503)
Age, y	54±13	53±13	60±11	51±11
Female sex, n (%)	2607 (63)	1983 (69)	381 (51)	243 (48)
BMI, kg/m^2	31±7	32±7	31±6	29±7
SBP, mm Hg	127±17	126±16	128±17	128±18
DBP, mm Hg	76±9	76±9	75±9	77±9
SBP (ABPM), mm Hg	135±28	135±32	136±15	137±16
DBP (ABPM), mm Hg	79±27	79±32	78±10	82±10
Hypertension, n (%)	2084 (50)	1398 (49)	453 (61)	233 (46)
Diabetes, n (%)	691 (17)	458 (16)	168 (23)	65 (13)
Current alcohol use, n (%)	1964 (48)	1223 (42)	367 (50)	374 (74)
Physical activity, n (%)				
Poor	1949 (47)	1321 (46)	340 (46)	288 (57)
Intermediate	1341 (32)	955 (33)	253 (34)	133 (26)
Recommended	839 (20)	608 (21)	149 (20)	82 (16)
Tc/HDL ratio	4.1±1.3	4.1±1.3	4.2±1.4	4.2±1.5
eGFR, mL·min^{-1}·1.73 m^{-2}	87±17	87±17	85±17	93±18
Calcium channel blocker use	650 (16)	440 (16)	154 (21)	56 (11)
β-Blocker use	301 (7)	201 (7)	68 (9)	32 (7)
ACEI or ARB use	506 (12)	345 (12)	126 (17)	35 (7)
Diuretic use	1072 (27)	739 (26)	249 (34)	84 (17)
Average number of cigarettes/d			10 (6–20)	10 (8–20)
Pack-years of cigarettes			21 (11–39)	17 (9–31)

ABPM indicates ambulatory blood pressure; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; and Tc/HDL ratio, total cholesterol/high density lipoprotein cholesterol ratio.

ers, and 2884 (70%) were never smokers. Never smokers were more likely to be women than the other smoking status groups. Former smokers were older and had a higher prevalence of hypertension and diabetes mellitus than the other smoking status groups. Current smokers had a higher prevalence of current drinking, a lower prevalence of achieving the recommended physical activity level, and a higher mean estimated glomerular filtration rate than the other smoking status groups. The prevalence of taking calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and diuretics was higher in former smokers than in the other groups, and the prevalence of taking these antihypertensive medications in current smokers was lower than in never smokers (Table 1).

Smoking Status and Cardiac Structure and Function Assessed by CMR at Visit 3

After adjustment for confounding factors, current smoking was associated with higher mean LV mass index (β-coefficient, 5.24; 95% CI, 2.71–7.77) and LV mass/volume ratio (β-coefficient, 0.12; 95% CI, 0.06–0.18), whereas smoking status was not associated with mean LV volume measurements or LV ejection fraction (Table 2). However, current smoking was significantly associated with lower mean LV systolic function assessed with LV circumferential strain (total peak systolic circumferential strain: β-coefficient, 0.74; 95% CI, 0.26–1.22). Current smoking also was associated with higher mean pulse wave velocity in model 2 (β-coefficient, 1.25; 95% CI, 0.09–2.41) (Table 2). After additional adjustment for medication class (model 3), the relationship between smoking status and cardiac structure and function was not remarkably changed (Table II in the online-only Data Supplement). However, in this model, former smoking was associated with lower LV mass index.

Smoking Status, Intensity, and Burden and BNP Levels at Visit 1

After adjustment for confounding factors, current smoking (model 2: β-coefficient, 0.182; 95% CI, 0.074–0.290), smoking intensity among current smokers (model 2, ≥20 cigarettes/d versus never smokers: β-coefficient, 0.298; 95% CI, 0.122–0.474), and smoking burden among ever smokers (model 2, ≥30 pack-years versus never smoker: β-coefficient, 0.139; 95% CI, 0.018–0.260) were significantly associated with higher mean BNP levels (Tables 3 through 5). Even after adjustment for mean systolic ambulatory blood pressure instead of office systolic blood pressure, the association was not remarkably changed (Tables 3 through 5, model 3). After adjustment for grade of aortic valve stenosis and mitral valve regurgitation severity, the association was not remarkably changed (Table III in the

Table 2. Smoking Status and Cardiac Structure and Function Assessed by CMR at Visit 3

Variable	Model 1			Model 2		
	Never Smoker (n=791)	Former Smoker (n=198)	Current Smoker (n=103)	Never Smoker (n=791)	Former Smoker (n=198)	Current Smoker (n=103)
		β (95% CI)	β (95% CI)		β (95% CI)	β (95% CI)
LVEDVI, mL/m²	Ref.	–2.27 (–4.55 to 0.14)	–1.86 (–4.81 to 1.08)	Ref.	–2.09 (–4.36 to 0.18)	–2.35 (–5.29 to 0.60)
LVESVI, mL/m²	Ref.	–1.06 (–2.55 to 0.43)	0.12 (–1.80 to 2.05)	Ref.	–1.02 (–1.92 to 1.94)	0.01 (–1.92 to 1.94)
SVI, mL/m²	Ref.	–1.21 (–2.68 to 0.25)	–1.99 (–3.88 to 0.10)	Ref.	–1.07 (–2.53 to 0.39)	–2.35 (–4.24 to –0.47)
LVEF, %	Ref.	0.01 (–1.41 to 1.43)	–0.75 (–2.58 to 1.08)	Ref.	0.09 (–1.33 to 1.51)	–0.82 (–2.66 to 1.02)
LVMI, g/m²	Ref.	–2.09 (–4.21 to 0.02)	4.97 (2.24 to 7.69)†§	Ref.	–1.73 (–3.69 to 0.22)	5.24 (2.71 to 7.77)†§
LV mass/volume	Ref.	0.01 (–0.04 to 0.06)	0.10 (0.04 to 0.17)†§	Ref.	0.01 (–0.03 to 0.06)	0.12 (0.06 to 0.18)†§
LV strain‡						
Total strain, %	Ref.	0.02 (–0.36 to 0.41)	0.56 (0.07 to 1.06)*§	Ref.	0.01 (–0.37 to 0.38)	0.74 (0.26 to 1.22)†§
Base strain, %	Ref.	0.08 (–0.39 to 0.55)	0.60 (–0.01 to 1.20)	Ref.	0.08 (–0.38 to 0.55)	0.71 (0.12 to 1.31)*§
Mid strain, %	Ref.	–0.13 (–0.63 to 0.38)	0.50 (–0.15 to 1.15)	Ref.	–0.16 (–0.66 to 0.33)	0.71 (0.07 to 1.34)*§
Apex strain, %	Ref.	0.16 (–0.31 to 0.63)	0.61 (0.01 to 1.21)*§	Ref.	0.14 (–0.32 to 0.59)	0.82 (0.23 to 1.41)†§
PWV, m/s	Ref.	0.23 (–0.65 to 1.12)	1.42 (0.27 to 2.57)*§	Ref.	0.24 (–0.64 to 1.12)	1.25 (0.09 to 2.41)*§

