ORIGINAL RESEARCH

Demystifying Smoker's Paradox: A Propensity Score–Weighted Analysis in Patients Hospitalized With Acute Heart Failure

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***Background*—**Smoker's paradox has been observed with several vascular disorders, yet there are limited data in patients with acute heart failure (HF). We examined the effects of smoking in patients with acute HF using data from a large multicenter registry. The objective was to determine if the design and analytic approach could explain the smoker's paradox in acute HF mortality.

***Methods and Results*—**The data were sourced from the acute HF registry (Gulf CARE [Gulf Acute Heart Failure Registry]), a multicenter registry that recruited patients over 10 months admitted with a diagnosis of acute HF from 47 hospitals in 7 Middle Eastern countries. The association between smoking and mortality (in hospital) was examined using covariate adjustment, making use of mortality risk factors. A parallel analysis was performed using covariate balancing through propensity scores. Of 5005 patients hospitalized with acute HF, 1103 (22%) were current smokers. The in-hospital mortality rates were significantly lower in current smoker's before (odds ratio, 0.71; 95% CI, 0.52–0.96) and more so after (odds ratio, 0.47; 95% CI, 0.31–0.70) covariate adjustment. With the propensity score–derived covariate balance, the smoking effect became much less certain (odds ratio, 0.63; 95% CI, 0.36–1.11).

***Conclusions*—**The current study illustrates the fact that the smoker's paradox is likely to be a result of residual confounding as covariate adjustment may not resolve this if there are many competing prognostic confounders. In this situation, propensity score methods for covariate balancing seem preferable.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov/. Unique identifier: NCT01467973. **(*J Am Heart Assoc*. 2019;8: e013056. DOI: 10.1161/JAHA.119.013056.)**

Key Words: covariate adjustment • covariate balance • heart failure • mortality • study design

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Smoking is a strong risk factor for premature atherosclerosis, myocardial infarction (MI), heart failure (HF), and sudden cardiac death. It is estimated that smokers lose at least one decade of life expectancy, compared with those who have never smoked.[1] Yet, despite the well-established and modifiable risk associated with smoking, several studies have demonstrated that the short-term mortality after acute coronary syndromes (ACSs) or associated HF[2] is lower in current smokers (CSs) compared with current nonsmokers (CNs), the so-called smoker's paradox.[3] This apparent

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Accompanying Figures S1 and S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013056

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Clinical Perspective

What Is New?

- This study examined the smoking paradox in relation to confounding by severity of illness related variables in a Middle Eastern population admitted for heart failure.
- The relationship between smoking behavior at admission and mortality is reexamined from a methodological perspective comparing traditional covariate adjustment with covariate balancing via propensity score–based weights.

What Are the Clinical Implications?

- The smoking paradox is probably not a causal effect but rather a bias that has been incompletely addressed analytically.
- There are many confounding variables related to severity of illness in registry-based observational cardiovascular studies, making residual confounding a serious problem when assessing causal effects, on outcome, of specific factors (such as smoking).
- The results in this article suggest that covariate balancing using propensity score–based weights can help avoid such paradoxical results when compared with traditional covariate adjustment in the assessment of causal effects.

paradox, whereby CS subjects appear to have more favorable outcomes compared with CN subjects, has also been reported in other disease states, including stroke,[4] trauma,[5] cardiac arrest,[6] and preeclampsia.[7]

Smoking perhaps is not the variable that improves the outcome; it is more likely confounded by the different baseline variables that worsen outcome and are likely to induce smoking cessation, most important factors related to severity of illness.[8] The conventional approach used in research has been to adjust for such baseline characteristics when looking for a causal association from observational data.[9] In the latter, an attempt is then made to incorporate key important covariates into a regression model examining the relationship between the exposure and the outcome. Studies using this approach seem to confirm the presence of such a smoking paradox, the paradox being that CS seems to be a "cause" of the improved prognosis.[10]

Unfortunately, such regression models may be overfitted when the numbers with the outcome are small compared with the number of participants and confounders. In addition, the adequacy of model specification needs to be checked and the relationship between the third variables and the outcome needs to meet model specifications (eg, linear within a linear model). All these are potential problems; and despite the fact that standard guidelines suggest having no less than 10 events for each covariate incorporated into the model,[11] it may not be possible to adhere to this when important confounders are many, as is the case in observational research in ACS and HF. An alternative strategy that has emerged is the propensity score (PS), which is progressively being used in observational studies of cardiovascular interventions.[12–14] A PS is characterized as the likelihood of a patient being allocated to an intervention, given a set of exposures.[15] As the PS reduces many patient covariates into a single covariate, it decreases the probability of overfitting.[16] The goal of the PS technique is to attain covariate balance, as is the case with randomized comparisons.

In this study, we decided to compare the covariate adjustment and PS approach to examine, in detail, the effect of smoking status on the in-hospital mortality of patients hospitalized with acute HF using data from a multicenter multinational HF registry: the Gulf CARE (Gulf Acute Heart Failure Registry).

