

# Secondhand Smoke Exposure and Quality of Life in Patients With Heart Failure

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**Background:** Secondhand smoke (SHS) exposure is associated with an increased risk of atherosclerotic heart disease and cardiac events. We sought to assess the effect of SHS on health-related quality of life (HRQOL) in patients with heart failure.

**Methods:** Current nonsmokers with heart failure (N=205) were enrolled in a cohort study. Exposure to SHS was assessed with a validated exposure questionnaire and a high-sensitivity assay for urinary cotinine level. Multidimensional HRQOL was evaluated with the RAND 36-Item Short Form Health Survey, which assesses 8 domains on a scale of 0 (worst) to 100 (best): physical functioning, bodily pain, role limitations due to physical health problems (role physical), role limitations due to emotional/personal problems (role emotional), emotional well-being, social functioning, energy/fatigue, and general health perceptions. A subset of patients (n=75) agreed to assessment of functional status with a 6-minute walk test.

**Results:** Self-reported exposure to SHS was associated with generally lower HRQOL scores in univariate analysis, with statistically and clinically significant reductions in 3 subscale scores: role physical (22.2 points), emotional well-being (11.0 points), and role emotional (16.2 points). Even after adjustment for clinical factors, such as age, sex, New York Heart Association class of heart failure, comorbidities, and medications, exposure to SHS remained an independent predictor of HRQOL scores in these domains. When increasing quartiles of urinary cotinine level were used as the exposure measure, qualitatively similar results were obtained.

**Conclusions:** Even low levels of SHS are associated with lower scores in several aspects of HRQOL. Physicians should advise patients with heart failure and their families to avoid SHS exposure.

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**H**EART FAILURE (HF) IS A common clinical syndrome, affecting millions of patients in the United States and resulting in extensive morbidity and increased mortality.

*See also pages 1894, 1901, 1907, and 1950*

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Annual mortality rates for patients with HF vary from approximately 15% for unselected patients in population-based studies<sup>1</sup> to as high as 50% in patients with New York Heart Association (NYHA) class IV HF<sup>2</sup> who experience symptoms even at rest. Moreover, HF is the most common reason for hospital admission in the Medicare population.<sup>3</sup> Although the causes of HF are diverse, there is significant overlap between the population of patients with coronary artery disease and those with HF. Analyses by Suskin et al,<sup>4</sup> using data from the Studies of Left Ventricular Dysfunc-

tion (SOLVD) trial, suggest that active smoking in the HF population is associated with more than a 40% increase in mortality vs the mortality in patients with HF who have never smoked. The incidence of death, myocardial infarction, or recurrent hospitalization for HF was also significantly greater in current smokers when compared with patients who had never smoked or those who no longer smoked (relative risk, 1.39).<sup>4</sup> Benefits of smoking cessation in this study accrued rapidly; within 2 years of quitting, the risk of patients who no longer smoked was not significantly different from that of those who never smoked.

Epidemiologic studies<sup>5</sup> have documented an increased risk of cardiovascular disease in persons with secondhand exposure to tobacco smoke. The 2005 meta-analysis of 29 studies in the general population conducted by Barnoya and Glantz<sup>6</sup> found a relative risk of 1.31 (95% CI, 1.21-1.41) for ischemic heart disease in nonsmokers exposed to secondhand smoke (SHS) compared with those not ex-

posed. When exposure is measured by cotinine levels (a metabolite of nicotine), the risks are even higher, with a hazard ratio for coronary heart disease of 1.57 (95% CI, 1.08-2.28) in the highest quartile of exposure compared with the lowest quartile,<sup>7</sup> likely the result of reduced misclassification bias when biomarkers are used.

We hypothesized that SHS might have deleterious effects on clinical outcomes in patients with HF similar to those in patients with coronary artery disease and may also have effects on health-related quality of life (HRQOL). We tested this hypothesis in a cohort study to assess the relationship of SHS exposure with functional status and HRQOL in patients with HF. The current analysis presents cross-sectional analyses of our baseline data at the time of enrollment.

## METHODS

With informed consent, self-reported current nonsmokers (never smokers or ex-smokers who quit >2 years ago) having the clinical diagnosis of HF (N=205), regardless of ejection fraction, were enrolled from the cardiology and HF clinics at the University of California, San Francisco, in a cohort study of the effects of SHS on patients with HF. Adults of any age, race, or ethnicity could participate. The protocol was approved by the University of California, San Francisco, Committee on Human Research.