Visit 3 smoking status information was used for the analysis. Model 1 was adjusted for age and sex. Model 2 was further adjusted for systolic blood pressure, antihypertensive medication use, body mass index, diabetes mellitus, and estimated glomerular filtration rate. CI indicates confidence interval; CMR, cardiac magnetic resonance; LV, left ventricular; LVEDVI, left ventricular end-diastolic volume indexed; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume indexed; LVMI, left ventricular mass index; Ref, reference; and PWV, pulse wave velocity from ascending aorta to descending aorta.

*P<0.05.

†P<0.01.

‡Strain indicators represent mean peak systolic circumferential strain.

§Statistically significant findings.

Table 3. Smoking Status and BNP Levels (Log Transformed) at Visit 1

Model	Never Smoker	Former Smoker	Current Smoker
		β (95% CI)	β (95% CI)
Model 1	Ref.	0.000 (–0.094 to 0.095)	0.218 (0.111 to 0.325)†‡
Model 2	Ref.	0.042 (–0.053 to 0.137)	0.182 (0.074 to 0.290)†‡
Model 3	Ref.	0.165 (–0.026 to 0.357)	0.329 (0.061 to 0.597)*‡

Model 1 was adjusted for age and sex. Model 2 was further adjusted for body mass index, systolic blood pressure, antihypertensive medication use, diabetes mellitus, and estimated glomerular filtration rate. Model 3 was adjusted for model 2, but including mean systolic ambulatory blood pressure instead of office systolic blood pressure. BNP indicates brain natriuretic peptide; CI, confidence interval; and Ref, reference.

*P<0.05.

†P<0.01.

‡Statistically significant findings.

online-only Data Supplement). Figure 2 shows the restricted cubic spline between smoking intensity (average cigarettes/d), smoking burden (pack-years), and log transformed BNP levels. Log-transformed BNP levels were positively associated with increased smoking intensity and burden.

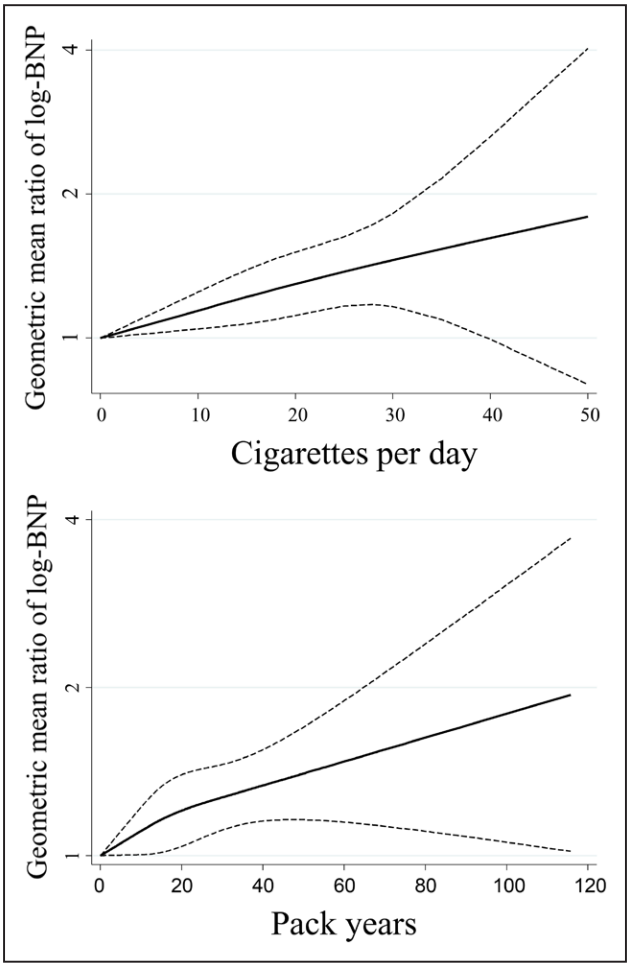

Figure 2. Smoking intensity, burden, and brain natriuretic peptide levels.
Restricted cubic spline analyses demonstrate increased log-transformed BNP levels with increased smoking intensity (**Top**) and burden (**Bottom**). BNP indicates brain natriuretic peptide.

Smoking Status, Intensity and Burden, and Incident HF Hospitalizations

At the time of January 1, 2005, 3633 participants of 4129 were alive and eligible for the longitudinal analysis. Over a median follow-up of 8.0 years (interquartile range, 7.7–8.0 years), there were 147 incident HF hospitalizations (incidence rate, 5.46/1000 person-years). Both former and current smokers had a higher incidence of HF than never smokers (log-rank P<0.01) (Figure 3). Current smoking was associated with increased incident HF hospitalizations after adjustment for conventional risk factors and incident CHD as a time-dependent variable (HR, 2.82; 95% CI, 1.71–4.64) (Table 6). Furthermore, smoking intensity among current smokers (model 2, ≥20 cigarettes/d versus never smoker: HR, 3.48; 95% CI, 1.65–7.32) was associated with incident HF hospitalization in multivariable analyses (Table 7). Smoking burden among ever smokers was associated with incident HF, albeit not linearly (model 2, ≥15 pack-years versus never smoker: HR, 2.06; 95% CI, 1.29–3.33, P<0.01 and ≥30 pack-years versus never smoker: HR, 1.60; 95% CI, 1.00–2.56) (Table 8). After additional adjustment for valvular heart disease, the association was not remarkably changed (Table IV in the online-only Data Supplement, model 5).

