

# UCSF

## UC San Francisco Previously Published Works

### Title

Risk Factor Burden, Heart Failure, and Survival in Women of Different Ethnic Groups: Insights From the Women's Health Initiative.

### Permalink

<https://escholarship.org/uc/item/997787r3>

### Journal

Circulation. Heart failure, 11(5)

### ISSN

1941-3289

### Authors

Breathett, Khadijah  
Leng, Iris  
Foraker, Randi E  
et al.

### Publication Date

2018-05-01

### DOI

10.1161/circheartfailure.117.004642

Peer reviewed

ORIGINAL ARTICLE

# Risk Factor Burden, Heart Failure, and Survival in Women of Different Ethnic Groups

## Insights From the Women's Health Initiative

**BACKGROUND:** The higher risk of heart failure (HF) in African-American and Hispanic women compared with white women is related to the higher burden of risk factors (RFs) in minorities. However, it is unclear if there are differences in the association between the number of RFs for HF and the risk of development of HF and death within racial/ethnic groups.

**METHODS AND RESULTS:** In the WHI (Women's Health Initiative; 1993–2010), African-American (n=11 996), white (n=18 479), and Hispanic (n=5096) women with 1, 2, or 3+ baseline RFs were compared with women with 0 RF within their respective racial/ethnic groups to assess risk of developing HF or all-cause mortality before and after HF, using survival analyses. After adjusting for age, socioeconomic status, and hormone therapy, the subdistribution hazard ratio (95% confidence interval) of developing HF increased as number of RFs increased ( $P<0.0001$ , interaction of race/ethnicity and RF number  $P=0.18$ )—African-Americans 1 RF: 1.80 (1.01–3.20), 2 RFs: 3.19 (1.84–5.54), 3+ RFs: 7.31 (4.26–12.56); Whites 1 RF: 1.27 (1.04–1.54), 2 RFs: 1.95 (1.60–2.36), 3+ RFs: 4.07 (3.36–4.93); Hispanics 1 RF: 1.72 (0.68–4.34), 2 RFs: 3.87 (1.60–9.37), 3+ RFs: 8.80 (3.62–21.42). Risk of death before developing HF increased with subsequent RFs ( $P<0.0001$ ) but differed by racial/ethnic group (interaction  $P=0.001$ ). The number of RFs was not associated with the risk of death after developing HF in any group ( $P=0.25$ ; interaction  $P=0.48$ ).

**CONCLUSIONS:** Among diverse racial/ethnic groups, an increase in the number of baseline RFs was associated with higher risk of HF and death before HF but was not associated with death after HF. Early RF prevention may reduce the burden of HF across multiple racial/ethnic groups.

Khadijah Breathett, MD, MS  
Iris Leng, PhD  
Randi E. Foraker, PhD  
William T. Abraham, MD  
Laura Coker, PhD  
Keith E. Whitfield, PhD  
Sally Shumaker, PhD  
JoAnn E. Manson, MD, DrPH  
Charles B. Eaton, MD  
Barbara V. Howard, PhD  
Nkechinyere Ijioma, MBBS  
Crystal W. Cené, MD, MPH  
Lisa W. Martin, MD  
Karen C. Johnson, MD, MPH  
Liviu Klein, MD

**Key Words:** ethnic groups ■ heart failure ■ risk factors ■ survival ■ women

© 2018 American Heart Association, Inc.

<http://circheartfailure.ahajournals.org>

### WHAT IS NEW?

- Across multiple racial/ethnic groups, the number of risk factors for heart failure (HF) is associated with risk of developing new-onset HF and death before HF.
- The number of risk factors for HF is not associated with risk of death after HF.

### WHAT ARE THE CLINICAL IMPLICATIONS?

- Public efforts should target primary prevention of risk factors for HF, especially among African-Americans who have the highest rates of HF.