Baseline demographic and clinical data were collected. Exposure to SHS was assessed by data from self-report, using a validated exposure questionnaire,<sup>8</sup> and a high-sensitivity assay for urinary cotinine level. The questionnaire assesses primary smoking history, as well as passive smoking exposure at home, in the workplace, and in public places or social situations, and has been validated against airborne nicotine.<sup>8</sup> For this analysis, exposure was gauged by responses to the following question: "How many hours per week are you exposed to other people's tobacco smoke?" The answers were organized as a multilevel categorical variable with levels of 0, 1 to 9, 10 to 39, and more than 40 hours weekly. Exposed patients were grouped in analysis because of the small number of individuals reporting higher levels of exposure. The high-sensitivity liquid chromatography cotinine assay had a lower limit of detection of 0.2 ng/mL at the start of the study. An improved assay with a lower limit of detection of 0.05 ng/mL was introduced partway through the study. For the purposes of this analysis, individuals with urinary cotinine determinations higher than 50 ng/mL (n=3) were excluded as probable smokers,<sup>9</sup> resulting in a final sample of 202 patients.

Multidimensional HRQOL was assessed with the RAND 36-Item Short Form Health Survey.<sup>10,11</sup> Individual components were used to construct subscale scores in 8 health-related domains: physical functioning, bodily pain, role limitations due to physical health problems (role physical), role limitations due to emotional/personal problems (role emotional), emotional well-being, social functioning, energy/fatigue, and general health perceptions. For each domain, the point scores range from 0 (worst) to 100 (best). A subset of patients (n=75) agreed to perform a 6-minute walk test, which measures the maximal distance (meters) they could walk in 6 minutes, along with oxygen saturation and heart rate before and after the walk test.<sup>12</sup> Effort on the walk test was measured by the Borg dyspnea scale.<sup>13</sup>

All end points were selected a priori as end points for analysis. Each was assessed by means of unadjusted mean (SD) in unexposed and exposed patients according to their questionnaire responses. Bivariate and multivariate linear regressions

using 2-sided *P* values were performed to allow adjustment for important clinical factors. Age and sex were forced into each model. Other potential confounding variables (NYHA class, diabetes mellitus, hypertension, past smoking, systolic blood pressure at enrollment visit, ejection fraction, Charlson comorbidity index, and use of common medications grouped by class) were tested as predictors of HRQOL in univariate analysis. If the *P* value in univariate analysis was less than .10, it was included in the multivariate model. All analyses were performed using commercial software (SAS version 8; SAS Institute, Inc, Cary, North Carolina).

For analyses of the relationship between urinary cotinine level and HRQOL measures, participants were considered to have no SHS exposure if urinary cotinine level measured less than 0.2 ng/mL (n=100). This cut point was chosen because it was the lower limit of detection for the high-sensitivity cotinine assay used at the start of the study. Remaining cotinine levels were divided into quartiles (with breakpoints at 0.27, 0.43, and 1.30 ng/mL) to determine whether the quartile of urinary cotinine level predicted HRQOL measures. Parallel univariate and multivariate linear regression analyses were performed using urinary cotinine level as the measure of exposure.

## RESULTS

### BASELINE CHARACTERISTICS

Baseline characteristics by questionnaire exposure status are reported in **Table 1**. Exposed patients were slightly younger, and just over half in both groups were men. Cardiac risk factor profiles were similar, as was ejection fraction. The majority of patients (59%) had preserved ejection fraction ( $\geq 40\%$ ), and 41% had more significant systolic dysfunction. Other comorbidities, as measured by the Charlson comorbidity index,<sup>14</sup> were not significantly different between groups. New York Heart Association class of HF was distributed broadly, with 23% of unexposed participants in class I, 44% in class II, 29% in class III, and 5% in class IV. The corresponding numbers for exposed patients were 15% in class I, 40% in class II, 36% in class III, and 9% in class IV. The data suggest somewhat worse functional status in exposed patients, although the differences did not reach statistical significance. Most patients in the exposed and unexposed groups were being treated with standard HF medications, such as  $\beta$ -blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, although there was a suggestion of higher use of  $\beta$ -blockers in exposed patients. The subset of patients undergoing a 6-minute walk test was slightly younger (mean age, 64.2 vs 66.0 years), with slightly better functional status (mean NYHA class, 2.0 vs 2.3).