DISCUSSION

In our community-based cohort of blacks, current smoking was associated with a higher LV mass and lower LV

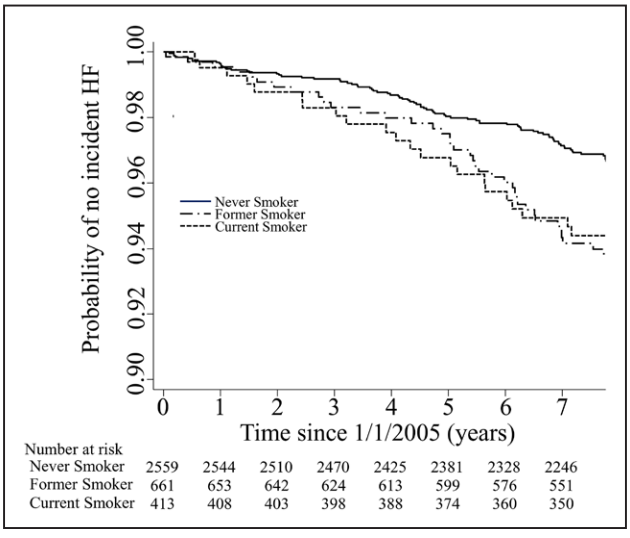

Figure 3. Kaplan-Meier survival curves of the study participants.
Kaplan-Meier curves separated by smoking status. HF indicates heart failure.

Table 4. Smoking Intensity and BNP Levels (Log Transformed) at Visit 1

Model	Never Smoker	<10 Cigarettes/d	10–19 Cigarettes/d	≥ 20 Cigarettes/d
		β (95% CI)	β (95% CI)	β (95% CI)
Model 1	Ref.	0.101 (–0.086 to 0.288)	0.203 (0.038 to 0.367)*†	0.341 (0.165 to 0.516)†
Model 2	Ref.	0.065 (–0.123 to 0.252)	0.151 (–0.015 to 0.317)	0.298 (0.122 to 0.474)†
Model 3	Ref.	0.135 (–0.297 to 0.568)	0.321 (–0.098 to 0.741)	0.711 (0.206 to 1.215)†

Model 1 was adjusted for age and sex. Model 2 was further adjusted for body mass index, systolic blood pressure, antihypertensive medication use, diabetes mellitus, and estimated glomerular filtration rate. Model 3 was adjusted for model 2, but including mean systolic ambulatory blood pressure instead of office systolic blood pressure. Smoking intensity analyses include only never smoker and current smoker. BNP indicates brain natriuretic peptide; CI, confidence interval; and Ref, reference.

*P<0.01.

†Statistically significant findings.

circumferential strain assessed by CMR. Current smoking status and higher levels of smoking intensity and burden were associated with higher mean BNP levels at baseline. Furthermore, current smoking and higher levels of smoking intensity and burden also were associated with increased risk of incident HF hospitalization after adjusting for possible confounding factors including incident CHD.

Limited evidence on the relationship between smoking and HF currently exists.[1–5,23,24] In the Health ABC study (Aging, and Body Composition), both current smoking and past smoking were associated with incident HF independently of incident CHD, and smoking burden was associated with incident HF among former smokers, but not among current smokers.[1] The impact of current smoking on incident HF was higher in our study (HRs 1.93 versus 2.82 in ours) than in their study. To our knowledge, their study was the first that examined the relationship between smoking status and incident HF with adjustment for incident CHD, and the examination of the relationships between smoking burden and incident HF, as well. Our study results are consistent with the Health ABC Study, and extend the findings to a large cohort of blacks. However, in contrast to the Health ABC Study, our study showed dose-dependent associations of smoking intensity among current smokers on incident HF accounting for incident CHD. This difference may be attributed to the difference in the numbers of current smokers in their study (n=221) and ours (n=503). In their study, past smoking was associated with incident HF, and there was dose dependency between smoking burden and incident HF among former smokers. Thus, the relationship between smoking behavior and incident HF could be different because of other factors including different ethnicities (40% blacks in the Health ABC Study and 100% blacks in our study). Recently published articles reported the relationships between smoking and different phenotypes of incident HF. In the PREVEND study (The Prevention of Renal and Vascular Endstage Disease Intervention Trial), current smoking was associated with incident HF with reduced ejection fraction.[4] However, in the Framingham Heart Study, current smoking was associated with incident HF with preserved ejection fraction.[3] In the JHS, the information on phenotypes of incident HF is currently not available, and further investigation is warranted to determine whether smoking status is associated with specific phenotypes of incident HF in blacks.

There are several previous studies that examined the relationship between smoking and LV mass.[25–30] Many of them showed a positive association; however, there are some studies that showed neutral or negative associations.[27,28] We showed a positive association between current smoking and LV mass among those without CHD. These observations are supported by several previous studies that demonstrated a positive relationship between current smoking and LV hypertrophy.[25,26] Our study

Table 5. Smoking Burden and BNP Levels (Log Transformed) at Visit 1

Model	Never Smoker	< 7.5 Pack-Years	7.5–15 Pack-Years	15–30 Pack-Years	≥30 Pack-Years
		β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Model 1	Ref.	0.036 (–0.132 to 0.204)	0.083 (–0.061 to 0.228)	0.075 (–0.050 to 0.200)	0.119 (–0.002 to 0.240)
Model 2	Ref.	0.030 (–0.139 to 0.199)	0.104 (–0.040 to 0.248)	0.069 (–0.055 to 0.193)	0.139 (0.018 to 0.260)*‡
Model 3	Ref.	–0.001 (–0.385 to 0.384)	0.112 (–0.216 to 0.441)	0.213 (–0.056 to 0.482)	0.375 (0.124 to 0.626)†‡

Model 1 was adjusted for age and sex. Model 2 was further adjusted for body mass index, systolic blood pressure, antihypertensive medication use, diabetes mellitus, and estimated glomerular filtration rate. Model 3 was adjusted for model 2, but including mean systolic ambulatory blood pressure instead of office systolic blood pressure. Smoking burden analyses include never smoker and ever smoker. BNP indicates brain natriuretic peptide; CI, confidence interval; and Ref, reference.

*P<0.05.

†P<0.01.

‡Statistically significant findings.

Table 6. Smoking Status and Incident HF Hospitalization

Model	Never Smoker	Former Smoker	Current Smoker
		HR (95% CI)	HR (95% CI)
Model 1	Ref. (1)	1.46 (0.99–2.13)	2.25 (1.39–3.65)†‡
Model 2	Ref. (1)	1.44 (0.98–2.12)	2.82 (1.71–4.64)†‡

Model 1was adjusted for age and sex. Model 2 was further adjusted for systolic blood pressure, antihypertensive medication use, body mass index, diabetes mellitus, estimated glomerular filtration rate, and incident coronary heart disease as a time-dependent variable. CI indicates confidence interval; HF, heart failure; HR, hazard ratio; and Ref, reference.

*P<0.05.

†P<0.01.

