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Cigarette smoking and incident heart failure: Insights from the Jackson Heart Study

Daisuke Kamimura, MD PhD[1], **Loretta R. Cain, PhD**[2], **Robert J. Mentz, MD**[3], **Wendy B. White, PhD**[4], **Michael J. Blaha, MD MPH**[5], **Andrew P. DeFilippis, MD MS**[6], **Ervin R. Fox, MD MPH**[1], **Carlos J. Rodriguez, MD MPH**[7], **Rachel J. Keith, PhD, NP**[8], **Emelia J. Benjamin, MD ScM**[9], **Javed Butler, MD MPH**[1], **Aruni Bhatnagar, PhD**[6,8], **Rose M. Robertson, MD**[10], **Michael D. Winniford, MD**[1], **Adolfo Correa, MD MPH PhD**[1], and **Michael E. Hall, MD MS**[1]

[1]Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi [2]Department of Data Sciences, University of Mississippi Medical Center, Jackson Mississippi [3]Department of Medicine, Division of Cardiology, Duke University School of Medicine, Durham, North Carolina [4]Tougaloo College, Tougaloo, Mississippi [5]Ciccarone Center for the Prevention of Heart Disease and Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland [6]Division of Cardiovascular Medicine, University of Louisville, Louisville, Kentucky [7]Department of Medicine and Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina [8]Diabetes and Obesity Center, University of Louisville School of Medicine, Louisville, Kentucky [9]Department of Medicine, Boston University School of Medicine and Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts [10]Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

Abstract

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, function and incident heart failure (HF) hospitalization.

Methods: We investigated 4129 (never smoker n=2884, current smoker n=503, and former smoker n=742) African American participants (mean age 54 years, 63% women) without a history of HF or coronary heart disease (CHD) at baseline in the Jackson Heart Study. We examined the relationship between cigarette smoking and LV structure and function using cardiac magnetic resonance imaging (CMR) among 1092 participants, cigarette smoking and brain natriuretic

Address correspondence: Michael E. Hall, MD, MS, FAHA, Department of Medicine, University of Mississippi, Medical Center, Jackson, Mississippi, 2500 North State Street, Jackson, Mississippi, 39216, Tel. 601-984-5678; Fax. 601-984-5638, mehall@umc.edu.

Disclosures

All authors have no significant disclosures to declare.

University of Mississippi Medical Center, Jackson, MS (DK, LRC, ERF, MDW, JB, AC, MEH); Jackson Heart Study, Jackson, MS (DK, LRC, RJM, WBW, ERF, AC, MEH); Duke University School of Medicine, Durham, NC (RJM); Tougaloo College, Tougaloo, MS (WBW); Johns Hopkins University, Baltimore, MD (MJB); University of Louisville, Louisville, KY (APD, RJK, AB); Wake Forest University School of Medicine, Winston-Salem, NC (CJR); Boston University School of Public Health, Boston, MA (EJB); Vanderbilt University Medical Center, Nashville, TN (RMR); American Heart Association Tobacco Regulation and Addiction Center (A-TRAC) (WBW, MJB, APD, CJR, RJK, EJB, JB, AB, RMR, MDW, MEH).

peptide (BNP) 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 all) compared with never smoking. Smoking status, intensity and burden were associated with higher mean BNP 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 CHD, current smoking (HR 2.82, 95%CI 1.71~4.64), smoking intensity among current smokers (≥20 cigarettes/day: HR 3.48, 95%CI 1.65~7.32) and smoking burden among ever smokers (≥15 pack-years: HR 2.06 95%CI 1.29~3.3) were significantly associated with incident HF hospitalization compared with never smoking.

Conclusions: In African Americans, cigarette smoking is an important risk factor for LV hypertrophy, systolic dysfunction and incident HF hospitalization even after adjusting for effects on CHD.