### EXPOSURE TO SHS

Almost 25% of the cohort reported exposure to SHS (Table 1), with most exposure at relatively low levels. Specifically, 155 patients (76.3%) reported no exposure, and 37 (18.3%), 7 (3.5%), and 3 (1.5%) reported 1 to 9, 10 to 29, and 30 or more hours per week of exposure, respectively. The mean (SD) urinary cotinine level in patients who reported no exposure to SHS (n=155) was 0.26 (0.54) ng/mL (range, <0.20-3.66 ng/mL); the mean level in those with reported exposure (n=47) was 1.43 (3.19)

**Table 1. Baseline Characteristics of the Cohort by Self-reported Exposure Status<sup>a</sup>**

Characteristic	Mean (SD)		P Value
	Unexposed (n=155)	Exposed (n=47) <sup>b</sup>	
Age, y	66.1 (15.8)	62.0 (19.0)	.13
Male sex, %	56	58	.83
Diabetes mellitus, %	27	30	.76
Hypercholesterolemia, %	66	68	.63
Family history of CAD, %	15	13	.66
Former smoker, %	55	55	.99
NYHA class, %			
I	23	15	.09
II	44	40	
III	29	36	
IV	5	9	
Ejection fraction	43.7 (16.4)	44.6 (18.1)	.75
Charlson comorbidity index	2.7 (1.9)	2.5 (1.5)	.43
Medication use, %			
β-Blocker	69	82	.09
ACE inhibitor	51	55	.80
ARB	30	32	.80
Cholesterol-lowering agent	66	59	.43
Antiplatelet agent	56	55	.90
General health, mean (SE)	41.6 (1.9)	39.2 (3.0)	.54
Physical function, mean (SE)	49.7 (2.4)	41.0 (4.6)	.10
Role physical, mean (SE) <sup>c</sup>	44.6 (3.8)	22.3 (5.3)	.003
Emotional well-being, mean (SE) <sup>c</sup>	76.5 (1.5)	65.5 (3.4)	<.001
Role emotional, mean (SE) <sup>c</sup>	69.3 (3.6)	53.1 (6.8)	.03
Vitality, mean (SE)	45.4 (2.0)	39.8 (3.5)	.17
Bodily pain, mean (SE)	70.0 (2.4)	61.8 (4.6)	.13
Social function, mean (SE)	69.1 (2.6)	59.6 (4.5)	.08
6-min walk distance, m (n=75)	342.6	332.9	.77

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; NYHA, New York Heart Association.

<sup>a</sup>Occasional data missing for each variable: diabetes mellitus (2 patients), hypercholesterolemia (1), family history (6), NYHA class (2), urinary cotinine level (16), medications (6), general health (12 [3 exposed, 9 unexposed]), physical function (30 [12 exposed, 18 unexposed]), role physical (15 [3 exposed, 12 unexposed]), emotional well-being (20 [6 exposed, 14 unexposed]), role emotional (19 [4 exposed, 15 unexposed]), vitality (21 [6 exposed, 15 unexposed]), bodily pain (15 [5 exposed, 10 unexposed]), and social function (14 [4 exposed, 10 unexposed]).

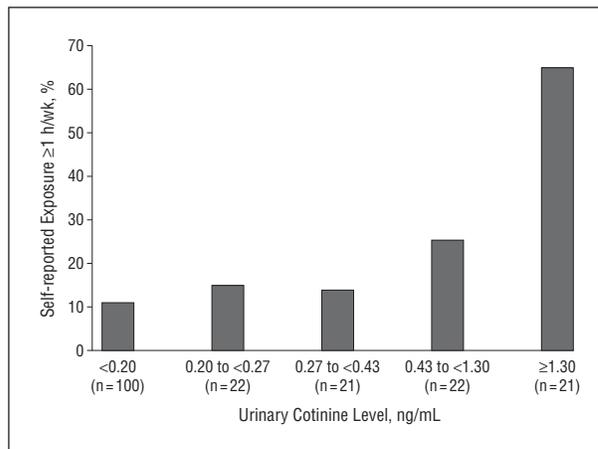
<sup>b</sup>Defined as any exposure greater than or equal to 1 h/wk.