Methods

Data will be available from the corresponding author on reasonable request.

Registry Design

Details of the Gulf CARE design were previously published.[17,18] In summary, Gulf CARE was a multicenter, multinational, prospective, observational study that recruited patients who were admitted with the final diagnosis of acute HF from 47 hospitals in 7 Middle Eastern countries in the Arabian Gulf (Oman, Saudi Arabia, United Arab Emirates, Qatar, Bahrain, Yemen, and Kuwait) during February 2012 to November 2012.[17] Data were collected on episodes of hospitalization, as per a standardized case report form beginning with point of initial care, and including patient's discharge, transfer out of hospital, or in-hospital death, and for those discharged alive at 3 and at 12 months of follow-up. Study ethical approval was obtained from all concerned authorities in the recruiting centers. Informed consent was obtained from all patients. Each patient was given a unique identification number to prevent double counting.

Study included patients with acute HF from both sexes who were ≥18 years of age and admitted to the participating hospitals. Acute HF was defined on the basis of the European Society of Cardiology definition.[19] Acute HF was further classified as either acute decompensated chronic HF or new-onset acute HF (de novo) based on European Society of Cardiology guidelines.[19] Acute decompensated chronic HF was defined as worsening of HF in patients with a previous diagnosis or hospitalization for HF. New-onset acute HF (de novo) was defined as acute HF in patients with no history of HF.

Patients were excluded from the study if the following occurred: (1) they were discharged from the emergency department without admission, (2) they were transferred from a nonregistry hospital, (3) they could not provide informed

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consent, and (4) their final diagnosis was not HF. Registry organization and data collection and validation have already been outlined in a prior published article of Gulf CARE.[17,18]

Definitions of variables in the case report form were based on the European Society of Cardiology guidelines 2008 and the American College of Cardiology clinical data standards 2005.[19,20] Diabetes mellitus (DM) was defined as having a history of DM diagnosed and treated with medication and/or insulin or fasting blood glucose of 7.0 mmol/L (126 mg/dL) or glycated hemoglobin ≥6.5%. Hypertension was defined as having a history of hypertension diagnosed and treated with medication, blood pressure >140 mm Hg systolic or >90 mm Hg diastolic on at least 2 occasions, or blood pressure >130 mm Hg systolic or >80 mm Hg diastolic on at least 2 occasions, for patients with DM or chronic kidney disease (CKD). Hyperlipidemia was defined as history of dyslipidemia diagnosed and/or treated by a physician or total cholesterol >5.18 mmol/L (200 mg/dL), low-density lipoprotein cholesterol ≥3.37 mmol/L (130 mg/dL), or high-density lipoprotein cholesterol <1.04 mmol/L (40 mg/dL). CS was defined as smoking cigarettes, water pipe, cigar, or chewing tobacco within 1 month of index admission. CKD was defined as glomerular filtration rate <60 mL/min per 1.73 m^2 for ≥3 months, with or without kidney damage or on dialysis. If no glomerular filtration rate was available, serum creatinine >177 mmol/L or 2 mg/dL was marked as CKD. Obesity was defined as body mass index >25 kg/m^2. Cardiomyopathy was defined as a myocardial disorder in which the heart muscle is structurally and functionally abnormal (in the absence of coronary artery disease [CAD], hypertension, valvular disease, or congenital heart disease), sufficient to cause the observed myocardial abnormality. Infection definition in the registry was any systemic infection needing antibiotics. The presence of CAD was defined as history of CAD, MI, or coronary revascularization procedure, including percutaneous coronary intervention and coronary artery bypass grafting surgery.

Statistical Analysis

Baseline and outcome data were presented as frequency and percentages for categorical variables; and for interval variables, they were presented as means and SDs (and median and interquartile range for nonnormally distributed variables), as appropriate. χ^2 Tests (or Fisher exact tests for cells <5) were applied to see if there were associations between CSs and CNs for categorical variables, whereas Student *t* tests were used for normally distributed interval variables and Wilcoxon rank sum tests were used for nonnormally distributed interval variables. The association between smoking and mortality (in hospital) was examined using multivariable logistic regression, adjusting for risk factors potentially related to mortality. These included 3 from *demographics*: age, sex, and country of origin in the Gulf Cooperation Council countries; 9 from *previous history*: prior DM, prior CKD/dialysis, prior hyperlipidemia, prior CAD, prior asthma/chronic obstructive pulmonary disease, prior ACS, prior admission for HF, prior syncope in past 1 year, and prior use of aspirin; 3 from a*dmission status*: body mass index on admission, New York Heart Association class at admission, and admitted to intensive care unit; and, finally, 2 from *course in hospital:* intubation/ventilation and atrial fibrillation requiring therapy. Adjusted odds ratios (ORs) and 95% CIs were used to quantify the association between baseline variables and mortality.