Keywords

smoking; heart failure; cardiac MRI; Jackson Heart Study (JHS); blacks

Introduction

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 artery 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]

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

We hypothesized that cigarette smoking is associated with cardiac remodeling, left ventricular dysfunction and incident heart failure (HF) hospitalization in African Americans. 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 Jackson Heart Study (JHS).

Methods

Study participants

The JHS is a large prospective community-based observational study designed to investigate risk factors for cardiovascular diseases in African Americans. Details of the JHS study design, recruitment and data collection have been described previously.[16] Briefly, 5301 African American participants residing in the Jackson, Mississippi tri-county area (Hinds, Rankin and Madison) were recruited for the baseline exam 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. 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.

For the present analysis, we excluded all individuals with 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 Supplemental Table 1.

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, Sussex, United Kingdom). 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 two measurements was used. Body mass index (BMI) was calculated as body weight (kg) / (height (m))^2. Self-reported anti-hypertensive medication use was collected at the time of each examination. Venous blood samples were drawn from each participant after more than twelve hours of fasting. Fasting plasma glucose, hemoglobin A1c, and serum creatinine levels were assessed 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 (eGFR) was calculated using the Modification of Diet in Renal Disease Study equation.[17]

Cardiac and aortic MRI

Cardiac magnetic resonance (CMR) images were obtained with 1.5T MR Siemens Espree scanner (Siemens Medical Solutions, Erlangen, Germany) 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 mid-wall circumferential strain was assessed at the apex, middle and base of the LV, and these three 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: base strain 19.0%, mid strain 20.2%, apex strain 18.3% and total strain 15.5%. CMR aortic pulse wave velocity (PWV) was calculated as follows: PWV (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 (BNP) measurements

Plasma BNP levels were measured at Visit 1 using a chemiluminescent immunoassay performed on the Siemens Advia Centaur (Siemens Medical Solutions, Erlangen, Germany) (Figure 1).[18] The coefficient of variation of the assay was previously discribed.[18] We included the histogram of raw BNP data in Supplemental Data (Supplemental figure).

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 (ICD-9-CM) codes were reviewed by trained medical personnel and adjudicated by trained adjudicators based on signs and symptoms, clinical documentation, labs, chest x rays and other imaging modalities including echocardiography, multiple gated acquisition scans and MRIs.[20] Incident CHD was ascertained through directed patient queries during 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 standard deviations for normally distributed continuous variables, median with interquartile ranges for non-normally distributed continuous variables and frequencies and proportions for categorical variables. Analysis of variance with post-hoc Bonferroni test, Mann–Whitney U test and Chi-squared 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 heart failure hospitalization were assessed as prospective longitudinal analyses.

Cross-sectional study

Relationships between smoking status (current, former, never), intensity among current smokers (cigarettes / day) and burden among ever smokers (pack-years) and cardiac structure and function measured using CMR (LV volume variables, LV EF, LV mass index, LV mass / volume, and LV systolic strain variables) and BNP levels were assessed using linear regression analysis. Two models, minimally and further adjusted models were constructed to evaluate associations of smoking and cardiac structure and function. Model 1 included adjustment for age and sex, whereas Model 2 additionally included BMI, systolic blood pressure, use of anti-hypertension medications, history of diabetes mellitus and eGFR based on a previous meta-analysis which examined several risk factors and incident HF and we additionally included eGFR 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 MRI with additional adjustment for classes of medications (calcium channel blocker use, beta blocker use, angiotensin converting enzyme inhibitor or angiotensin receptor blocker use, and diuretics use; Supplemental Table 2) instead of anti-hypertensive 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 (ABPM) instead of office systolic blood pressure (Model 3). ABPM was performed as previously described.[22] ABPM was evaluated only at Visit 1 and the number of included participants who underwent ABPM was small (n=711). Therefore, we were only able to examine the relationship between smoking status and BNP levels (Model 3). Aortic valve stenosis (AS) and mitral valve regurgitation (MR) can increase LV load and promote LV hypertrophy. Thus, we additionally adjusted for AS and MR severity evaluated by echocardiography at Visit 1. Analyses of smoking status and BNP levels (Supplemental Table 3, Model 4), and smoking status and incident HF hospitalization (Supplemental Table 4, Model 5) were additionally performed with adjustment for the grade of AS and MR. Detailed information on the echocardiographic methods is described in the supplemental material. 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) /

day 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% 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 / day) and burden among ever smokers (pack-years), and compared using log-rank tests. Cox proportional hazards models were used to estimate the hazard ratios (HR) of incident HF 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 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, except in Model 2 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, College Station, TX). A 2-sided P value <0.05 was considered significant.

