Relation Between Cigarette Smoking and Heart Failure (from the Multiethnic Study of Atherosclerosis)

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We studied the association between cigarette smoking and incident heart failure (HF) in a racially diverse US cohort. We included 6,792 participants from the Multi-Ethnic Study of Atherosclerosis with information on cigarette smoking at baseline, characterized by status, intensity, burden, and time since quitting. Adjudicated outcomes included total incident HF cases and HF stratified by ejection fraction (EF) into HF with reduced EF (HFrEF; EF ≤ 40%) and preserved EF (HFpEF; EF ≥ 50%). We used Cox proportional hazards models adjusted for traditional cardiovascular risk factors and accounted for competing risk of each HF type. Mean age was 62 ± 10 years; 53% were women, 61% were nonwhite, and 13% were current smokers. A total of 279 incident HF cases occurred over a median follow-up of 12.2 years. The incidence rates of HFrEF and HFpEF were 2.2 and 1.9 cases per 1000 person-years, respectively. Current smoking was associated with higher risk of HF compared with never smoking (hazard ratio [HR], 2.05; 95% confidence interval [CI], 1.36 to 3.09); this was similar for HFrEF (HR, 2.58; 95% CI, 1.27 to 5.25) and HFpEF (HR, 2.51; 95% CI, 1.15 to 5.49). Former smoking was not significantly associated with HF (HR, 1.17; 95% CI, 0.88 to 1.56). Smoking intensity, burden, and time since quitting did not provide additional information for HF risk after accounting for smoking status. **(Am J Cardiol 2019;123:1972−1977)**

Approximately 6.5 million Americans have heart failure (HF),[1] and 960,000 people are newly diagnosed each year.[1] Despite stable incidence rates, the number of Americans living with HF is expected to increase by 46% from 2012 to 2030.[2] The increasing prevalence of HF with reduced ejection fraction (HFrEF) can be partially attributed to the use of guideline-directed medical therapies.[3−6] Similarly, the prevalence of HF with preserved ejection fraction (HFpEF) will likely continue to rise given the aging population and rising prevalence of co-morbidities, particularly obesity, and diabetes mellitus.[3,5−8] Reducing the burden of HF depends on the continued use of proven therapies and risk factor modification.[4,9] Cigarette smoking is a leading cardiovascular disease (CVD) risk factor and accounts for nearly 40% of CVD deaths.[10] A 2015 systematic review and meta-analysis found smoking to be associated with a 60% higher risk of HF.[11] In this study, we examine the association between smoking patterns and incident HF in a multiethnic and sex-balanced US cohort, hypothesizing that there is a graded relationship between cigarette smoking and HF risk.

Methods

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study designed to assess the prognostic significance of subclinical CVD.[12] Between 2000 and 2002, 6,814 participants, aged 45 to 84 years and without previous, self-reported CVD events were recruited from the following US sites: Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; St. Paul, Minnesota. The MESA protocols[12] were approved by the National Heart, Lung and Blood Institute and institutional review boards at all participating institutions. We

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excluded participants who were missing information on cigarette smoking status (n = 22).

Cigarette smoking was assessed at the baseline visit. Smoking status was self-reported and characterized as never, former, or current. Participants who answered "No" to having smoked at least 100 cigarettes in their lifetime were defined as never smokers. Those who answered "Yes" were defined as current or former smokers depending on whether they had smoked in the past 30 days. We measured urinary cotinine,[13] a biomarker of recent tobacco exposure, in a random subgroup (n = 3,965) of participants using the Immulite 2000 Nicotine Metabolite Assay (Diagnostic Products Corporation, Los Angeles, California).[14] Never and former smokers with urinary cotinine level >500ng/ml (n = 28 and 56, respectively) were reclassified as current smokers. Smoking intensity was defined as the number of cigarettes smoked per day among current smokers only. Smoking burden, quantified in pack-years, was calculated as packs (of 20 cigarettes) per day of cigarettes multiplied by the number of years of smoking among current and former smokers. Time since quitting smoking, recorded in years, was assessed for former smokers.

N-terminal Pro-B-type brain natriuretic peptide (NT-proBNP) levels were obtained at baseline for all participants using the highly sensitive and specific Elecsys electrochemiluminescence immunoassay based on the double-antibody sandwich method (Roche Diagnostics Corporation, Indianapolis, Indiana).[15] Elevated NT-proBNP may represent subclinical or ACCF/AHA Stage B HF, defined as having structural heart disease without signs or symptoms.[4]

Incident HF was defined as having symptoms, such as shortness of breath or peripheral edema, in addition to objective criteria by chest x-ray (pulmonary edema) and/or echocardiography or ventriculography (dilated left ventricle [LV], poor LV function or evidence of LV diastolic dysfunction). EF was available in 70% (n = 195) of participants with incident HF. Among those with available EF measurements, HFrEF was defined as EF ≤40% and HFpEF was defined as EF ≥50%.[4] HF events were adjudicated by 2 paired physicians; disagreements were reviewed by a full committee.