<sup>c</sup> $P < .05$  in analyses of subscale score by exposure status.

ng/mL (range, 0.2-24.2 ng/mL). The relationship between self-reported exposure and urinary cotinine level is shown in the **Figure**.

#### EFFECT OF EXPOSURE TO SHS ON HRQOL

In unadjusted (bivariate) analyses, self-reported exposure to SHS was associated with lower mean HRQOL scores in each of the 8 domains of the RAND 36-Item Short Form Health Survey (Table 1). The decrement was particularly striking and statistically significant in 3 subscales: role physical (22.2 points), emotional well-being (11.0 points), and role emotional (16.2 points). Other domains exhibited smaller effects that did not achieve statistical significance but were negative associations. For example, mean physical function scores were 8.7 points



**Figure.** The relationship between secondhand smoke exposure by urinary cotinine levels and by self-report. A cotinine level of less than 0.2 ng/mL indicates no discernible exposure.

**Table 2. Univariate Models of Unadjusted Quality of Life Scores as a Function of Urinary Cotinine Quartile**

Scale	Variable Estimate per Quartile (SE)	P Value
General health	-1.37 (1.18)	.24
Physical function	-1.49 (1.62)	.36
Role physical <sup>b</sup>	-4.50 (2.31)	.05
Emotional well-being <sup>b</sup>	-3.18 (1.0)	.002
Role emotional	-2.38 (2.27)	.30
Vitality	-1.77 (1.29)	.17
Bodily pain	-2.61 (1.55)	.10
Social function	-2.52 (1.62)	.12
6-min walk distance, m (n=71) <sup>b</sup>	-20.28 (9.74)	.04

<sup>a</sup>Occasional data unavailable for each analysis: general health (27 patients), physical function (43), role physical (29), emotional well-being (34), role emotional (33), vitality (35), bodily pain (30), and social function (29).

<sup>b</sup> $P < .05$  in analyses of subscale score by exposure status.

lower in exposed patients ( $P = .10$ ). Similarly, in the subset of patients who agreed to objective assessment of functional status by means of a 6-minute walk test ( $n = 75$ ), the maximal distance walked was lower in those exposed (332.9 m) vs unexposed (342.6 m), although this finding did not reach statistical significance ( $P = .77$ ). The level of urinary cotinine was also associated with lower HRQOL scores in similar domains in univariate analysis (**Table 2**). Specifically, urinary cotinine quartile was a significant predictor of emotional well-being and role physical scores, with decrements of 3.18 ( $P = .002$ ) and 4.50 ( $P = .05$ ) points per quartile, respectively. Urinary cotinine quartiles also predicted the maximal distance walked in 6 minutes, with a mean decrement of 20.28 m per quartile ( $P = .04$ ).

#### EFFECT OF CLINICAL FACTORS ON HRQOL

Several clinical factors also had strong effects on HRQOL in this cohort. Increasing age was associated with significantly lower general health, emotional well-being, and social functioning scores in bivariate analysis. Women