Results

Baseline characteristics

Among the study participants (n=4129), 503 (12%) were current smokers, 742 (18%) were former smokers and 2884 (70%) were never smokers. Never smokers were more likely to be women than the other smoking status groups. Former smokers were older, had higher prevalence of hypertension and diabetes than the other smoking status groups. Current smokers had higher prevalence of current drinking, lower prevalence of achieving the recommended physical activity level and had higher mean eGFR than the other smoking status groups. The prevalence of taking calcium channel blockers, beta-blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers and diuretics were higher in former smokers than the other groups, and the prevalence of taking these anti-hypertensive medications in current smokers were 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 (beta coefficient 5.24, 95% CI 2.71~7.77) and LV mass / volume ratio (beta coefficient 0.12, 95% CI 0.06~0.18), whereas smoking status was not associated with mean LV volume measurements or LVEF (Table 2). However, current smoking was significantly associated with lower mean LV systolic function assessed with LV circumferential strain (total peak systolic circumferential strain: beta coefficient 0.74, 95% CI 0.26~1.22). Current smoking also was associated with higher mean pulse wave velocity in Model 2 (beta 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 (Supplemental Table 2). 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: beta coefficient 0.182, 95% CI 0.074~0.290), smoking intensity among current smokers (Model 2, ≥20 cigarettes/day vs. never smokers: beta coefficient 0.298, 95%CI 0.122~0.474) and smoking burden among ever smokers (Model 2, ≥30 pack-years vs. never smoker: beta coefficient 0.139, 95%CI 0.018~0.260) were significantly associated with higher mean BNP levels (Table 3). Even after adjustment for mean systolic ambulatory blood pressure instead of office systolic blood pressure, the association was not remarkably changed (Table 3, Model 3). After adjustment for grade of AS and MR severity, the association was not remarkably changed (Supplemental Table 3). Figure 2 shows the restricted cubic spline between smoking intensity (average cigarettes / day), smoking burden (pack-years) and log transformed BNP levels. Log-transformed BNP levels were associated were positively associated with increased smoking intensity and burden.

Smoking status, intensity and burden and incident HF hospitalizations

At the time of January 1st 2005, 3633 participants out 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 per 1,000 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 4). Furthermore, smoking intensity among current smokers (model 2, ≥20 cigarettes/day vs never smoker: HR 3.48, 95% CI 1.65~7.32) was associated with incident HF hospitalization in multivariable analyses (Table 4). Smoking burden among ever smokers was associated with incident HF, albeit not linearly (model 2, ≥15 pack-years vs never smoker: HR 2.06, 95% CI 1.29~3.33, P<0.01 and ≥30 pack-years vs never smoker: HR 1.60, 95% CI 1.00~2.56) (Table 4). After additional adjustment for valvular heart disease, the association was not remarkably changed (Supplemental Table 4, Model 5).