Incident coronary heart disease (CHD) was defined as myocardial infarction, resuscitated cardiac arrest, or CHD death, in addition to definite angina and probable angina if followed by revascularization. Coronary artery calcium (CAC) was measured using an electron-beam CT in Chicago, Los Angeles, and New York and a multidetector CT in Baltimore, Forsyth County, and St. Paul. Participants were scanned twice, and the mean CAC score was used. All images were interpreted at the LA Biomedical Research Institute (Harbor-UCLA Medical Center, Torrance, California) with excellent intraobserver and interobserver agreement (kappa 0.93 and 0.90, respectively).[16]

Demographic data, including age, gender, race/ethnicity, education, and medication use, were self-reported using validated questionnaires. Body mass index was calculated as weight in kilograms divided by height in meters squared. Systolic and diastolic blood pressure (SBP and DBP, respectively) were measured 3 times using an automated sphygmomanometer, and the mean of the final 2 measurements was used. Hypertension was defined as SBP ≥140 mm Hg or DBP ≥90 mm Hg or use of antihypertensive medications. A central laboratory (University of Vermont, Burlington, Vermont) measured concentrations of fasting total cholesterol, high-density lipoprotein cholesterol, triglycerides, and plasma glucose. Low-density lipoprotein cholesterol was calculated using the Friedewald equation. Diabetes mellitus was defined according to the 2003 American Diabetes Association criteria of fasting glucose ≥126 mg/dl or use of hypoglycemic medications or insulin.[17] Alcohol use was self-reported and defined as never, former, or current. Physical activity was defined using the MESA Typical Week Physical Activity Survey, which quantifies the time spent in, and frequency of, physical activity recorded as number of metabolic equivalents of task-minutes per week (MET-min/week).[18] Diet was defined using a 120-item food frequency questionnaire, which resulted in a summary Mediterranean-style diet score ranging from 0 to 11, with 0 representing poor adherence.[19] High-sensitivity C-reactive protein (hsCRP) was measured in mg/L using the BNII nephelometer (N high-sensitivity CRP; Dade Behring Inc., Deerfield, Illinois) at the University of Vermont.[20]

Baseline characteristics were summarized, by category of smoking status, using mean (standard deviation) or median (25th to 75th percentile) for continuous variables and counts (percentages) for categorical variables. Between-group differences were tested using ANOVA, Kruskal-Wallis, and chi-square tests as appropriate.

Smoking intensity was categorized as 1 to 9, 10 to 20 and >20 cigarettes per day among current smokers.[21] Smoking burden was grouped into tertiles of <8, 8 to 25, and ≥26 pack-years. Similarly, time since quitting smoking was evaluated by tertiles of <16, 16 to 28 and ≥29 years.

We studied the cross-sectional association of cigarette smoking and NT-proBNP using multivariable adjusted linear regression models. Model 1 was adjusted for demographic risk factors: age, gender, and race/ethnicity. Model 2 was additionally adjusted for educational status and CVD risk factors: body mass index, SBP, antihypertensive medication use, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, lipid-lowering medication use, diabetes mellitus (DM), physical activity, Mediterranean diet score, salt intake, and alcohol use. To test whether the association between smoking and HF was mediated by inflammation or subclinical atherosclerosis, Model 3 further adjusted for hsCRP and CAC.

Incidence rates for total HF, HFrEF, and HFpEF were calculated as number of events per 1,000 person-years. We used Cox proportional hazards models to study the association of smoking and total HF outcomes after confirming the proportionality assumption with log-log plots. For HFrEF, the Fine-Gray model was used to account for the competing risk of developing HFpEF.[22] The same was done for HFpEF, taking into account the competing risk of developing HFrEF. We used sequential models as described above.