In the second analysis, the PS for an individual was defined as the probability of being in the exposure group given all relevant covariates. The PS was estimated using a logistic regression model that incorporated all variables listed above used for the covariate adjustment model. After the PS was calculated, weights were applied to the regression model corresponding to 1/PS for patients in the CS cohort and [1/(1−PS)] for those in the CN cohort. No trimming was performed of these weights in the main analysis, but a sensitivity analysis restricting data to a subsample with PS between 0.01 and 0.99 as well as between 0.1 and 0.9 was performed as a sensitivity analysis. The weighted data were checked for covariate balance using standardized differences between CS and CN subjects before and after weighting. On the graph of standardized differences, horizontal lines denoting standardized differences of ±0.1 are indicated as it has been suggested that standardized differences that exceed these thresholds may be indicative of meaningful imbalance.[21] For comparison, we provide the crude effect estimate, the covariate-adjusted effect estimate, and the PS model weighted estimate. $P<0.05$ (2 tailed) was considered statistically significant. Stata, version 15 (StataCorp, College Station, TX), was used for the analysis.

Results

Baseline Characteristics

The study included 5005 patients hospitalized with acute HF, of whom 1103 (22%) were CSs. CS subjects were 6 years younger and more likely to present with acute decompensated chronic HF. Compared with nonsmokers, smokers were less likely to present with a history of CAD, left ventricular dysfunction, valvular heart disease, stroke/transient ischemic attacks, DM, hypertension, hyperlipidemia, CKD, asthma/chronic obstructive pulmonary disease, and thyroid disease, whereas CN subjects were more likely to have family history of cardiomyopathy/HF. CS subjects were less likely to be taking aspirin, digoxin, oral nitrates, and other evidence-based medications before admission (Table 1).

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Table 1. Baseline Characteristics of Subjects in the Registry

Characteristics	Smokers (n=1103; 22%)	Nonsmokers (n=3902; 78%)	*P* Value
HF type			
Acute new-onset HF	428 (39)	2289 (59)	0.001
Acute decompensated chronic HF	675 (61)	1613 (41)	
Age, mean±SD, y	55±12	61±15	0.001
Women	83 (7.5)	1791 (46)	0.001
Ethnicity/race			
Arab	945 (85.7)	3571 (91.5)	
Asian	154 (14)	319 (8.2)	
Other	4 (0.4)	12 (0.3)	
Previous cardiovascular history			
Known systolic LV dysfunction	351 (32)	1930 (50)	0.001
Known CAD	432 (39)	1905 (49)	0.001
Valvular heart disease	63 (6)	612 (16)	0.001
Congenital heart disease	7 (0.6)	34 (0.9)	0.44
PVD	46 (4)	177 (4.5)	0.60
Stroke/TIA	65 (6)	339 (8.7)	0.003
Family history of cardiomyopathy/heart failure	96 (8.7)	163 (4)	0.001
Other comorbidities			
Diabetes mellitus	439 (40)	2053 (53)	0.001
Hypertension	540 (49)	2519 (65)	0.001
Hyperlipidemia	345 (31)	1454 (37)	0.001
CKD/dialysis	69 (6)	675 (17)	0.001
Sleep apnea requiring therapy	11 (1)	88 (2.3)	0.008
Asthma/COPD	88 (8)	413 (10.6)	0.01
Thyroid disease	8 (0.7)	173 (4.4)	0.001
Clinical and biochemical parameters			
HR, mean±SD, bpm	100±20	96±23	0.001
Systolic blood pressure, mean±SD, mm Hg	137±33	137±34	0.95
Diastolic blood pressure, mean±SD, mm Hg	85±19	80±20	0.001
RR, median (IQR), /min	25 (22–29)	24 (20–28)	0.001
BMI, mean±SD, kg/m^2	27±5	28±6.6	0.001
Pulse oximetry saturation, mean±SD, %	92±6	93±7	0.88
NT-proBNP, median (IQR), pg/mL	3324 (1445–6246)	3190 (1313–7428)	0.06
Elevated troponin	458 (42)	1444 (37)	0.006
HbA1c, mean±SD, %	7.0±2.4	7.3±2.0	0.07
Total cholesterol, mean±SD, mmol/L	5.5±2.7	4.6±2.1	0.001
Creatinine, mean±SD, μmol/L	123±112	132±117	0.03
ECG rhythm AF/flutter	79 (7)	600 (15)	0.001
LVEF, mean±SD, %	35±12.5	37±14	0.001

Continued

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Table 1. Continued

Characteristics	Smokers (n=1103; 22%)	Nonsmokers (n=3902; 78%)	*P* Value
Cause			
Noncompliance with medications	209 (19)	755 (19)	0.77
Noncompliance with diet	18 (1.6)	118 (3)	0.01
Acute coronary syndromes	428 (39)	937 (24)	0.001
Uncontrolled hypertension	77 (7)	333 (8.5)	0.10
Uncontrolled arrhythmia	42 (4)	259 (6.6)	0.001
Anemia	24 (2)	130 (3)	0.05
Infection	130 (12)	601 (15)	0.003

Data are given as number (percentage), unless otherwise indicated. Analyses were performed using Student *t* test, Wilcoxon-Mann-Whitney test, or Pearson's χ^2 test, wherever appropriate. AF indicates atrial fibrillation; BMI, body mass index; bpm, beats per minute; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HbA1c, glycated hemoglobin; HF, heart failure; HR, heart rate; IQR, interquartile range; LV, left ventricular; LVEF, LV ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PVD, peripheral vascular disease; RR, respiratory rate; TIA, transient ischemic attack.