**Table 3. Multivariate Models for Health-Related Quality of Life as a Function of Self-reported Exposure to SHS**

Scale	Variable	Estimate (SE)	P Value
Emotional well-being	Age	0.19 (0.08)	.02
	Sex	-9.32 (2.77)	.001
	NYHA class	-3.24 (1.69)	.06
	Exposure to SHS <sup>a</sup>	-10.07 (3.32)	.003
Role emotional	Age	0.06 (0.19)	.74
	Sex	-13.19 (6.51)	.04
	NYHA class	-9.73 (4.05)	.02
	β-Blocker use	13.48 (7.41)	.07
	Exposure to SHS <sup>a</sup>	-17.76 (7.83)	.02
Role physical	Age	-0.18 (0.19)	.33
	Sex	-11.83 (6.16)	.06
	NYHA class	-16.41 (3.81)	<.001
	Charlson comorbidity index	-4.23 (1.68)	.01
	Exposure to SHS <sup>a</sup>	-19.75 (7.26)	.007
Social function	Age	0.52 (0.14)	<.001
	Sex	-6.80 (4.60)	.15
	NYHA class	-8.47 (2.80)	.003
	Ejection fraction	-0.40 (0.15)	.008
	Exposure to SHS	-4.01 (5.30)	.45
Vitality	Age	0.15 (0.09)	.10
	Sex	-9.25 (3.19)	.004
	NYHA class	-10.97 (1.90)	<.001
	Diabetes mellitus	8.09 (3.48)	.02
	ACE inhibitor use	3.84 (3.10)	.22
	Exposure to SHS	-4.40 (3.78)	.25
Pain	Age	0.37 (0.13)	.005
	Sex	-3.12 (4.37)	.48
	NYHA class	-10.99 (2.66)	<.001
	Charlson comorbidity index	-2.10 (1.32)	.11
	Diabetes mellitus	5.31 (5.49)	.33
	ACE inhibitor use	4.32 (4.22)	.31
	Ejection fraction	-0.43 (0.15)	.004
	Exposure to SHS	-4.55 (5.10)	.37
Physical function	Age	-0.02 (0.12)	.87
	Sex	-3.67 (3.90)	.35
	NYHA class	-18.5 (2.35)	<.001
	Charlson comorbidity index	-0.68 (1.25)	.59
	Ejection fraction	-0.33 (0.13)	.01
	Diabetes mellitus	4.82 (4.86)	.32
	ACE inhibitor use	1.92 (3.68)	.60
	Exposure to SHS	-7.53 (4.77)	.12
General health	Age	0.23 (0.10)	.02
	Sex	-5.95 (3.21)	.07
	NYHA class	-8.56 (1.95)	<.001
	Charlson comorbidity index	-1.32 (0.89)	.14
	Systolic blood pressure	0.12 (0.10)	.22
	Exposure to SHS	1.44 (3.70)	.70

Abbreviations: ACE, angiotensin-converting enzyme; NYHA, New York Heart Association; SHS, secondhand smoke.

<sup>a</sup>  $P < .05$  for exposure to SHS.

had significantly lower emotional well-being, role emotional, pain, energy/fatigue, and social functioning scores than men. Advancing NYHA class was associated with significantly lower scores in all subscales; ejection fraction was a predictor only of pain and physical function

scores. Greater comorbidity, as determined by the Charlson comorbidity index, was associated with significantly lower physical function, role physical, and pain scores. Of the common medications used for HF, only angiotensin-converting enzyme inhibitor use was associated with higher energy/fatigue scores (by 7.9 points;  $P = .02$ ); β-blocker use was associated with higher role emotional scores (by 17.9 points;  $P = .01$ ).

In analyses of SHS adjusted for age and sex, as well as for other pertinent confounders, such as NYHA class and Charlson comorbidity index, exposure to SHS as assessed by questionnaire remained an independent predictor of emotional well-being, role physical, and role emotional subscales (**Table 3**). Even after adjustment, scores of exposed patients for emotional well-being were more than 10 points lower, role physical scores were almost 20 points lower, and role emotional scores were more than 17 points lower than those of their unexposed counterparts. Of note, the Charlson comorbidity index was not a significant univariate predictor of the emotional well-being and role emotional subscale scores and so was not included in the final parsimonious multivariate models.

When increasing quartiles of urinary cotinine level were used as the exposure measure in multivariate analysis, qualitatively similar results were obtained (**Table 4**). There was a 2.58-point decrement per quartile in the emotional well-being score, which remained statistically significant ( $P = .01$ ) after adjustment for NYHA class, age, and sex. There was a trend ( $P = .09$ ) for increasing quartiles of urinary cotinine level to be associated with a 3.78-point drop in role physical scores after adjustment for age, sex, NYHA class, and comorbidity scores. Urinary cotinine level was also associated with a 1.48-point decrement per quartile in role emotional scores; however, this did not reach statistical significance after adjustment for clinical factors. All variables in the multivariate models had variance inflation factors of less than 1.5, suggesting there is no significant multicollinearity.

#### COMMENT

Growing evidence<sup>15</sup> during the past 2 decades suggests that SHS exposure is associated with adverse clinical outcomes. However, much less is known about the effects of SHS on HRQOL and patients' perceptions of their health, especially those with HF. In this well-characterized cohort, exposure to SHS was associated with generally lower scores in all domains of HRQOL and substantial and significant declines in 3 scales dealing with emotional well-being, role limitations due to emotional problems, and role limitations related to physical health. This novel finding is important not only because patients' perception of their health is a vital outcome in its own right but also because measures of health status may identify patients with HF at risk for hospitalization or death.<sup>16</sup>

Secondhand smoke was associated with lower HRQOL scores with self-reported exposure and urinary cotinine determination, although this latter association was less statistically significant. This difference may relate to the potential for bias inherent in self-reported information or to the differing duration of exposure measured. Our vali-

dated questionnaire is based on participants' estimate of ambient weekly exposure<sup>8</sup>; urinary cotinine, with a biological half-life of 19 hours, assesses more recent exposure.