Discussion

In our community-based cohort of African Americans, current smoking was associated with a higher LV mass and lower LV circumferential strain assessed by CMR. Current smoking status, higher levels of smoking intensity and burden were associated with higher mean BNP levels at baseline. Furthermore, current smoking, 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, Aging, and Body Composition Study, 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 vs 2.82 in ours) than in their study. To our knowledge, their study was the first which examined the

relationship between smoking status and incident HF with adjustment for incident CHD, as well as examination of the relationships between smoking burden and incident HF. Our study results are consistent with the Health Aging, and Body Composition Study, and extend the findings to a large cohort of African Americans. However, in contrast to the Health, Aging, and Body Composition 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 due to other factors including different ethnicities (40% African Americans in the ABC study and 100% African Americans in our study). Recently published papers reported the relationships between smoking and different phenotypes of incident HF. In the PREVEND study, current smoking was associated with incident HF with reduced ejection fraction (HFrEF).[4] On the other hand, in the Framingham Heart Study, current smoking was associated with incident HF with preserved ejection fraction (HFpEF).[3] In the JHS, the information of 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 African Americans.

There are several previous studies which examined the relationship between smoking and LV mass.[25–30] Many of them showed a positive association; however, there are some studies which 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 which demonstrated a positive relationship between current smoking and LV hypertrophy[25, 26]. Our study confirmed this finding in a large community based cohort of African Americans. Importantly, our study used CMR data. CMR is a more accurate technique for assessment of LV wall thickness, volumes and ejection fraction compared to 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 which 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 additionally adjusted 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 non-significant 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 upon this work by utilizing a large cohort of African

Americans 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 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 (NT pro-BNP) levels, and active smokers had a higher incidence of elevated NT pro-BNP levels after 15 years of follow up.[35] Otsuka and colleagues also showed smoking status was positively associated with higher NT pro-BNP levels.[36] Our study results showed that all measures of smoking (status, intensity and burden) were associated with higher BNP levels, and extend these findings to large cohort of African Americans. 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-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-African American cohort in Jackson, MS 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 utilized has been previously used and validated in other JHS analyses as well as Atherosclerosis Risk in Communities Study (ARIC). 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, due to 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 EF).

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 African Americans. African Americans 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 African Americans. Due to 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 due to 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 African Americans, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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 African Americans).
- 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 African Americans.
- 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?