Precipitating Factors for HF Hospitalization

ACS was significantly more common in CSs, whereas noncompliance with diet, uncontrolled arrhythmias, and systemic infections were more common in CNs as possible precipitating factors for hospitalization. (Table 1)

Clinical and Biochemical Parameters

On presentation, CSs had significantly lower rates of atrial arrhythmia and a lower mean ejection fraction. CSs had higher rates of serum troponin and a lower creatinine compared with CNs (Table 1).

In-Hospital Course

CSs were more likely to be treated with inotropes, whereas the rates of noninvasive ventilations and acute dialysis or blood transfusion for major bleeding were more commonly used in CNs. Also, CNs were more likely to have systemic infections requiring antibiotics. The rates of invasive ventilation, intra-aortic balloon pump insertion, and the risk of development of stroke were comparable between the 2 groups. At discharge, CSs were more likely to be prescribed digoxin, aspirin, clopidogrel, β blockers, angiotensin-converting enzyme inhibitors, and aldosterone antagonists, whereas CNs were more likely to be discharged on hydralazine and oral anticoagulants. Cardiac procedures, including interventions and device therapy, were low in the 2 groups, with percutaneous coronary interventions performed more often in CSs. The CS subjects had higher rates of ventricular tachycardia/fibrillation requiring therapy, whereas CNs had higher rates of atrial fibrillation requiring therapy. The crude in-hospital mortality rate was lower in CSs than CNs (4.8% versus 6.7%; *P*=0.02) (Table 2).

Regression Models

The crude OR for in-hospital mortality, according to smoking status (CS versus CN) at admission, was 0.71 (95% CI, 0.52–0.96; *P*=0.025). Multivariable logistic regression using covariate adjustment to determine the possibility of a causal effect of smoking on in-hospital mortality revealed an even stronger protective effect for CS, with ≈50% reduction in odds of in-hospital mortality (OR, 0.47; 95% CI, 0.31–0.70; *P*<0.001), Using untrimmed PS values, the inverse probability of exposure-weighted logistic regression with robust error variances resulted in a mortality OR of 0.63 (95% CI, 0.36–1.11; *P*=0.11). The trimmed data sets revealed a similar result after exclusion of 285 subjects (retained if PS values were between 0.01 and 0.99); the in-hospital mortality OR for CS was 0.71 (95% CI, 0.41–1.24; *P*=0.233). After exclusion of 2057 subjects (retained if PS values were between 0.1 and 0.9), the in-hospital mortality OR was 0.67 (95% CI, 0.45–1.00; *P*=0.049). Covariate balance was clearly achieved using the inverse probability weights, as depicted in the Figure and Figures S1 and S2.

Discussion

In the current study, we compared clinical presentation, risk factors, in-hospital course, and mortality, stratified by smoking status, in a large group of patients hospitalized with acute HF. CS subjects were younger and had a lower risk profile compared with CN subjects. The in-hospital mortality rates were also significantly lower in CS patients before and more so after covariate adjustment. After using the PS-derived inverse probability of exposure weights, the smoking effect weakened and was no longer statistically significant. Given our results, we may be looking at reverse causality: healthier patients are more likely to continue to smoke. The smoking advantage

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Table 2. In-Hospital Course of Registry Subjects