The magnitude of these effects is clinically significant and of the order seen with other chronic diseases. In a prior analysis<sup>17</sup> of HRQOL in association with pacemaker placement for sick sinus syndrome, a history of HF was associated with a 13.1-point drop in role physical scores and a 5-point drop in role emotional scores in analyses adjusted for age and sex. Similarly, percutaneous coronary revascularization in patients with symptomatic coronary artery disease was associated with improvements in HRQOL ranging from 5.5 points for mental health to 23.2 points in role physical functioning.<sup>18</sup>

There are few studies on the effect of SHS on HRQOL as an outcome, predominantly from the pulmonary literature, emphasizing the novel nature of our results. Directly measured SHS exposure, as classified by urinary cotinine level, was associated with increased severity and worse disease-specific HRQOL ( $P = .06$ ) in patients with chronic obstructive pulmonary disease.<sup>19</sup> In the pediatric population, randomization to a school-based asthma treatment program was associated with improved parent and caregiver HRQOL, but benefits were seen predominantly in children without SHS exposure.<sup>20</sup> In a Swiss study<sup>21</sup> of never smokers, self-reported exposure to SHS was associated with generally lower HRQOL, particularly in the role physical and physical, pain, and social function domains for women and the role physical domain in men, suggesting that detrimental effects of SHS on HRQOL are not limited to patients with pulmonary disease. Interestingly, SHS exposure in our study was associated with sizable effects on role limitations related to physical health, but with smaller, nonsignificant differences in the physical function subscale score or the functional status of patients as measured by the maximal distance walked in 6 minutes. This finding suggests that exposure significantly lowers patients' ability to fulfill expectations at home or work despite relatively small differences in physical capacity. Emotional well-being scores reflect levels of happiness or sadness, anxiety, and depression. The role emotional subscale measures "problems with work or other daily activities as a result of emotional problems"<sup>11,22</sup> and, therefore, is consistent with the improved well-being scores seen.

The mechanisms by which SHS may be associated with these detrimental effects on HRQOL are not clear, although several potential mechanisms exist. For example, endothelial dysfunction has been implicated in the increased risk for atherosclerotic heart disease in patients exposed to SHS. Celermajer et al<sup>23</sup> showed that flow-mediated, endothelium (nitric oxide)-dependent brachial artery vasodilation was significantly impaired in smokers (4.4%) and passive smokers (3.1%) compared with control individuals (8.2%). The magnitude of these effects in an HF population remains unknown. Moreover, HF is associated with endothelial dysfunction and abnormal arterial vasoreactivity,<sup>24,25</sup> which may modulate and change the effect of SHS on this measure. Although little is known about the effects of SHS on neurohormonal and sympathetic activation in patients with HF, active smoking has been associated with higher con-

