



Published in final edited form as:

*Am J Cardiol.* 2019 June 15; 123(12): 1972–1977. doi:10.1016/j.amjcard.2019.03.015.

## Relation Between Cigarette Smoking and Heart Failure (From the Multi-Ethnic Study of Atherosclerosis)

Megan Watson, MD, MPH<sup>a</sup>, Zeina Dardari, MS<sup>b</sup>, Sina Kianoush, MD, MPH<sup>b,c</sup>, Michael E. Hall, MD<sup>d</sup>, Andrew P. DeFilippis, MD<sup>b,e,f</sup>, Rachel J. Keith, PhD<sup>e,f</sup>, Emelia J. Benjamin, MD, ScM<sup>g,h</sup>, Carlos J. Rodriguez, MD<sup>i</sup>, Aruni Bhatnagar, PhD<sup>e,f</sup>, Joao A. Lima, MD<sup>j</sup>, Javed Butler, MBBS, MPH<sup>k</sup>, J. Blaha, MD, MPH<sup>b</sup>, and Mahmoud Al Rifai, MD, MPH<sup>b,l</sup>

<sup>a</sup>Department of Internal Medicine, University of Michigan, Ann Arbor, MI ;

<sup>b</sup>The Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, MD;

<sup>c</sup>Department of Medicine, Yale-Waterbury Waterbury, CT;

<sup>d</sup>Division of Cardiology, University of Mississippi Medical Center, Jackson, MS;

<sup>e</sup>Diabetes and Obesity Center, University of Louisville School of Medicine, Louisville, KY;

<sup>f</sup>Division of Cardiology, University of Louisville School of Medicine, Louisville, KY;

<sup>g</sup>Department of Medicine, Division of Cardiology, Boston University School of Medicine, Boston, MA;

<sup>h</sup>Department of Epidemiology, Boston University School of Public Health, Boston, MA;

<sup>i</sup>Maya Angelou Center for Health Equity, Wake Forest University, Winston-Salem, NC;

<sup>j</sup>Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD;

<sup>k</sup>Department of Medicine, University of Mississippi Medical Center, Jackson, MS;

<sup>l</sup>Department of Medicine, University of Kansas School of Medicine, Wichita, KS

### Abstract

We studied the association between cigarette smoking and incident heart failure (HF) in a racially diverse U.S. cohort. We included 6792 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) 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

**Corresponding Author:** Mahmoud Al Rifai, MD MPH, Telephone: (347) 471-7060, mahrifai@gmail.com, Mail: 1010 N Kansas St, Wichita, KS 67214.

**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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(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 non-white, 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 to never smoking (HR, 2.05; 95% CI, 1.36–3.09); this was similar for HFrEF (HR, 2.58; 95% CI, 1.27–5.25) and HFpEF (HR, 2.51; 95% CI, 1.15–5.49). Former smoking was not significantly associated with HF (HR, 1.17; 95% CI, 0.88–1.56). Smoking intensity, burden, and time since quitting did not provide additional information for HF risk after accounting for smoking status.

## Keywords

Cigarettes; Smoking; Heart failure

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Approximately 6.5 million Americans have heart failure (HF),<sup>1</sup> and 960,000 people are newly diagnosed each year.<sup>1</sup> Despite stable incidence rates, the number of Americans living with HF is expected to increase by 46% from 2012 to 2030.<sup>2</sup> The increasing prevalence of HF with reduced ejection fraction (HFrEF) can be partially attributed to the use of guideline-directed medical therapies.<sup>3–6</sup> Similarly, the prevalence of HF with preserved ejection fraction (HFpEF) will likely continue to rise given the aging population and rising prevalence of comorbidities, particularly obesity and diabetes mellitus.<sup>3,5–8</sup> Reducing the burden of HF depends on the continued use of proven therapies and risk factor modification.<sup>4,9</sup> Cigarette smoking is a leading cardiovascular disease (CVD) risk factor and accounts for nearly 40% of CVD deaths.<sup>10</sup> A 2015 systematic review and meta-analysis found smoking to be associated with a 60% higher risk of HF.<sup>11</sup> In this study, we examine the association between smoking patterns and incident HF in a multi-ethnic and sex-balanced U.S. 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.<sup>12</sup> Between 2000 and 2002, 6814 participants, aged 45–84 years and without prior, self-reported CVD events were recruited from the following U.S. 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<sup>12</sup> were approved by the National Heart, Lung and Blood Institute (NHLBI) and institutional review boards at all participating institutions. We 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,<sup>13</sup> a biomarker of recent tobacco exposure, in a random subgroup (N=3965) of participants using the Immulite 2000 Nicotine