Variables	Smokers (n=1103; 22%)	Nonsmokers (n=3902; 78%)	*P* Value
In-hospital course			
NIV	79 (7.2)	394 (10)	0.003
Intubation/ventilation	97 (8.8)	327 (8.4)	0.66
Inotropes	231 (21)	552 (14)	0.001
IABP insertion	21 (2)	61 (1.6)	0.43
Acute dialysis/ ultrafiltration	16 (1.5)	119 (3)	0.004
VT/VF requiring therapy	74 (6.7)	148 (3.8)	0.001
AF requiring therapy	48 (4.4)	263 (6.7)	0.004
Major bleeding	2 (0.2)	38 (1.0)	0.009
Blood transfusion	28 (2.5)	226 (5.8)	0.001
Stroke	13 (1.2)	55 (1.4)	0.56
Systemic infection requiring antibiotics	229 (21)	979 (25)	0.003
Cardiac procedures			
PCI	112 (10)	187 (5)	0.001
CABG	20 (2)	49 (1.3)	0.16
Discharge medications			
Digoxin	306 (28)	901 (23)	0.001
Oral nitrates	405 (37)	1417 (36)	0.81
Hydralazine	42 (4)	311 (8)	0.001
Aspirin	925 (84)	2926 (75)	0.001
Clopidogrel	522 (47)	1276 (33)	0.001
Oral anticoagulants	157 (14)	740 (19)	0.001
Statin	775 (70)	2660 (68)	0.19
Ivabradine	66 (6)	173 (4.4)	0.03
Antiarrhythmic	57 (5)	187 (5)	0.61
β Blockers	798 (72)	2564 (66)	0.001
ACE inhibitors	753 (68)	2129 (55)	0.001
ARBs	160 (15)	642 (17)	0.12
Aldosterone antagonists	526 (48)	1530 (39)	0.001
Diuretics	975 (88)	3489 (89)	0.32
Length of stay, median (IQR), d	7 (4–10)	6 (4–11)	0.16
In-hospital mortality	53 (4.8)	260 (6.7)	0.02

Data are given as number (percentage), unless otherwise indicated. Analyses were performed using Student *t* test, Wilcoxon-Mann-Whitney test, Pearson's χ^2 test, or Fisher exact test, wherever appropriate. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pump; IQR, interquartile range; NIV, noninvasive ventilation; PCI, percutaneous coronary intervention; VF, ventricular fibrillation; VT, ventricular tachycardia.

demonstrated after covariate adjustment may be because the latter has been inadequate, as we have demonstrated herein and which has also been suggested by others.[22] However, there have been studies suggesting attenuated endothelial dysfunction[23] in CS subjects, although this may still reflect less severity of illness and, thus, reverse causality. Some researchers suggest that it is the smoking cessation enforced by hospitalization that improves outcome,[10] although this is unlikely because of the result of this study.

From first mention of the smoker's paradox in 1995 and in the 15 years after this, there had been 7 randomized trials and 10 observational studies/registries published presenting the idea of the smoker's paradox in ACS[3] but only one on HF per se.[2] Since then, several studies using covariate adjustment have shown that CS status is protective. In one study, which defined CS to also include patients reported to have quit smoking during the past year, the in-hospital mortality rate was lower in smokers, but smoking status was not an independent predictor of mortality.[24] This paradoxical result can also be shown in young patients with acute MI in whom CS was an independent predictor of 8-month cardiac death (OR, 0.25; 95% CI, 0.07–0.92; *P*=0.037) and total death (OR, 0.26; 95% CI, 0.09–0.82; *P*=0.021).[25] The same has been found for the benefit resulting from routine early invasive management of unselected patients with acute non–ST-segment–elevation MI, in whom the treatment effect of an early invasive strategy was more pronounced among CSs and not entirely explained by covariate adjustment.[26] Finally, the only study in HF, to date, has demonstrated that someone who has smoked cigarettes any time during the year before hospital arrival (which was how CS was defined) had a better prognosis than CNs (labeled in their article as "nonsmokers").[2]

PS analyses have also been previously done. One study that examined 29 199 patients with acute MI found that 42% were CS subjects, and the hazard ratio (HR) was 0.52 (95% CI, 0.47–0.58; *P*<0.001), in favor of reduced mortality in the CS subjects at up to 1 year after acute MI. Covariate adjustment attenuated the effect, but the HR remained statistically significant (HR, 0.85; 95% CI, 0.76–0.95; *P*=0.005). However, the use of PS matching corroborated the results of reduced mortality among CSs (6.7% versus 7.6%; *P*=0.005).[27] This suggests that PS matching may not be as effective as PS-based weighting. Indeed, in other studies that have used PS-based weights, the CS factor lost its influence in prognosis and the authors suggest that the smoking paradox is a finding that could be explained by other prognostic factors.[28] This may also explain why CS seems to impart a covariate-adjusted survival benefit in patients with other conditions, such as traumatic injuries.[5]

In studies of smoking cessation on subjects with left ventricular dysfunction after MI using PS-adjusted Cox proportional hazard models, the benefit of this cessation has been confirmed.[29] In baseline smokers who survived to 6 months without interval events, smoking cessation at 6-month follow-up was associated with a significantly lower