**Table 4. Multivariate Models for Health-Related Quality of Life as a Function of Urinary Cotinine Levels**

Scale	Variable Estimate (SE)	P Value
Emotional well-being		
Age	0.19 (0.08)	.03
Sex	-8.34 (2.88)	.004
NYHA class	-3.58 (1.73)	.04
Urinary cotinine quartile <sup>a</sup>	-2.58 (1.00)	.01
Role emotional		
Age	0.09 (0.20)	.64
Sex	-10.30 (6.86)	.14
NYHA class	-11.08 (4.23)	.01
β-Blocker use	11.80 (7.73)	.13
Urinary cotinine quartile	-1.48 (2.37)	.53
Role physical		
Age	-0.22 (0.20)	.26
Sex	-13.11 (6.51)	.05
NYHA class	-17.51 (3.98)	<.001
Charlson comorbidity index	-2.94 (1.96)	.14
Urinary cotinine quartile	-3.78 (2.23)	.09
Social function		
Age	0.52 (0.14)	<.001
Sex	-7.1 (4.87)	.15
NYHA class	-7.92 (2.91)	.007
Ejection fraction	-0.36 (0.15)	.02
Urinary cotinine quartiles	-0.65 (1.61)	.69
Vitality		
Age	0.15 (0.10)	.12
Sex	-8.4 (3.41)	.01
NYHA class	-11.04 (1.98)	<.001
Diabetes mellitus	9.12 (3.79)	.02
ACE inhibitor use	4.48 (3.30)	.17
Urinary cotinine quartiles	-1.23 (1.19)	.30
Pain		
Age	0.38 (0.13)	.005
Sex	-2.30 (4.51)	.61
NYHA class	-11.22 (2.72)	<.001
Charlson comorbidity index	-2.85 (1.46)	.05
Diabetes mellitus	7.29 (5.67)	.20
ACE inhibitor use	4.00 (4.42)	.37
Ejection fraction	-0.41 (0.15)	.007
Urinary cotinine quartile	-0.71 (1.53)	.64
Physical function		
Age	-0.05 (0.12)	.71
Sex	-2.68 (4.06)	.51
NYHA class	-19.25 (2.41)	<.001
Charlson comorbidity index	0.35 (1.31)	.79
Ejection fraction	-0.36 (0.13)	.009
Diabetes mellitus	4.92 (5.05)	.33
ACE inhibitor use	3.90 (3.85)	.31
Urinary cotinine quartiles	-1.13 (1.42)	.43
General health		
Age	0.19 (0.11)	.07
Sex	-6.02 (3.39)	.08
NYHA class	-8.84 (2.03)	<.001
Charlson comorbidity index	-1.07 (1.00)	.29
Systolic blood pressure	0.15 (0.10)	.14
Urinary cotinine quartiles	-1.15 (1.15)	.32

Abbreviations: ACE, angiotensin-converting enzyme; NYHA, New York Heart Association; SHS, secondhand smoke.

<sup>a</sup>  $P < .05$  for urinary cotinine by quartile.

centrations of serum epinephrine and norepinephrine.<sup>26</sup> In habitual smokers, smoking 2 cigarettes was associated with a 100% increase in plasma adrenaline (epinephrine) and a 21% decrease in plasma renin; angiotensin II levels did not change significantly.<sup>27</sup> These

data suggest a potential interaction of smoke exposure on this important regulatory system, although data from animal models of myocardial infarction have been unable to confirm this.<sup>28</sup> An increase in platelet aggregability has also been implicated in the increased risk of cardiovascular events associated with SHS. Platelet sensitivity to antiaggregatory prostaglandins was reduced acutely after 15 minutes of SHS exposure.<sup>29,30</sup> Repeated exposure produced more long-term changes similar to those seen in smokers.<sup>30,31</sup> Exposure to SHS in humans has been associated with increased white blood cell counts, C-reactive protein, homocysteine, fibrinogen, and low-density lipoprotein cholesterol levels, all suggesting a generalized increase in inflammatory markers.<sup>32</sup> Inflammation may also play an important role in HF outcomes, with statin therapy linked to significant reductions in inflammatory markers, such as high-sensitivity C-reactive protein, interleukin-6, and type 2 tumor necrosis factor receptor in patients with nonischemic cardiomyopathy.<sup>33</sup> However, a large, more recent clinical trial<sup>34</sup> of rosuvastatin use in patients with HF was unable to demonstrate improved clinical outcomes. Thus, there are several mechanisms by which SHS could exert a detrimental effect on outcomes and ultimately on HRQOL.

Our results should be interpreted within the context of the study design. Information on exposure was obtained, in part, through self-report and therefore may be prone to bias or underestimation of the level of exposure.<sup>7</sup> There also may be some degree of misclassification with regard to exposure, but this would tend to bias to the null hypothesis and minimize differences between groups. The qualitatively similar results seen when exposure is measured by biomarker results are reassuring, although the findings using urinary cotinine level as the measure of exposure are slightly less robust. Exposure to SHS was present in about a quarter of the cohort; this, along with the sample size and occasional missing data, may limit power. As in any cohort study, there is the potential for selection bias. In addition, confounding by socioeconomic status or other unmeasured variables may influence results. Also, these cross-sectional analyses cannot confirm a cause-effect relationship. Finally, although we selected all end points a priori for analysis, multiple analyses could increase the risk of a chance result.

Nonetheless, these data suggest that SHS exposure is associated with detrimental effects on several important aspects of HRQOL. Physicians should advise patients with HF and their families to avoid exposure to SHS.<sup>35</sup>

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