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

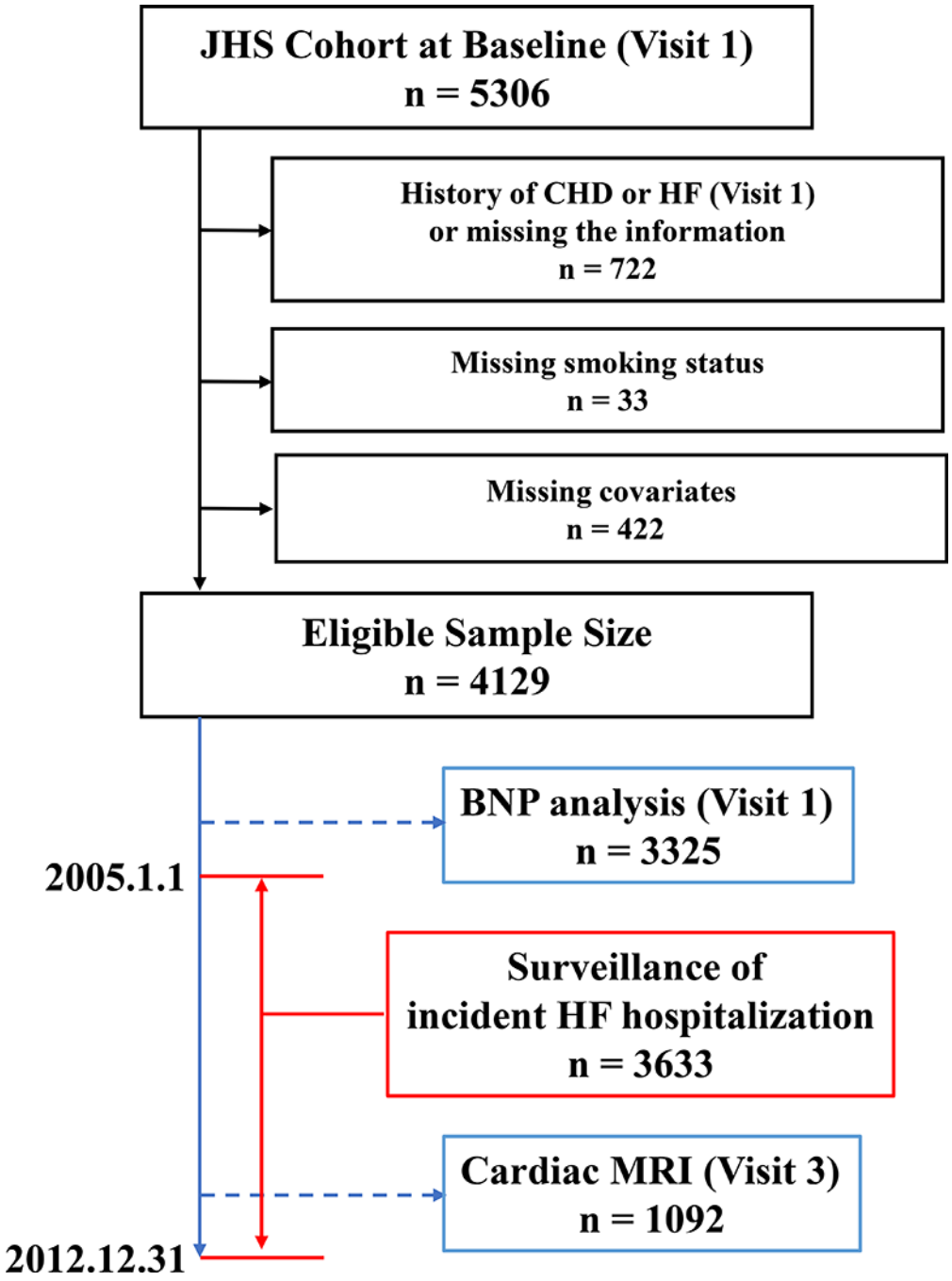


Figure 1.
Exclusion criteria and the numbers of participants for each study.