Metabolite Assay (Diagnostic Products Corporation, Los Angeles, CA, U.S.).<sup>14</sup> 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, IN).<sup>15</sup> Elevated NT-proBNP may represent subclinical or ACCF/AHA Stage B HF, defined as having structural heart disease without signs or symptoms.<sup>4</sup>

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 heart failure. Among those with available EF measurements, HF<sub>r</sub>EF was defined as EF < 40% and HF<sub>p</sub>EF was defined as EF ≥ 50%.<sup>4</sup> HF events were adjudicated by two paired physicians; disagreements were reviewed by a full committee.

Incident 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 multi-detector 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, CA, U.S.) with excellent intra-observer and inter-observer agreement (kappa 0.93 and 0.90, respectively).<sup>16</sup>

Demographic data, including age, sex, race/ethnicity, education and medication use, was self-reported using validated questionnaires. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Systolic and diastolic blood pressure (SBP and DBP, respectively) were measured three times using an automated sphygmomanometer, and the mean of the final two 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, VT, U.S.) measured concentrations of fasting total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, and plasma glucose. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation. Diabetes mellitus was defined according to the 2003 American Diabetes Association (ADA) criteria of fasting glucose ≥ 126mg/dL or use of hypoglycemic medications or insulin.<sup>17</sup> 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).<sup>18</sup> 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.<sup>19</sup> 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.<sup>20</sup>

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

Smoking intensity was categorized as 1–9, 10–20 and >20 cigarettes per day among current smokers.<sup>21</sup> Smoking burden was grouped into tertiles of <8, 8–25 and ≥26 pack-years. Similarly, time since quitting smoking was evaluated by tertiles of <16, 16–28 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, sex, and race/ethnicity. Model 2 was additionally adjusted for educational status and CVD risk factors: BMI, SBP, antihypertensive medication use, LDL-C, HDL-C, lipid-lowering medication use, 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, HF<sub>rEF</sub>, and HF<sub>pEF</sub> were calculated as number of events per 1000 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 HF<sub>rEF</sub>, the Fine-Gray model was used to account for the competing risk of developing HF<sub>pEF</sub>.<sup>22</sup> The same was done for HF<sub>pEF</sub>, taking into account the competing risk of developing HF<sub>rEF</sub>. We used sequential models as described above.

In a sensitivity analysis, we adjusted for interim incident CHD occurring prior to the development of HF events. We also accounted for the competing risk of non-cardiovascular causes of mortality (e.g. cancer mortality) using Fine and Gray models. Finally, we examined the subset of participants with EF between 41–49%, described as having HF with mid-range EF (HF<sub>mrEF</sub>),<sup>4</sup> to determine whether associations with smoking more closely resembled HF<sub>rEF</sub> or HF<sub>pEF</sub> phenotypes.

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

## Results

Our study population included 6792 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: 3418 never smokers, 2487 former

smokers, and 887 current smokers. Compared to never smokers, current smokers were younger, more likely to be male and African American and had baseline CAC>0 (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 1000 person-years and that of HFpEF was 1.9 per 1000 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 (HR, 2.05; 95% CI, 1.36–3.09; 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, 1.27–5.25 and HR, 2.51; 95% CI, 1.15–5.49 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 to those with a <8 pack-year history in Model 2. We also found a non-significantly higher risk of total HF and HFpEF among former smokers who smoked >26 pack-years compared to those with a <8 pack-year history (Supplementary Table 3). Non-significant 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  $\geq 130$  mm Hg or DBP  $\geq 90$  mm Hg,<sup>23</sup> and our results did not change.