In a sensitivity analysis, we adjusted for interim incident CHD occurring before the development of HF events. We also accounted for the competing risk of noncardiovascular causes of mortality (e.g., cancer mortality) using Fine and Gray models. Finally, we examined the subset of participants with EF 41% to 49%, described as having HF with midrange EF

Table 1
Baseline characteristics by cigarette smoking status

Variable	Total (n = 6,792)	Never smokers (n = 3,418)	Former smokers (n = 2,487)	Current smokers (n = 887)
Age (years)	62 ± 10	62 ± 11	63 ± 10	58 ± 9
Men	3203 (47%)	1297 (38%)	1439 (58%)	467 (53%)
Race/ethnicity				
White	2615 (39%)	1157 (34%)	1157 (47%)	301 (34%)
Chinese-American	802 (12%)	604 (18%)	153 (6%)	45 (5%)
Black	1879 (28%)	850 (25%)	691 (28%)	338 (38%)
Hispanic	1496 (22%)	807 (24%)	486 (20%)	203 (23%)
Bachelor's degree	1171 (17%)	610 (18%)	450 (18%)	111 (13%)
Body mass index (kg/m^2)	28.3 ± 5.5	28.1 ± 5.5	28.8 ± 5.5	28.0 ± 5.3
Systolic blood pressure (mm Hg)	127 ± 21	127 ± 22	127 ± 21	124 ± 22
LDL-C (mg/dl)	117 ± 31	118 ± 31	116 ± 31	116 ± 33
HDL-C (mg/dl)	51 ± 15	52 ± 15	51 ± 15	48 ± 14
Lipid-lowering medication use	1099 (16%)	543 (16%)	449 (18%)	107 (12%)
Hypertension	3044 (45%)	1540 (45%)	1173 (47%)	331 (37%)
Antihypertensive medication use	2524 (37%)	1286 (38%)	975 (39%)	263 (30%)
Diabetes mellitus	857 (13%)	425 (12%)	321 (13%)	111 (13%)
Current alcohol use	3749 (55%)	1596 (47%)	1551 (63%)	602 (68%)
Moderate-vigorous physical activity (MET-min/week)	1080 [1515]	1050 [1480]	1080 [1440]	1233 [1890]
Mediterranean diet score	5 [3]	5 [3]	5 [3]	4 [3]
Frequent addition of salt to food	2513 (40%)	1071 (33%)	1035 (45%)	407 (51%)
High-sensitivity C-reactive protein (mg/L)	1.9 [3.4]	1.8 [3.2]	1.9 [3.4]	2.6 [3.8]
Coronary artery calcium (CAC) score >0	3391 (50%)	1513 (44%)	1442 (58%)	(49%)

Continuous variables: mean ± SD or median [interquartile range].
Categorical variables: count (%)

(HFmrEF),[4] to determine whether associations with smoking more closely resembled HFrEF or HFpEF phenotypes.

All reported p values are 2-sided and p <0.05 was considered statistically significant. Analyses were performed using Stata version 13.1 (StataCorp, College Station, Texas).

Results

Our study population included 6,792 MESA participants. Mean age was 62 ± 10 years, 53% were women, 39% were white, 28% black, 22% Hispanic, and 12% Chinese-American. The distribution of cigarette smoking status was as follows: 3,418 never smokers, 2,487 former smokers, and 887 current smokers. Compared with never smokers, current smokers were younger, more likely to be men and African-American and had baseline CAC >0 (Table 1; all p <0.05).

Smoking status was not associated with NT-proBNP levels, and neither was smoking intensity, burden or time since quitting (Supplementary Table 1).

Over a median 12.2 years of follow-up, there were 279 cases of incident HF. Among those participants for whom an EF was available (n = 195), there were 94 cases of HFrEF and 96 cases of HFpEF. The unadjusted incidence rate of HFrEF was 2.2 cases per 1,000 person-years and that of HFpEF was 1.9 per 1,000 person-years.

Adjusting for demographic characteristics (Model 1), current smoking was associated with HF risk. This association remained significant in Model 2. Adjusting for hsCRP and CAC (Model 3) slightly attenuated our results; but, they remained statistically significant (hazard ratio [HR], 2.05; 95% confidence interval [CI], 1.36 to 3.09; Table 2).

Current smoking was associated with HFrEF, but not HFpEF, in Model 1. After adjusting for CVD risk factors (Model 2), current smoking remained associated with both subtypes (HR, 2.58; 95% CI, 1.27 to 5.25 and HR, 2.51; 95% CI, 1.15 to 5.49 for HFrEF and HFpEF, respectively; Table 2). Results were similar when smoking status was reclassified by urinary cotinine (Supplementary Table 2).

Smoking intensity, burden and time since quitting were not statistically significantly associated with HF, HFrEF, or HFpEF (Table 2). After stratifying the results for smoking burden by smoking status, we found a significantly lower risk of total HF among current smokers who smoked >26 pack-years compared with those with a <8 pack-year history in Model 2. We also found a nonsignificantly higher risk of total HF and HFpEF among former smokers who smoked >26 pack-years compared with those with a <8 pack-year history (Supplementary Table 3). Nonsignificant results were also obtained when smoking intensity and burden were evaluated as continuous variables (Supplementary Table 4).