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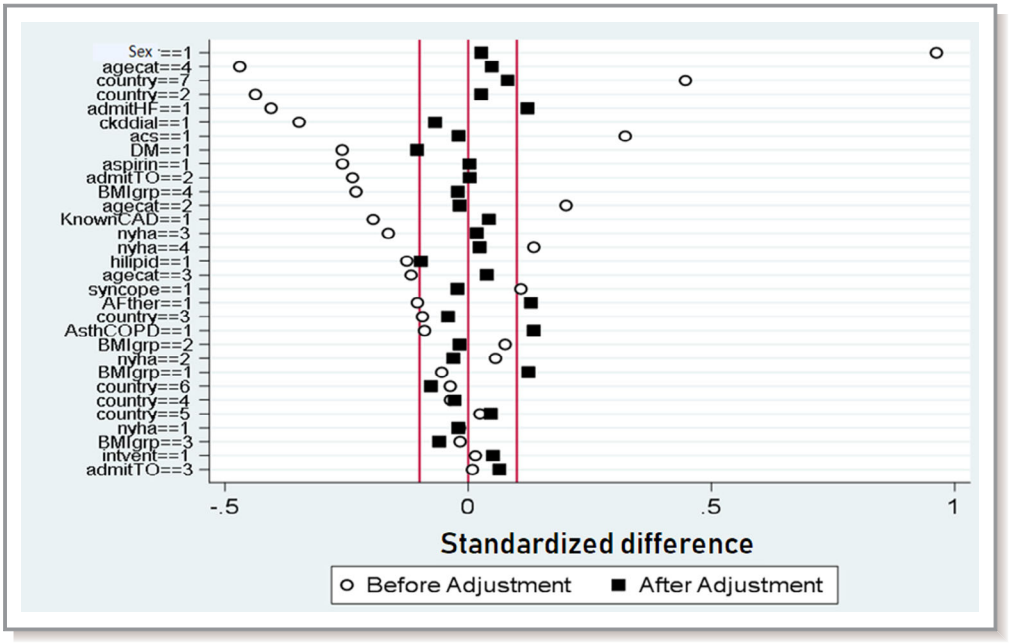

Figure. All subjects included. Covariate balance after using the inverse probability weights; horizontal lines denoting standardized differences of ±0.1; standardized differences that exceed thresholds are indicative of meaningful imbalance. Circles indicate standardized differences before propensity score (PS) adjustment, and squares indicate standardized differences after PS adjustment. acs Indicates precipitating acute coronary syndrome; admitHF, previous admission for heart failure; admitTO, where admitted in hospital; AFther, had atrial fibrillation requiring therapy; agecat, age category; aspirin, on aspirin before admission; AsthCOPD, history of asthma or chronic obstructive pulmonary disease; BMIgrp, body mass index category; CAD, coronary artery disease; ckddial, history of chronic kidney disease or dialysis; country, country of hospitalization; DM, diabetes mellitus; hilipid, history of hyperlipidemia; intvent, was intubated and/or on a ventilator; nyha, New York Heart Association class (heart failure); syncope, history of syncope in the past 1 year.

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adjusted risk of all-cause mortality (HR, 0.57; 95% CI, 0.31–0.91), death or recurrent MI (HR, 0.68; 95% CI, 0.47–0.99), and death or acute HF hospitalization (HR, 0.65; 95% CI, 0.46–0.92).[29] These findings indicate that within a CS cohort, smoking cessation (beyond hospital admission) is beneficial after high-risk MI, and this clearly indicates that smoking cannot be causally related to better prognosis if cessation itself leads to better prognosis. Other studies have shown that smoking is associated with lower 30-day mortality (HR, 0.91; 95% CI, 0.87–0.94) but higher long-term mortality (17-year HR, 1.19; 95% CI, 1.17–1.20) after acute MI, in keeping with the hypothesis that continuing to smoke on admission is essentially a marker of a reduced severity of illness in terms of the underlying diagnosis.[30] Overall, crude life expectancy estimates are also lower for smokers than nonsmokers at all ages, which translates into sizeable numbers of life-years lost attributable to smoking.[30] Given these and other similar findings,[31] it is unlikely that the covariate-adjusted estimates reported do imply causality. Finally, a recent study of HF has shown that if never smokers are the reference category, then there is a worse prognosis for CS.[32] This suggests that smoking *per se* is harmful, but quitting because of illness on its own selects out those who have a worse prognosis. We could not test this hypothesis using our data as never smokers were not identified.

This study has a limitation of evaluating smoking history only at admission. In other words, people were classified as CSs or CNs. Thus, the burden of smoking was ignored and only behavior on admission was assessed. Therefore, the results in this article indicate the prognostic value of the smoking behavior at one time point (admission) and do not reflect the morbidity caused by smoking. This classification is in keeping with other epidemiological studies published previously.[33] Another limitation is that with PS methods, there is the issue of extreme weights. It has been suggested that an analysis be done on a subsample with PS between 0.1 and 0.9. In the case of this study, this eliminates 41% of the sample and, thus, is ill advised. We suggest creating a subsample with PS between 0.01 and 0.99 as this limits the exclusions markedly. However, with either subsample, covariate balance was achieved, more so with PS values between 0.1 and 0.9.