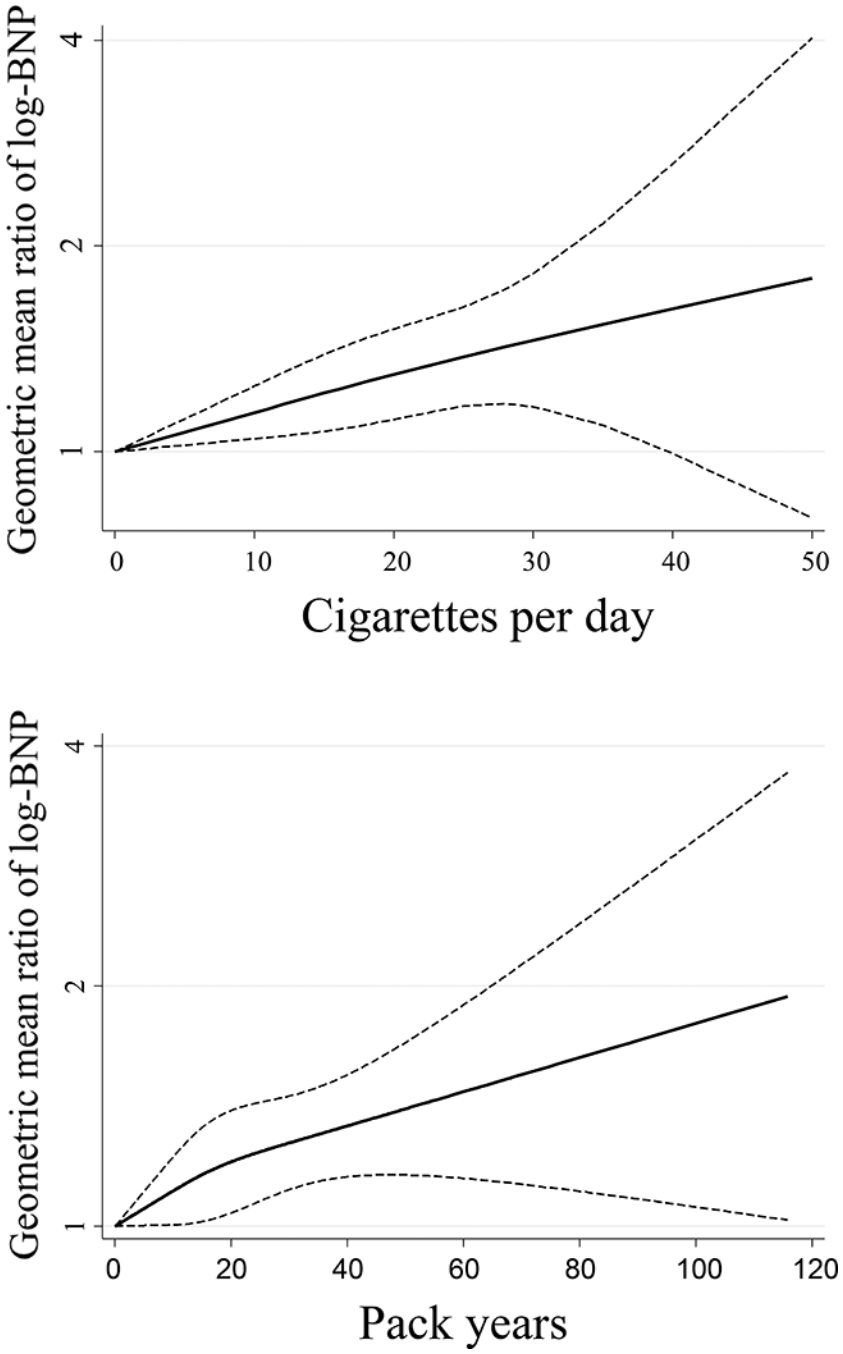
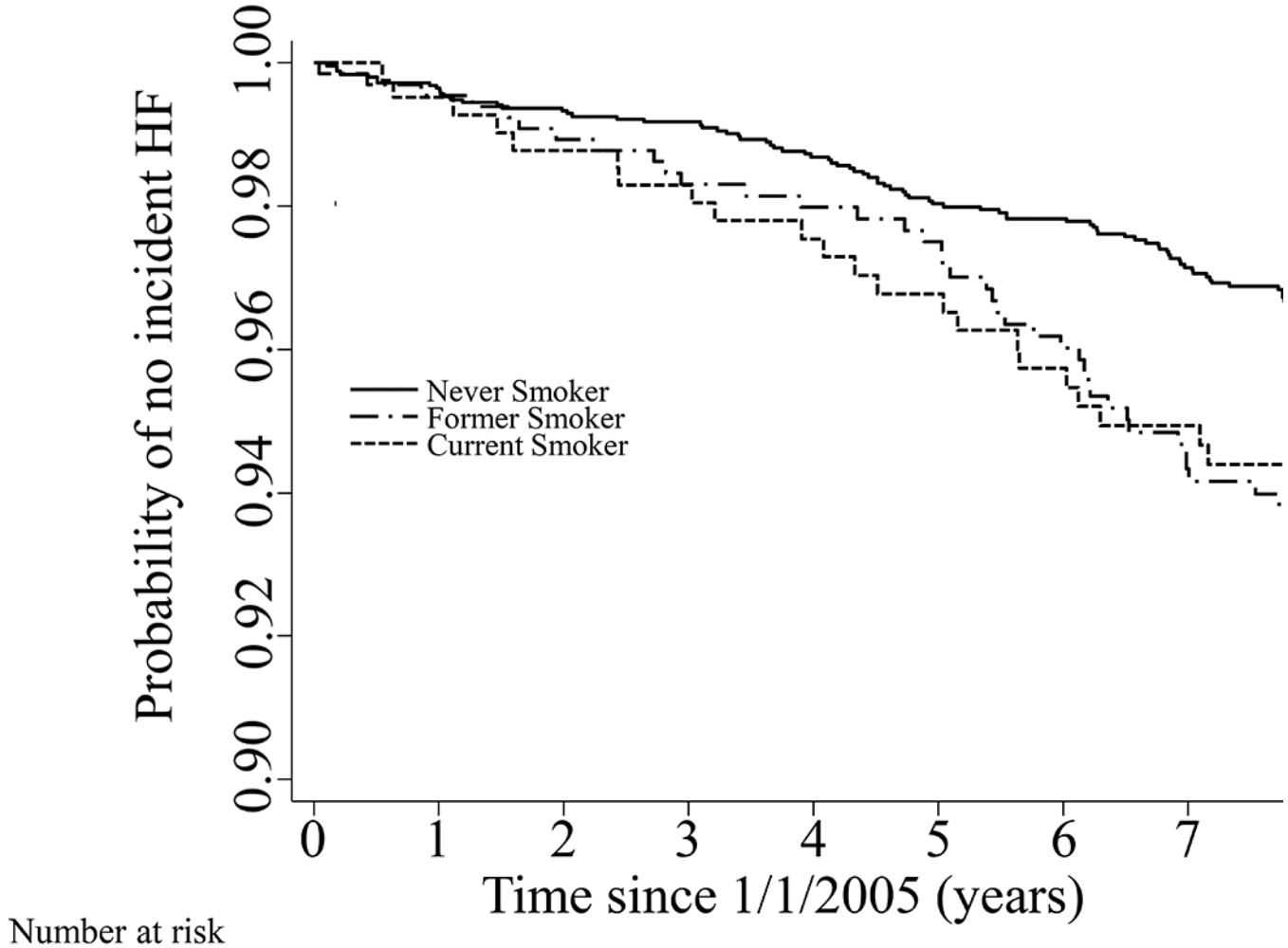