‡Statistically significant findings.

confirmed this finding in a large community-based cohort of blacks. It is important to note that our study used CMR data. CMR is a more accurate technique for assessment of LV wall thickness, volumes, and ejection fraction than echocardiography; therefore, CMR offers diagnostic advantages over echocardiography.[31–33] Furthermore, our results are consistent with other studies evaluating risk factors such as smoking and CMR-derived measures of cardiac structure.[29] One prior study that showed a negative association between smoking and LV mass or LV mass index used a unique cohort of Army Training Regiment recruits with an average age of 20 years.[28] Thus, the results of that study may not be generalizable to the general community or older smokers. In our analysis, after additional adjustment for class of medication use, former smoking was associated with lower LV mass index. The mechanism of this association is unclear at this point, and further investigation on this issue is warranted.

A recently published study showed a significant correlation between current smoking and LV diastolic dysfunction assessed by tissue Doppler echo imaging.[26] This study also found a nonsignificant relationship between smoking and global longitudinal strain. Another study showed an adverse association between smoking status and burden on LV circumferential strain assessed by CMR among those without any symptoms or history of cardiovascular disease.[34] These study findings are somewhat limited by their cross-sectional design and lack of HF outcomes. Our study builds on this work by using a large cohort of blacks and demonstrating and linking the associations of adverse structural and functional cardiac effects of cigarette smoking with incident HF hospitalizations.

In our study, smoking status, intensity, and burden were associated with higher BNP levels. Nadruz and colleagues[35] showed that, among those free of overt CHD and HF, cumulative cigarette exposure assessed by pack-years was associated with higher N-terminal pro-BNP levels, and active smokers had a higher incidence of elevated N-terminal pro-BNP levels after 15 years of follow up. Otsuka and colleagues[36] also showed smoking status was positively associated with higher N-terminal pro-BNP levels. Our study results showed that all measures of smoking (status, intensity, and burden) were associated with higher BNP levels, and extended these findings to a large cohort of blacks. Both larger LV mass index and higher BNP levels reflect higher LV wall stress. Based on our findings, it is possible that current smoking, smoking intensity, and smoking burden are associated with higher LV wall stress, increasing the risk of HF.

Cigarette smoking has been associated with higher levels of inflammatory cytokines and dysfunction and death of endothelial cells through increased oxidative stress.[9,10,37,38] Endothelial dysfunction and inflammation may affect cardiac structure and function either through direct influences on the myocardium or indirectly by accelerating arterial atherosclerosis and augmented LV afterload. In turn, carbon monoxide exposure may cause LV hypertrophy and systolic dysfunction independently of its effect on endothelial function or blood pressure.[11] These collective effects of smoking may result in the larger LV mass and systolic dysfunction seen in our study. Furthermore, cigarette smoking is independently associated with worsening of kidney function.[12] Thus, cigarette smoking–related alterations of cardiac structure and function, combined with impairment of renal function, may lead to incident HF independently of CHD. In this study, smoking burden among ever smokers was associated with incident HF, albeit nonlinearly. This may be related to a longer time since quitting in the group with the highest smoking burden (≥30 pack-

Table 7. Smoking Intensity and Incident HF Hospitalization

Model	Never Smoker	<10 Cigarettes/d	10–19 Cigarettes/d	≥20 Cigarettes/d
		HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1	Ref. (1)	1.42 (0.52–3.89)	2.08 (0.99–4.35)	2.67 (1.30–5.50)†‡
Model 2	Ref. (1)	1.57 (0.57–4.35)	2.64 (1.24–5.62)*‡	3.48 (1.65–7.32)†‡

Model 1was adjusted for age and sex. Model 2 was further adjusted for systolic blood pressure, antihypertensive medication use, body mass index, diabetes mellitus, estimated glomerular filtration rate, and incident coronary heart disease as a time-dependent variable. Smoking intensity and burden analyses include only never smoker and current smoker. The number of each smoking status is as follows: never smoker, n=2884; former smoker, n=742; and current smoker, n=503. The number of each smoking intensity is as follows: <10 cigarettes/d, n=143; 10–19 cigarettes/d, n=187; ≥20 cigarettes/d, n=162. CI indicates confidence interval; HF, heart failure; HR, hazard ratio; and Ref, reference.

*P<0.05.

†P<0.01.

‡Statistically significant findings.

Table 8. Smoking Burden and Incident HF Hospitalization

Model	Never Smoker	<7.5 Pack-Years	7.5–15 Pack-Years	15–30 Pack-Years	≥30 Pack-Years
		β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Model 1	Ref.	0.304 (0.042–2.192)	1.349 (0.701–2.598)	2.194 (1.385–3.475)*†	1.479 (0.928–2.356)
Model 2	Ref.	0.310 (0.043–2.240)	1.425 (0.735–2.765)	2.056 (1.290–3.275)*†	1.601 (1.002–2.557)*†

Model 1was adjusted for age and sex. Model 2 was further adjusted for systolic blood pressure, antihypertensive medication use, body mass index, diabetes mellitus, estimated glomerular filtration rate, and incident coronary heart disease as a time-dependent variable. The number of each smoking burden is as follows: <7.5 pack-years, n=234; 7.5–15 pack-years, n=256; 15–30 pack-years, n=362; and ≥30 pack-years, n=393. CI indicates confidence interval; HF, heart failure; and Ref, reference.

*P<0.05.

†Statistically significant findings.

years). Regardless, higher smoking burdens (both ≥15 pack-years and ≥30 pack-years) were significantly associated with more incident HF hospitalization.

In the current study, former smoking was not associated with adverse cardiac remodeling, impaired cardiac function, BNP levels, or incident HF hospitalization after adjusting for possible confounding factors. These findings suggest that smoking cessation may be an important strategy to reduce the risk of impaired cardiac function and HF in current smokers.

Our study has a few limitations including lack of information about the type of cigarettes (including tar concentration or menthol) that the participants smoked. Self-reported smoking status was not confirmed with cotinine levels, which are currently unavailable in JHS. Our data were obtained from an all-black cohort in Jackson, Mississippi, and may not be generalizable to other ethnic/racial groups or other regions. Unmeasured confounding may have influenced the results. It is also possible that HF cases may have been missed (or misclassified); however, the definition for HF that was used has been previously used and validated in other JHS analyses, and in ARIC (Atherosclerosis Risk in Communities Study), as well. In our study, the relationships between smoking status and BNP levels and cardiac structure and function were assessed at visits 1 and 3, respectively. The longitudinal relationship between smoking status and HF hospitalization was evaluated beginning 5 years after visit 1 (2005). Therefore, time differences of performed examinations may limit the causal inference of the effect of smoking on cardiac structure and function and BNP with the relationship between smoking and HF hospitalization. Finally, because of the lack of follow-up echocardiograms and appropriate clinical data, we were unable to assess the type of HF (ie, HF with preserved versus reduced ejection fraction).