We conclude that in studies of HF or of ACS, conditioning on the PS-derived weight is better and obviates the need for adjustment. In addition, PS techniques allow one to measure

marginal (or population-average) treatment effects as opposed to covariate adjustment-based approaches that allow one to estimate conditional (or adjusted) estimates of treatment effects. However, a recent evaluation of PS versus covariate adjustment in 4 large cardiovascular observational studies did not reveal a major difference between covariate adjustment and PS methods.[9] This may be the case when confounding variables are not many, but if there are a multitude of confounders, then clearly PS methods are superior. The novel parts of this study include demonstration of this paradox in a Middle Eastern population and the documentation of residual confounding, even after accounting for known confounders in this understudied population. It is possible that such unknown confounders could be specific to this particular population and similarly hypothesized for other population studies. This paradox may be investigated further by collecting data on never smokers and using them as the reference for the analysis, but this needs to be tested in future studies or with existing data. Finally, we should point out that we examined potential confounding in this article as an explanation for the paradoxical results. Others[34] have looked at the potential for paradoxical results caused by collider stratification bias (a form of selection bias). Obviously, if we balance/stratify/adjust on a collider, we introduce, rather than remove, bias, as indicated by Lajous et al[34]; in their article, DM was a collider when the obesity-mortality relationship was being examined and, thus, adjusting for or stratifying on DM induced bias, with strata based on DM having opposite associations. In the case of the "current smoking" behavior at admission and its association with mortality, all variables we adjust for or balance are confounders determined *a priori* by examining their putative association with exposure and outcome.

Conclusions

Our study shows that there is no survival advantage for CSs in patients hospitalized with HF. The current study underlines the need for future studies to also review the smoker`s paradox phenomena reported in other chronic conditions with appropriate covariate balancing as this may demystify erroneous conclusions currently present in the medical literature. In addition, future studies should also focus on discovering the effect of unknown confounders using novel statistical methods, such as machine learning and use of electronic health records, which have a potential to improve our understanding of residual confounding in studies of chronic diseases.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

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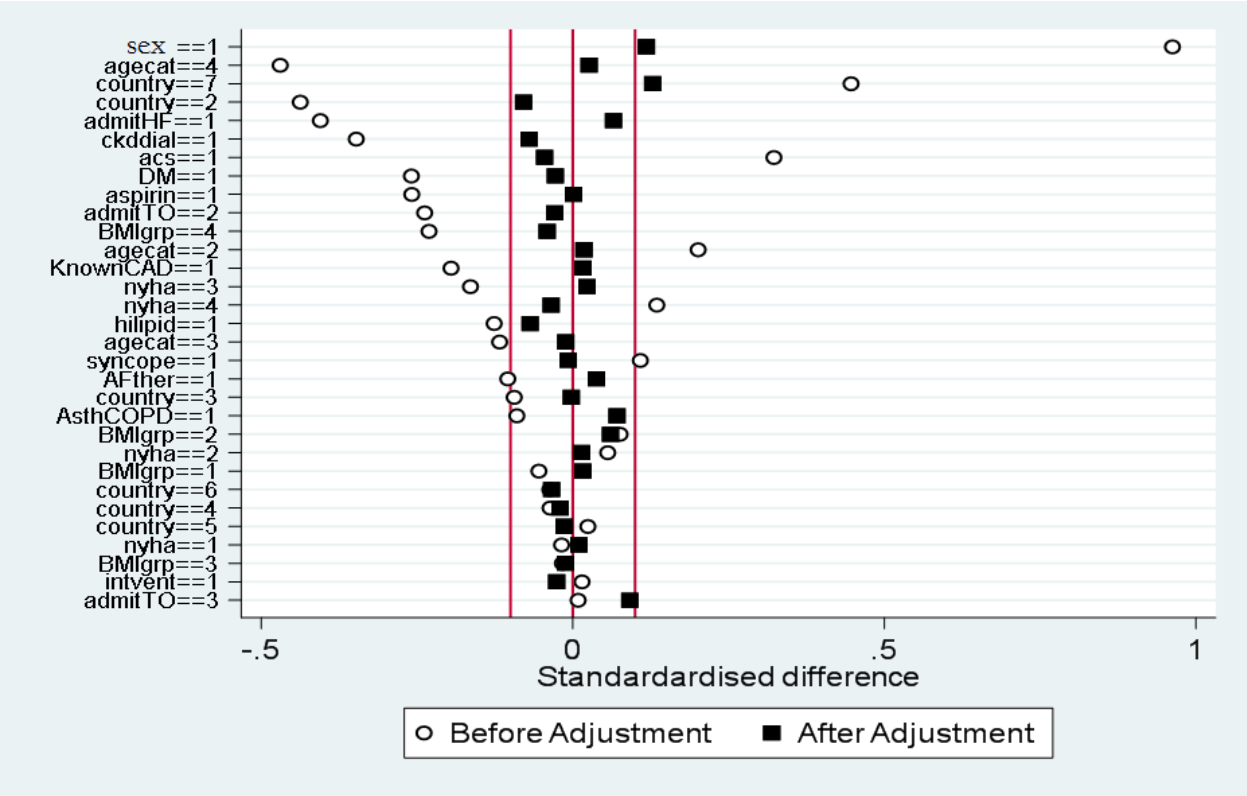
Figure S1. Limited to PS between 0.01 and 0.99.