Figure 2. Smoking Intensity, Burden, and Brain Natriuretic Peptide Levels.
Restricted cubic spline analyses demonstrate increased log-transformed BNP levels with increased smoking intensity (top panel) and burden (bottom panel).



Number at risk

Never Smoker	2559	2544	2510	2470	2425	2381	2328	2246
Former Smoker	661	653	642	624	613	599	576	551
Current Smoker	413	408	403	398	388	374	360	350

Figure 3. Kaplan Meier Survival Curves of the Study Participants.
Kaplan Meier Curves separated by smoking status.

Table 1.

Baseline characteristics

Variable	Overall (n=4129)	Never Smoker (n=2884)	Former Smoker (n=742)	Current Smoker (n=503)
Age, years	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, mmHg	127 ± 17	126 ± 16	128 ± 17	128 ± 18
DBP, mmHg	76 ± 9	76 ± 9	75 ± 9	77 ± 9
SBP (ABPM), mmHg	135 ± 28	135 ± 32	136 ± 15	137 ± 16
DBP (ABPM), mmHg	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/1.73m^2	87 ± 17	87 ± 17	85 ± 17	93 ± 18
Calcium channel blocker use	650 (16)	440 (16)	154 (21)	56 (11)
Beta 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 / day			10 (6, 20)	10 (8, 20)
Pack-years of cigarettes			21 (11, 39)	17 (9, 31)

ABPM: 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, Tc / HDL ratio: Total cholesterol / high density lipoprotein cholesterol ratio.

Table 2.