Our study also has several strengths. To our knowledge, this study is the first prospective study to show a dose relationship between cigarette smoking and incident HF in a large cohort of blacks. Blacks have a higher incidence of HF than whites, Hispanics, and Asians.[14,39] Thus, smoking cessation may be a potential strategy to attenuate the higher rate of HF in blacks. Because of superior reliability, we used CMR instead of echocardiography to assess cardiac structure and function.[40]

Cigarette smoking is a well-known risk factor for cardiovascular disease. However, the influences on cardiac structure and function may not be fully recognized because of the strong association with CHD. In our study, cigarette smoking was associated with higher mean LV mass index and LV mass/volume assessed with CMR among those without known CHD. Smoking intensity and burden also are associated with higher mean BNP levels and incident HF in a dose-dependent manner. Therefore, in blacks, cigarette smoking is a strong risk factor for higher LV mass and systolic dysfunction, and incident HF hospitalization independent of its effects on incident CHD.

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Disclosures

None.

REFERENCES

1. Gopal DM, Kalogeropoulos AP, Georgiopoulou VV, Smith AL, Bauer DC, Newman AB, Kim L, Bibbins-Domingo K, Tindle H, Harris TB, Tang WW, Kritchevsky SB, Butler J. Cigarette smoking exposure and heart failure risk in older adults: the Health, Aging, and Body Composition Study. *Am Heart J*. 2012;164:236–242. doi: 10.1016/j.ahj.2012.05.013.
2. Ahmed AA, Patel K, Nyaku MA, Kheirbek RE, Bittner V, Fonarow GC, Filippatos GS, Morgan CJ, Aban IB, Mujib M, Desai RV, Allman RM, White M, Deedwania P, Howard G, Bonow RO, Fletcher RD, Aronow WS, Ahmed A. Risk of heart failure and death after prolonged smoking cessation: role of amount and duration of prior smoking. *Circ Heart Fail*. 2015;8:694–701. doi: 10.1161/CIRCHEARTFAILURE.114.001885.
3. Ho JE, Lyass A, Lee DS, Vasan RS, Kannel WB, Larson MG, Levy D. Predictors of new-onset heart failure: differences in preserved versus reduced ejection fraction. *Circ Heart Fail*. 2013;6:279–286. doi: 10.1161/CIRCHEARTFAILURE.112.972828.
4. Brouwers FP, de Boer RA, van der Harst P, Voors AA, Gansevoort RT, Bakker SJ, Hillege HL, van Veldhuisen DJ, van Gilst WH. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. *Eur Heart J*. 2013;34:1424–1431. doi: 10.1093/eurheartj/eht066.
5. Eaton CB, Pettinger M, Rossouw J, Martin LW, Foraker R, Quddus A, Liu S, Wampler NS, Hank Wu WC, Manson JE, Margolis K, Johnson KC, Allison M, Corbie-Smith G, Rosamond W, Breathett K, Klein L. Risk factors for incident hospitalized heart failure with preserved versus reduced ejection fraction in a multiracial cohort of postmenopausal women. *Circ Heart Fail*. 2016;9:e002883. doi: 10.1161/CIRCHEARTFAILURE.115.002883.
6. Fox KF, Cowie MR, Wood DA, Coats AJ, Gibbs JS, Underwood SR, Turner RM, Poole-Wilson PA, Davies SW, Sutton GC. Coronary artery disease as the cause of incident heart failure in the population. *Eur Heart J*. 2001;22:228–236. doi: 10.1053/euhj.2000.2289.
7. Nicolozakes AW, Binkley PF, Leier CV. Hemodynamic effects of smoking in congestive heart failure. *Am J Med. Sci*. 1988;296:377–380.
8. Zhang J, Piantadosi CA. Mitochondrial oxidative stress after carbon monoxide hypoxia in the rat brain. *J Clin Invest*. 1992;90:1193–1199. doi: 10.1172/JCI115980.
9. Morris PB, Ference BA, Jahangir E, Feldman DN, Ryan JJ, Bahrami H, El-Chami MF, Bhakta S, Winchester DE, Al-Mallah MH, Sanchez Shields M, Deedwania P, Mehta LS, Phan BA, Benowitz NL. Cardiovascular effects of exposure to cigarette smoke and electronic cigarettes: clinical perspectives from the Prevention of Cardiovascular Disease Section Leadership Council and Early Career Councils of the American College of Cardiology. *J Am Coll Cardiol*. 2015;66:1378–1391. doi: 10.1016/j.jacc.2015.07.037.
10. Levitzky YS, Guo CY, Rong J, Larson MG, Walter RE, Keaney JF Jr, Sutherland PA, Vasan A, Lipinska I, Evans JC, Benjamin EJ. Relation of smoking status to a panel of inflammatory markers: the Framingham offspring. *Atherosclerosis*. 2008;201:217–224. doi: 10.1016/j.atherosclerosis.2007.12.058.
11. Bye A, Sørhaug S, Ceci M, Høydal MA, Stølen T, Heinrich G, Tjønna AE, Najjar SM, Nilsen OG, Catalucci D, Grimaldi S, Contu R, Steinshamn S, Condorelli G, Smith GL, Ellingsen O, Waldum H, Wisløff U. Carbon monoxide levels experienced by heavy smokers impair aerobic capacity and cardiac contractility and induce pathological hypertrophy. *Inhal Toxicol*. 2008;20:635–646. doi: 10.1080/08958370701883821.
12. Hall ME, Wang W, Okhomina V, Agarwal M, Hall JE, Dreisbach AW, Juncos LA, Winniford MD, Payne TJ, Robertson RM, Bhatnagar A, Young BA. Cigarette smoking and chronic kidney disease in African Americans in the Jackson Heart Study. *J Am Heart Assoc*. 2016;5:e003280. doi: 10.1161/JAHA.116.003280.
13. Reboul C, Boissière J, André L, Meyer G, Bideaux P, Fouret G, Feillet-Coudray C, Obert P, Lacampagne A, Thireau J, Cazorla O, Richard S. Carbon monoxide pollution aggravates ischemic heart failure through oxidative stress pathway. *Sci Rep*. 2017;7:39715. doi: 10.1038/srep39715.
14. Bahrami H, Kronmal R, Bluemke DA, Olson J, Shea S, Liu K, Burke GL, Lima JA. Differences in the incidence of congestive heart failure by ethnicity: the multi-ethnic study of atherosclerosis. *Arch Intern Med*. 2008;168:2138–2145. doi: 10.1001/archinte.168.19.2138.
15. Jamal A, Homa DM, O'Connor E, Babb SD, Caraballo RS, Singh T, Hu SS, King BA. Current cigarette smoking among adults - United States, 2005-2014. *MMWR Morb Mortal Wkly Rep*. 2015;64:1233–1240. doi: 10.15585/mmwr.mm6444a2.
16. Taylor HA, Jr. The Jackson Heart Study: an overview. *Ethn Dis*. 2005;15:S6-1–3.
17. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461–470.
18. Fox ER, Musani SK, Bidulescu A, Nagarajarao HS, Samdarshi TE, Gebreab SY, Sung JH, Steffes MW, Wang TJ, Taylor HA, Vasan RS. Relation of obesity to circulating B-type natriuretic peptide concentrations in blacks: the Jackson Heart Study. *Circulation*. 2011;124:1021–1027. doi: 10.1161/CIRCULATIONAHA.110.991943.
19. Mentz RJ, Greiner MA, DeVore AD, Dunlay SM, Choudhary G, Ahmad T, Khazanie P, Randolph TC, Griswold ME, Eapen ZJ, O'Brien EC, Thomas KL, Curtis LH, Hernandez AF. Ventricular conduction and long-term heart failure outcomes and mortality in African Americans: insights from the Jackson Heart Study. *Circ Heart Fail*. 2015;8:243–251. doi: 10.1161/CIRCHEARTFAILURE.114.001729.
20. Keku E, Rosamond W, Taylor HA Jr, Garrison R, Wyatt SB, Richard M, Jenkins B, Reeves L, Sarpong D. Cardiovascular disease event classification in the Jackson Heart Study: methods and procedures. *Ethn Dis*. 2005;15(4 suppl 6):S6–62.
21. Yang H, Negishi K, Otahal P, Marwick TH. Clinical prediction of incident heart failure risk: a systematic review and meta-analysis. *Open Heart*. 2015;2:e000222. doi: 10.1136/openhrt-2014-000222.
22. Ravenell J, Shimbo D, Booth JN 3rd, Sarpong DF, Agyemang C, Beatty Moody DL, Abdalla M, Spruill TM, Shallcross AJ, Bress AP, Muntner P, Ogedegbe G. Thresholds for ambulatory blood pressure among African Americans in the Jackson Heart Study. *Circulation*. 2017;135:2470–2480. doi: 10.1161/CIRCULATIONAHA.116.027051.
23. Avery CL, Loehr LR, Baggett C, Chang PP, Kucharska-Newton AM, Matsushita K, Rosamond WD, Heiss G. The population burden of heart failure attributable to modifiable risk factors: the ARIC (Atherosclerosis Risk in Communities) study. *J Am Coll Cardiol*. 2012;60:1640–1646. doi: 10.1016/j.jacc.2012.07.022.
24. Butler J, Kalogeropoulos A, Georgiopoulou V, Belue R, Rodondi N, Garcia M, Bauer DC, Satterfield S, Smith AL, Vaccarino V, Newman AB, Harris TB, Wilson PW, Kritchevsky SB; Health ABC Study. Incident heart failure prediction in the elderly: the health ABC heart failure score. *Circ Heart Fail*. 2008;1:125–133. doi: 10.1161/CIRCHEARTFAILURE.108.768457.
25. Markus MR, Stritzke J, Baumeister SE, Siewert U, Baulmann J, Hannemann A, Schipf S, Meisinger C, Dörr M, Felix SB, Keil U, Völzke H, Hense HW, Schunkert H; MONICA/KORA Augsburg Cohort Study. Effects of smoking on arterial distensibility, central aortic pressures and left ventricular mass. *Int J Cardiol*. 2013;168:2593–2601. doi: 10.1016/j.ijcard.2013.03.045.
26. Nadruz W Jr, Claggett B, Gonçalves A, Querejeta-Roca G, Fernandes-Silva MM, Shah AM, Cheng S, Tanaka H, Heiss G, Kitzman DW, Solomon SD. Smoking and cardiac structure and function in the elderly: the ARIC Study (Atherosclerosis Risk in Communities). *Circ Cardiovasc Imaging*. 2016;9:e004950. doi: 10.1161/CIRCIMAGING.116.004950.
27. Hasegawa T, Boden-Albala B, Eguchi K, Jin Z, Sacco RL, Homma S, Di Tullio MR. Impaired flow-mediated vasodilatation is associated with increased left ventricular mass in a multiethnic population. The Northern Manhattan Study. *Am J Hypertens*. 2010;23:413–419. doi: 10.1038/ajh.2009.261.
28. Payne JR, James LE, Eleftheriou KI, Hawe E, Mann J, Stronge A, Banham K, World M, Humphries SE, Pennell DJ, Montgomery HE. The association of left ventricular mass with blood pressure, cigarette smoking and alcohol consumption; data from the LARGE Heart study. *Int J Cardiol*. 2007;120:52–58. doi: 10.1016/j.ijcard.2006.08.043.
29. Heckbert SR, Post W, Pearson GD, Arnett DK, Gomes AS, Jerosch-Herold M, Hundley WG, Lima JA, Bluemke DA. Traditional cardiovascular risk factors