The association between current smoking and HF did not change after we additionally adjusted for interim CHD (Supplementary Table 5) or accounted for competing risk of non-CV causes of mortality (Supplementary Table 6). Smoking was not associated with HFmrEF, but this analysis was largely under-powered. Lastly, we performed a sensitivity analysis using SBP ≥130 mm Hg or DBP ≥90 mm Hg,[23] and our results did not change.

Table 2
Hazard ratio (95% confidence interval) for the association of smoking and heart failure

	HF			HFrEF			HFpEF		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
					Smoking status				
Never	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Former	1.18 (0.91, 1.53)	1.17 (0.88, 1.56)	1.11 (0.83, 1.48)	1.02 (0.64, 1.61)	1.05 (0.62, 1.79)	0.97 (0.57, 1.64)	1.56 (0.97, 2.50)	1.36 (0.81, 2.27)	1.29 (0.77, 2.15)
Current	**1.73 (1.19, 2.52)**	**2.05 (1.36, 3.09)**	**1.80 (1.19, 2.73)**	**2.21 (1.26, 3.88)**	**2.58 (1.27, 5.25)**	**2.11 (1.06, 4.21)**	1.97 (0.95, 4.07)	**2.51 (1.15, 5.49)**	**2.25 (1.04, 4.90)**
					Smoking intensity (cigarettes/day) among current smokers				
1-9	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
10-20	0.70 (0.36,1.37)	0.59 (0.27,1.27)	0.55 (0.25,1.19)	1.20 (0.42,3.43)	1.08 (0.29,4.02)	0.79 (0.22,2.84)	0.62 (0.16,2.41)	0.102 (0.004,2.778)	0.071 (0.001,6.636)
>20	0.42 (0.12,1.49)	0.57 (0.15,2.12)	0.48 (0.12,1.85)	0.43 (0.04,4.28)	0.84 (0.07,9.65)	0.61 (0.05,7.74)	1.09 (0.15,8.01)	5.80 (0.89,37.80)	7.01 (0.04,1297.0)
p Value for trend	0.13	0.21	0.13	0.67	0.97	0.63	0.91	0.76	0.83
					Smoking burden (pack-years) among current and former smokers				
Tertile 1: <8	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Tertile 2: 8-25	1.05 (0.70, 1.57)	1.00 (0.64, 1.55)	0.96 (0.62, 1.49)	0.85 (0.44, 1.66)	0.89 (0.42, 1.90)	0.81 (0.36, 1.79)	0.96 (0.46, 2.00)	0.87 (0.40, 1.90)	0.86 (0.39, 1.88)
Tertile 3: >26	1.21 (0.83, 1.79)	1.16 (0.76, 1.77)	1.04 (0.68, 1.60)	0.86 (0.44, 1.68)	0.99 (0.46, 2.16)	0.74 (0.33, 1.64)	1.13 (0.58, 2.23)	0.98 (0.47, 2.03)	0.89 (0.43, 1.86)
p Value for trend	0.33	0.48	0.82	0.67	1.00	0.47	0.71	0.96	0.78
					Time since quitting (quit-years) among former smokers				
Tertile 1: <16	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Tertile 2: 16-28	0.89 (0.57,1.41)	0.76 (0.46,1.25)	0.83 (0.50,1.38)	1.07 (0.43,2.69)	1.02 (0.33,3.12)	1.28 (0.44,3.72)	0.77 (0.34,1.75)	0.61 (0.25,1.48)	0.65 (0.25,1.65)
Tertile 3: >29	0.62 (0.39,0.97)	0.66 (0.41,1.06)	0.71 (0.44,1.14)	0.93 (0.37,2.30)	0.95 (0.31,2.94)	1.10 (0.38,3.19)	0.68 (0.32,1.46)	0.77 (0.34,1.71)	0.81 (0.36,1.80)
p Value for trend	0.03	0.09	0.16	0.85	0.93	0.89	0.33	0.58	0.66

Model 1: Age, sex, and race/ethnicity.

Model 2: Age, sex, race/ethnicity, education, BMI, SBP, antihypertensive medication, LDL-C, HDL-C, lipid-lowering medication, DM, moderate-vigorous physical activity, Mediterranean diet, salt intake, and alcohol use.