Smoking status and cardiac structure and function assessed by CMR at Visit 3

	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)**
Variable		**β (95%CI)**	**β (95%CI)**		**β (95%CI)**	**β (95%CI)**
LVEDVI, ml/m^2	Ref.	−22.27 (−4.55, 0.14)	−1.86 (−4.81, 1.08)	Ref.	−2.09 (−4.36, 0.18)	−2.35 (−5.29, 0.60)
LVESVI, ml/^{2}	Ref.	−1.06 (−2.55, 0.43)	0.12 (−1.80, 2.05)	Ref.	−1.02 (−1.92, 1.94)	0.01 (−1.92, 1.94)
SVI, ml/^{2}	Ref.	−1.21 (−2.68, 0.25)	−1.99 (−3.88, 0.10)	Ref.	−1.07 (−2.53, 0.39)	−2.35 (−4.24, −0.47)
LVEF, %	Ref.	0.01 (−1.41, 1.43)	−0.75 (−2.58, 1.08)	Ref.	0.09 (−1.33, 1.51)	−0.82 (−2.66, 1.02)
LVMI, g/m^2	Ref.	−2.09 (−4.21, 0.02)	**4.97 (2.24, 7.69)** †	Ref.	−1.73 (−3.69, 0.22)	**5.24 (2.71, 7.77)** †
LV mass / volume	Ref.	0.01 (−0.04, 0.06)	**0.10 (0.04, 0.17)** †	Ref.	0.01 (−0.03, 0.06)	**0.12 (0.06, 0.18)** †
LV Strain#						
Total Strain, %	Ref.	0.02 (−0.36, 0.41)	**0.56 (0.07, 1.06)** *	Ref.	0.01 (−0.37, 0.38)	**0.74 (0.26, 1.22)** †
Base Strain, %	Ref.	0.08 (−0.39, 0.55)	0.60 (−0.01, 1.20)	Ref.	0.08 (−0.38, 0.55)	**0.71 (0.12, 1.31)** *
Mid Strain, %	Ref.	−0.13 (−0.63, 0.38)	0.50 (−0.15, 1.15)	Ref.	−0.16 (−0.66, 0.33)	**0.71 (0.07, 1.34)** *
Apex Strain, %	Ref.	0.16 (−0.31, 0.63)	**0.61 (0.01, 1.21)** *	Ref.	0.14 (−0.32, 0.59)	**0.82 (0.23, 1.41)** †
PWV, m/sec	Ref.	0.23 (−0.65, 1.12)	**1.42 (0.27, 2.57)** *	Ref.	0.24 (−0.64, 1.12)	**1.25 (0.09, 2.41)** *

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 1: adjusted for age and sex. Model 2: further adjusted for systolic blood pressure, anti-hypertensive medication use, body mass index, diabetes, and estimated glomerular filtration rate.

*: p<0.05

†: p<0.01.

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Table 3.

Smoking status, intensity, burden and BNP levels (log transformed) at Visit 1

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

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 1	Ref.	0.101 (−0.086, 0.288)	**0.203 (0.038, 0.367)** *	**0.341 (0.165, 0.516)** †
Model 2	Ref.	0.065 (−0.123, 0.252)	0.151 (−0.015, 0.317)	**0.298 (0.122, 0.474)** †
Model 3	Ref.	0.135 (−0.297, 0.568)	0.321 (−0.098, 0.741)	**0.711 (0.206, 1.215)** †

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 1	Ref.	0.036 (−0.132, 0.204)	0.083 (−0.061, 0.228)	0.075 (−0.050, 0.200)	0.119 (−0.002, 0.240)
Model 2	Ref.	0.030 (−0.139, 0.199)	0.104 (−0.040, 0.248)	0.069 (−0.055, 0.193)	**0.139 (0.018, 0.260)** *
Model 3	Ref.	−0.001 (−0.385, 0.384)	0.112 (−0.216, 0.441)	0.213 (−0.056, 0.482)	**0.375 (0.124, 0.626)** †

body mass index, systolic blood pressure, anti-hypertensive medication use, diabetes and estimated glomerular filtration rate. Model 3: adjusted for Model 2, but including mean systolic ambulatory blood pressure instead of office systolic blood pressure

*: 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.

Table 4.

Smoking status, intensity, burden and incident HF hospitalization

Smoking Status	Never Smoker	Former Smoker	Current Smoker
Model		**H.R. (95%CI)**	**H.R. (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)** †

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 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)** †

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 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 1: adjusted for age and sex. Model 2: further adjusted for systolic blood pressure, anti-hypertensive medication use, body mass index, diabetes, estimated glomerular filtration rate 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.