in relation to left ventricular mass, volume, and systolic function by cardiac magnetic resonance imaging: the Multiethnic Study of Atherosclerosis. *J Am Coll Cardiol*. 2006;48:2285–2292. doi: 10.1016/j.jacc.2006.03.072.
30. Leigh A, Balfour P, Kaplan R, Swett K, Kansal MM, Talavera GA, Perreira K, Blaha M, Benjamin E, Robertson R, Bhartnagar A,Rodriguez CJ. Association of the intensity and duration of cigarette smoking exposure with cardiac structure and function in current daily smokers: the Echocardiographic Study of Hispanic/Latinos. *Open Heart*. 2017;4:e000614.
31. Buddhe S, Lewin M, Olson A, Ferguson M, Soriano BD. Comparison of left ventricular function assessment between echocardiography and MRI in Duchenne muscular dystrophy. *Pediatr Radiol*. 2016;46:1399–1408. doi: 10.1007/s00247-016-3622-y.
32. Corona-Villalobos CP, Sorensen LL, Pozios I, Chu L, Eng J, Abraham MR, Abraham TP, Kamel IR, Zimmerman SL. Left ventricular wall thickness in patients with hypertrophic cardiomyopathy: a comparison between cardiac magnetic resonance imaging and echocardiography. *Int J Cardiovasc Imaging*. 2016;32:945–954. doi: 10.1007/s10554-016-0858-4.
33. Brunklaus A, Parish E, Muntoni F, Scuplak S, Tucker SK, Fenton M, Hughes ML, Manzur AY. The value of cardiac MRI versus echocardiography in the pre-operative assessment of patients with Duchenne muscular dystrophy. *Eur J Paediatr Neurol*. 2015;19:395–401. doi: 10.1016/j.ejpn.2015.03.008.
34. Rosen BD, Saad MF, Shea S, Nasir K, Edvardsen T, Burke G, Jerosch-Herold M, Arnett DK, Lai S, Bluemke DA, Lima JA. Hypertension and smoking are associated with reduced regional left ventricular function in asymptomatic: individuals the Multi-Ethnic Study of Atherosclerosis. *J Am Coll Cardiol*. 2006;47:1150–1158. doi: 10.1016/j.jacc.2005.08.078.
35. Nadruz W Jr, Gonçalves A, Claggett B, Querejeta Roca G, Shah AM, Cheng S, Heiss G, Ballantyne CM, Solomon SD. Influence of cigarette smoking on cardiac biomarkers: the Atherosclerosis Risk in Communities (ARIC) Study. *Eur J Heart Fail*. 2016;18:629–637. doi: 10.1002/ejhf.511.
36. Otsuka T, Kawada T, Seino Y, Ibuki C, Katsumata M, Kodani E. Relation of smoking status to serum levels of N-terminal pro-brain natriuretic peptide in middle-aged men without overt cardiovascular disease. *Am J Cardiol*. 2010;106:1456–1460. doi: 10.1016/j.amjcard.2010.06.075.
37. Messner B, Bernhard D. Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. *Arterioscler Thromb Vasc Biol*. 2014;34:509–515. doi: 10.1161/ATVBAHA.113.300156.
38. McEvoy JW, Nasir K, DeFilippis AP, Lima JA, Bluemke DA, Hundley WG, Barr RG, Budoff MJ, Szklo M, Navas-Acien A, Polak JF, Blumenthal RS, Post WS, Blaha MJ. Relationship of cigarette smoking with inflammation and subclinical vascular disease: the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2015;35:1002–1010. doi: 10.1161/ATVBAHA.114.304960.
39. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29–322. doi: 10.1161/CIR.0000000000000152.
40. Breitenbach I, Harringer W, Tsui S, Amorim MJ, Herregods MC, Bogaert J, Goiti JJ, Gerosa G. Magnetic resonance imaging versus echocardiography to ascertain the regression of left ventricular hypertrophy after bioprosthetic aortic valve replacement: results of the REST study. *J Thorac Cardiovasc Surg*. 2012;144:640–645.e1. doi: 10.1016/j.jtcvs.2011.11.017.