## Discussion

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

Smoking promotes the development of atherosclerotic CVD<sup>14,26,27</sup> via impaired endothelium-dependent vasodilation.<sup>28,29</sup> Additionally, smoking induces a hypercoagulable

state<sup>30,31</sup> 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.<sup>28</sup> Additionally, chronic inflammation, which is associated with smoking,<sup>14,21,26</sup> alters myocardial structure and function.<sup>32,33</sup> In our study, however, smoking retained its association with HF after adjusting for hsCRP, a pro-inflammatory 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 have lower SBP; they also had a trend towards lower salt intake. This is possibly related to current smokers being younger than other participants (Table 1) though 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 prior study reported that abstaining 15 years resulted in HF risk equivalent to having never smoked.<sup>34</sup> Our study demonstrated a lower risk of HF among former smokers with higher quit-years, but these results were not significant. The non-significant findings regarding smoking burden differ from the existing literature, in which pack-years are significantly associated with HF risk among past smokers compared to never smokers.<sup>24</sup> 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 to <8. This is likely the result of small sample size, with 370 participants and only 10 HF events among current smokers.

Our study re-classified 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<sup>14,27,35</sup> and HF,<sup>36</sup> is another strength of our study. Similarly, we incorporated hsCRP, a marker of inflammation that exhibits a dose-response relationship with smoking.<sup>14,21</sup> 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

The authors thank the other investigators, staff, and participants of the MESA study for their valuable contributions. A full list of participating investigators and institutions can be found at <http://www.mesa-nhlbi.org>. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the Food and Drug Administration. This research was supported by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the NHLBI and by grants UL1-TR-000040 and UL1-TR-001079 from NCR. Exam 1 and 5 Urinary Cotinine measurements are available to the MESA study courtesy of MESA Lung contract HL077612. Research reported in this work was supported by grant number 5P50HL120163 from the NHLBI and FDA Center for Tobacco Products (CTP).

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**Table 1.**

## Baseline Characteristics by Cigarette Smoking Status

Variable	Total (N=6792)	Never Smokers (N=3418)	Former Smokers (N=2487)	Current Smokers (N=887)
<i>Age (years)</i>	62±10	62±11	63±10	58±9
<i>Men</i>	3203 (47%)	1297 (38%)	1439 (58%)	467 (53%)
<i>Race/Ethnicity</i>				
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%)
<i>Bachelor's Degree</i>	1171 (17%)	610 (18%)	450 (18%)	111 (13%)
<i>Body mass index (kg/m<sup>2</sup>)</i>	28.3±5.5	28.1±5.5	28.8±5.5	28.0±5.3
<i>Systolic blood pressure (mm Hg)</i>	127±21	127±22	127±21	124±22
<i>LDL-C (mg/dL)</i>	117±31	118±31	116±31	116±33
<i>HDL-C (mg/dL)</i>	51±15	52±15	51±15	48±14
<i>Lipid-lowering medication use</i>	1099 (16%)	543 (16%)	449 (18%)	107 (12%)
<i>Hypertension</i>	3044 (45%)	1540 (45%)	1173 (47%)	331 (37%)
<i>Antihypertensive medication use</i>	2524 (37%)	1286 (38%)	975 (39%)	263 (30%)
<i>Diabetes Mellitus</i>	857 (13%)	425 (12%)	321 (13%)	111 (13%)
<i>Current alcohol use</i>	3749 (55%)	1596 (47%)	1551 (63%)	602 (68%)
<i>Moderate-vigorous physical activity (MET-min/week)</i>	1080 [1515]	1050 [1480]	1080 [1440]	1233 [1890]
<i>Mediterranean Diet score</i>	5 [3]	5 [3]	5 [3]	4 [3]
<i>Frequent addition of salt to food</i>	2513 (40%)	1071 (33%)	1035 (45%)	407 (51%)
<i>High-sensitivity C-reactive protein (mg/L)</i>	1.9 [3.4]	1.8 [3.2]	1.9 [3.4]	2.6 [3.8]
<i>Coronary artery calcium (CAC) score &gt;0</i>	3391 (50%)	1513 (44%)	1442 (58%)	436 (49%)

- Continuous variables: mean±SD or median [interquartile range]

- Categorical variables: count (%)