Model 3: Age, sex, race/ethnicity, education, BMI, SBP, antihypertensive medication, LDL-C, HDL-C, lipid-lowering medication, DM, moderate-vigorous physical activity, Mediterranean diet, salt intake, alcohol use, hsCRP, and CAC.

Bolded results are significant.

Discussion

In a racially diverse and sex-balanced US cohort, current smoking was associated with a higher risk of HF. This finding expands upon existing knowledge[11,24] by demonstrating that the association between current smoking and HF[25] is observed in both HFrEF and HFpEF after adjusting for CVD risk factors.

Smoking promotes the development of atherosclerotic CVD[14,26,27] via impaired endothelium-dependent vasodilation.[28,29] Additionally, smoking induces a hypercoagulable state[30,31] that increases CVD risk. These mechanisms are postulated to explain the association between smoking and HFrEF. We observed an association between smoking and HFrEF that was independent of CAC or incident CHD events, suggesting that there are additional mechanisms by which smoking is associated with higher risk of HFrEF, although this is difficult to determine in an epidemiologic study.

Less is known about the association between smoking and HFpEF. Smoking is purported to be directly toxic to cardiac myocytes.[28] Additionally, long-term inflammation, which is associated with smoking,[14,21,26] alters myocardial structure and function.[32,33] In our study, however, smoking retained its association with HF after adjusting for hsCRP, a proinflammatory marker. This suggests that there are mechanisms other than inflammation that help explain the relationship between smoking and HFpEF, although, again, this is difficult to evaluate based on our results.

Interestingly, current smokers in our study were less likely to have hypertension or take antihypertensives and had lower SBP; they also had a trend toward lower salt intake. This is possibly related to current smokers being younger than other participants (Table 1) although current smoking was associated with HF even after adjustment for these variables.

Although current smoking was associated with both HFrEF and HFpEF, there was no significant association between intensity, burden, or time since quitting and incident HF after accounting for smoking status. The lack of association between intensity and HF is not surprising given the small sample size of current smokers (n = 887); further, intensity reflects acute exposure, while the burden of smoking accumulates over time. Regarding time since quitting, a previous study reported that abstaining ≥15 years resulted in HF risk equivalent to having never smoked.[34] Our study demonstrated a lower risk of HF among former smokers with higher quit-years, but these results were not significant. The nonsignificant findings regarding smoking burden differ from the existing literature, in which pack-years are significantly associated with HF risk among past smokers compared with never smokers.[24] Notably, this association was driven by smokers with ≥35 pack-years exposure, and participants were older. Further, we utilized the first tertile of smoking burden as the reference, as opposed to never smokers, to evaluate for a true dose-response relationship.

In stratifying our results for smoking burden by status, we found a paradoxically lower risk of HF among current smokers with >26 pack-year history compared with <8. This is likely the result of small sample size, with 370 participants and only 10 HF events among current smokers.

Our study reclassified smoking status using urinary cotinine in an attempt to mitigate reporting bias. The remaining variables used to assess smoking were self-reported; however, quantifying intensity, burden, and time since quitting allowed for a more granular analysis of the association between smoking and HF. The inclusion of CAC, associated with both smoking[14,27,35] and HF,[36] is another strength of our study. Similarly, we incorporated hsCRP, a marker of inflammation that exhibits a dose-response relationship with smoking.[14,21] By modeling these variables, we accounted for potential mediators of the association between smoking and HF.

Our results must be interpreted in the context of important limitations. First, we did not assess smoking as a time-varying exposure. Second, we did not evaluate the potential impact of second-hand smoke on the risk of developing HF. Third, our participants were free of CVD at baseline, which affects the external validity of our study. We also acknowledge that relying on self-reported baseline CVD might have resulted in selection bias. Fourth, EF was the only measure used to differentiate HFrEF from HFpEF. Further, we cannot exclude the possibility of bias due to interobserver differences in reading echocardiograms. Fifth, our limited duration of follow-up (12.2 years) may underestimate the long-term risks of smoking. Lastly, we cannot exclude the possibility of residual confounding in this observational study.

In conclusion, we found that current smoking was associated with higher risk of incident HFrEF and HFpEF. After accounting for smoking status, smoking intensity, smoking burden, and time since quitting smoking did not provide additional information regarding the risk of HFrEF or HFpEF.

Author Agreement

All authors have contributed to the development of this manuscript and agree with its submission to *The American Journal of Cardiology*; all funding and conflicts of interests are detailed therein. We confirm that this manuscript has not been published or submitted to any other journal; and, it will not be submitted while under consideration by *The American Journal of Cardiology*.

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Supplementary materials

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