Cigarette Smoking and Incident Heart Failure: Insights From the Jackson Heart Study

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SUPPLEMENTAL MATERIAL

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Supplemental Methods

Echocardiography

Echocardiograms were performed by appropriately trained sonographers and interpreted by experienced cardiologists in the Echocardiography Reading Center at the University of Mississippi Medical Center. Standard echocardiographic views were obtained by trained sonographers and measurements were performed by one interpreting cardiologist (TES) who was blinded to participants' clinical data.[1] Mitral and aortic leaflet morphology was evaluated. Then, a classification of "None or Minimal Sclerosis" was assigned when no more than a slight increase in echogenicity of the leaflets was present and valve motion was normal. "Definite sclerosis" was classified when echogenicity in the leaflets was clearly abnormal and/or there was leaflet thickening with no more than mild restriction to leaflet motion. "Definite stenosis" was assigned when leaflet motion was significantly restricted. The study protocol did not specifically call for continuous wave Doppler data to estimate valve gradient or area, but if obtained by the technician as supplemental data, this may have been used for assignment of valve abnormality. The presence and severity of valve regurgitation based on integration of all the color flow data was recorded.

Supplemental Table 1

		Smoking burden (pack-years) among Ever Smokers			
	Never Smoker	0~7.5	7.5~15	15~30	≥30
Never Smokers (n)	2884	0	0	0	0
Former Smokers (n)	0	126	144	215	257
Current Smokers (n)	0	108	112	147	136
Current Smokers Among Ever Smokers (%)	—	46.2	43.8	40.6	34.6
Time Since quitting Among Former Smokers (yrs)	—	13.7	14.9	16.2	16.8

Supplemental Table 2. Smoking status and cardiac structure and function assessed by CMR at Visit 3 additionally adjusting for class of anti-hypertensive medication use

	Model 3		
	Never Smoker (n=791)	**Former Smoker (n=198)**	**Current Smoker (N=103)**
Variable		**β (95%CI)**	**β (95%CI)**
LVEDVI, ml/m^2	Ref.	**-3.16 (-5.57, -0.756) ***	**-3.73 (-6.89, -0.581) ***
LVESVI, ml/^{2}	Ref.	-1.54 (-3.10, 0.02)	-0.75 (-2.79, 1.30)
SVI, ml/^{2}	Ref.	**-1.62 (-3.19, -0.05) ***	**-2.98 (-5.04, -0.93) †**
LVEF, %	Ref.	0.29 (-1.26, 1.85)	-0.92 (-2.95, 1.10)
LVMI, g/m^2	Ref.	**-2.93 (-5.03, -0.84) †**	**4.15 (1.42, 6.89) †**
LV mass /	Ref.	0.01 (-0.03, 0.06)	**0.13 (0.06, 0.19) †**

volume			
LV Strain#			
Total Strain, %	Ref.	0.02 (-0.38, 0.43)	**0.68 (0.15, 1.20)** *
Base Strain, %	Ref.	0.15 (-0.36, 0.65)	**0.73 (0.08, 1.39)** *
Mid Strain, %	Ref.	-0.12 (-0.66, 0.41)	0.51 (-0.18, 1.20)
Apex Strain, %	Ref.	0.06 (-0.43, 0.55)	**0.84 (0.20, 1.48)** *
PWV, m/sec	Ref.	0.18 (-0.80, 1.16)	**1.54 (0.24, 2.85)** *

LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction, LVESV: left ventricular end-systolic volume, LVMI: left ventricular mass index, PWV: pulse wave velocity from ascending aorta to descending aorta. #: Strain indicators represent mean peak systolic circumferential strain. Visit 3 smoking status information was used for the analysis. Model 6 adjusted for age, sex, systolic blood pressure, body mass index, diabetes, calcium channel blocker use, beta blocker use, diuretics use, angiotensin converting enzyme inhibitor or angiotensin receptor blocker use

and estimated glomerular filtration rate. *: $p<0.05$, †: $p<0.01$.