Covariate balance after using the inverse probability weights; horizontal lines denoting standardized differences of ±0.1, standardized differences that exceed thresholds indicative of meaningful imbalance. Circles indicate standardized differences prior to PS adjustment and squares indicate standardized differences after PS adjustment. agecat=Age category; ckddial=History of CKD or dialysis; hilipid=History of hyperlipidemia; acs=Precipitating acute coronary syndrome; aspirin=On aspirin before admission; nyha=NYHA Class (heart failure); AFther=Had atrial fibrillation requiring therapy; AsthCOPD=History of asthma or COPD; BMIgrp=BMI category; country=Country of hospitalization; intvent=Was intubated and/or on a ventilator; syncope=History of syncope in the last one year; admitHF=Previous admission for heart failure; admitTO=Where admitted in hospital.

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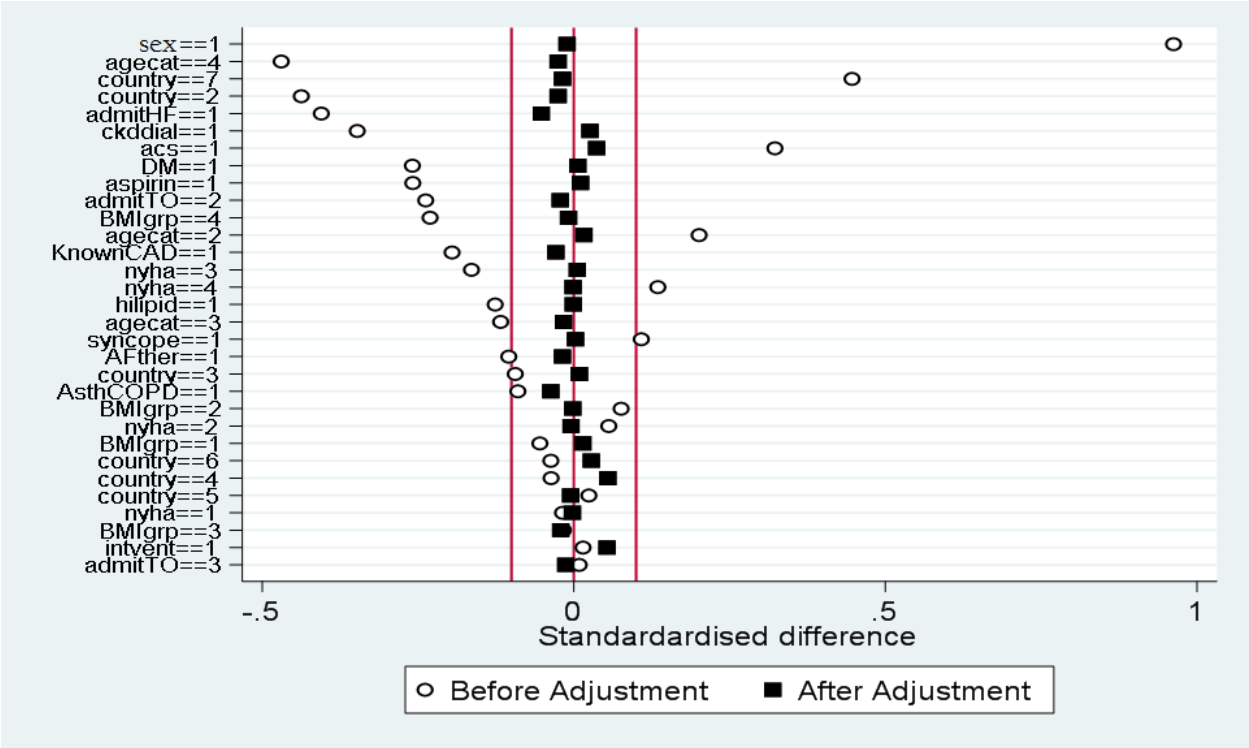
Figure S2. Limited to PS between 0.1 and 0.9.



Covariate balance after using the inverse probability weights; horizontal lines denoting standardized differences of ±0.1, standardized differences that exceed thresholds indicative of meaningful imbalance. Circles indicate standardized differences prior to PS adjustment and squares indicate standardized differences after PS adjustment. agecat=Age category; ckddial=History of CKD or dialysis; hilipid=History of hyperlipidemia; acs=Precipitating acute coronary syndrome; aspirin=On aspirin before admission; nyha=NYHA Class (heart failure); AFther=Had atrial fibrillation requiring therapy; AsthCOPD=History of asthma or COPD; BMIgrp=BMI category; country=Country of hospitalization; intvent=Was intubated and/or on a ventilator; syncope=History of syncope in the last one year; admitHF=Previous admission for heart failure; admitTO=Where admitted in hospital.

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