Supplemental Table 3. Smoking status, intensity, burden and BNP levels (log transformed) at visit 1 additionally adjusting for status of valvular heart disease

Smoking Status	**Never Smoker**	**Former Smoker**	**Current Smoker**
Model		**β (95%CI)**	**β (95%CI)**
Model 4	Ref.	0.057 (-0.017, 0.130)	**0.157 (0.070, 0.244)** *

Smoking Intensity‡	**Never Smoker**	**<10 Cigarettes/day**	**10-19 Cigarettes/day**	**≥ 20 Cigarettes/day**
Model		**β (95%CI)**	**β (95%CI)**	**β (95%CI)**
Model 4	Ref.	0.044 (-0.106, 0.193)	0.129 (-0.005, 0.263)	**0.285 (0.143, 0.427)** †

Smoking Burden‡	**Never Smoker**	**< 7.5 Pack-years**	**7.5-15 Pack-years**	**15-30 Pack-years**	**≥ 30 Pack-years**
Model		**β (95%CI)**	**β (95%CI)**	**β (95%CI)**	**β (95%CI)**

Model 4	Ref.	-0.020 (-0.157, 0.117)	0.109 (-0.002, 0.220)	0.074 (-0.024, 0.174)	**0.142 (0.049, 0.236) †**

Model 4: adjusted for age, sex, body mass index, systolic blood pressure, anti-hypertensive medication use, diabetes, estimated glomerular filtration rate, grade of aortic valve sclerosis or stenosis, and grade of mitral regurgitation. *: $p<0.05$, †: $p<0.01$. ‡Smoking intensity analyses include only never smoker and current smoker. Smoking burden analyses include never smoker and ever smoker.

Supplemental Table 4. Smoking status, intensity, burden and incident HF hospitalization additionally adjusting for status of valvular heart disease

Smoking Status	**Never Smoker**	**Former Smoker**	**Current Smoker**
Model		**H.R. (95%CI)**	**H.R. (95%CI)**
Model 5	Ref (1)	1.444 (0.964, 2.161)	**2.909 (1.727, 4.898) †**

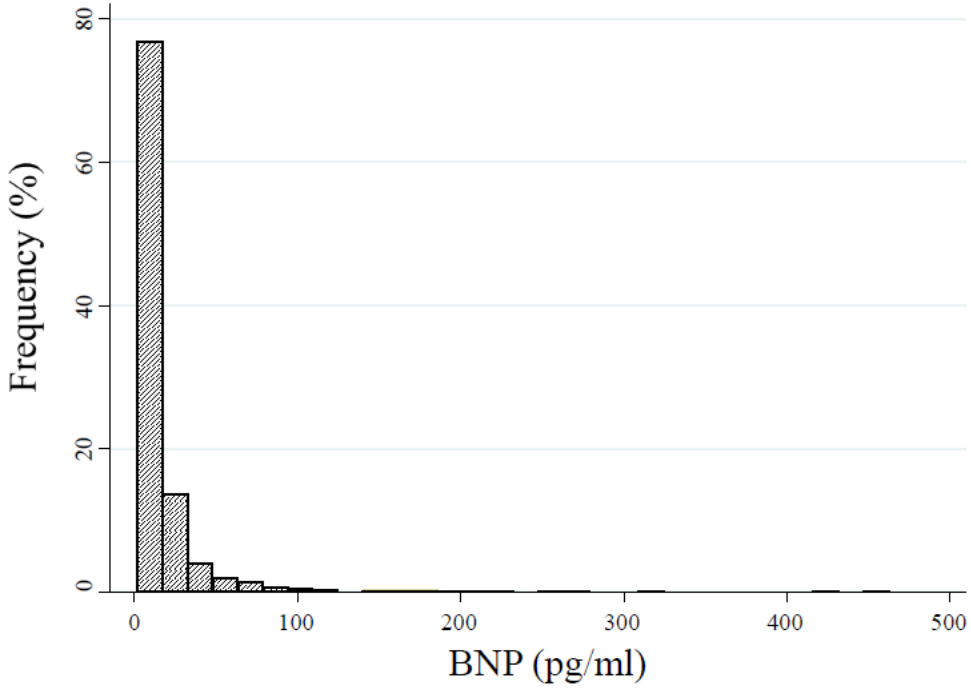
Smoking Intensity‡	**Never Smoker**	**<10 Cigarettes/day**	**10-19 Cigarettes/day**	**≥ 20 Cigarettes/day**
Model		**H.R. (95%CI)**	**H.R. (95%CI)**	**H.R. (95%CI)**
Model 5	Ref (1)	1.738 (0.626, 4.829)	**2.839 (1.269, 6.348)***	**3.476 (1.586, 7.618) †**

Smoking Burden‡	**Never Smoker**	**< 7.5 Pack-years**	**7.5-15 Pack-years**	**15-30 Pack-years**	**≥ 30 Pack-years**
Model		**β (95%CI)**	**β (95%CI)**	**β (95%CI)**	**β (95%CI)**

Model 5	Ref.	0.340 (0.047, 2.460)	1.360 (0.676, 2.735)	**2.220 (1.367, 3.606) ***	**1.512 (0.926, 2.468) ***

Model 5: adjusted for age, sex, systolic blood pressure, anti-hypertensive medication use, body mass index, diabetes, estimated glomerular filtration rate, grade of aortic valve sclerosis or stenosis, mitral valve regurgitation and incident coronary heart disease as a time dependent variable. *: $p<0.05$, †: $p<0.01$. ‡Smoking intensity and burden analyses include only never smoker and current smoker. The number of each smoking status is as follows; Never smoker n=2884, Former smoker n=742, Current smoker n=503. The number of each smoking intensity is as follows; <10 Cigarettes/day n=143, 10-19 Cigarettes/day n=187, ≥ 20 Cigarettes/day n=162. The number of each smoking burden is as follows; <7.5 pack years n=234, 7.5-15 pack years n=256, 15-30 pack years n=362, ≥30 n=393.

Supplemental Figure



Supplemental Figure Legend

Frequency and distribution of brain natriuretic peptide (BNP) levels in Jackson Heart Study participants

Supplemental References

1. Samdarshi TE, Taylor HA, Edwards DQ, Liebson PR, Sarpong DF, Shreenivas SS, Howard G, Garrison RJ and Fox ER. Distribution and determinants of Doppler-derived diastolic flow indices in African Americans: the Jackson Heart Study (JHS). *Am Heart J.* 2009;158:209-216.