**H**eat failure (HF) is one of the leading causes of morbidity and mortality in older women and is expected to rise in prevalence by 25% over the next 2 decades because of an aging US population.<sup>1-4</sup> Despite advances in therapy, HF continues to disproportionately affect African-American women compared with white women.<sup>2,5-7</sup> In general, socioeconomic factors and predisposing risk factors (RFs) including hypertension and diabetes mellitus have been identified as important contributors to this excess risk.<sup>2,6,8</sup> Despite data on the incidence and prevalence of HF in women, which demonstrate higher risk of HF in African-American and Hispanic women, data examining the differential development of HF and subsequent risk of death in these groups are lacking.<sup>2,9</sup>

African-American and Hispanic women have higher prevalence of established RFs for HF, including atherosclerosis, hypertension, diabetes mellitus, obesity, and sedentary activity.<sup>2,3</sup> The population attributable risk for HF based on individual RF has been widely described in whites, small populations of African-Americans, and to a lesser extent in Hispanics.<sup>2,10-12</sup> In most studies, individual RFs have been associated with greater risk of developing HF in African-Americans and Hispanics.<sup>2</sup> Yet, the impact of these RFs may be much greater in African-American and Hispanic women who often have multiple RFs.<sup>2</sup> A strong target for reducing racial/ethnic disparities in HF may include identifying the risk of HF and death before and after developing HF, dependent on the number of RFs.

To address these questions, we examined HF development among African-American, white, and Hispanic women, using data from the WHI study (Women's Health Initiative), a large population-based study of postmenopausal women. Within each racial/ethnic group, we tested the hypothesis that compared with women with 0 baseline RF, women with subsequently higher number of baseline RFs would have increased risk of developing HF and dying before or after developing HF.

## METHODS

The data, analytic methods, and study materials are available to other researchers for purposes of reproducing the results or replicating the procedure on request and approval of the WHI Publications and Presentations Committee.

### Data Source

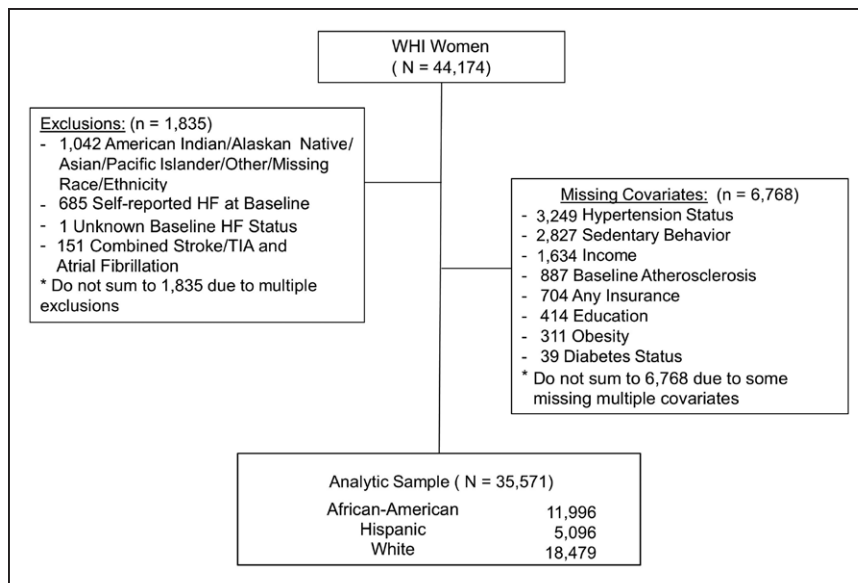
The WHI is a National Heart, Lung, and Blood Institute–supported study of US postmenopausal women followed for >20 years for evaluation of cardiovascular disease, cancer, and osteoporosis.<sup>13</sup> The original WHI population is one of the largest female-only population studies, including 161 808 diverse racial/ethnic women who were enrolled for either randomized clinical trials or an observational study.<sup>14</sup> The study includes self-reported medical information collected through interviews and surveys, anthropometric measurements by WHI personnel, and review of medical records for outcome determination.<sup>13</sup>

### Study Cohort

A subcohort of the original WHI population was selected to study the epidemiology of HF in postmenopausal women.<sup>5</sup> This sample included 44 174 postmenopausal women who underwent annual assessment for HF adjudication from baseline enrollment (1993–1998) through 2010. Race and ethnicity were self-identified as non-Hispanic African American (African-American), Hispanic, and non-Hispanic White (white). This population included all participants who were randomized to the WHI hormone therapy trial (n=27 347) and an oversampling of minorities to include all nonhormone trial African-American (n=11 880) and Hispanic (n=4947) women. Adjudicated HF and death were as of data release of December 2014. Overlapping exclusions included participants of other races/ethnicities because of their small number of events (n=1042), self-report of HF or unknown HF at baseline (n=686), and participants with stroke attributed to atrial fibrillation because the covariates could not be separated (n=151). Participants with missing covariates (n=6768) were also excluded because the objective of this study was to assess risk based on number of RFs on study enrollment. Patients with missing covariates had no difference in incident HF or death than the final analysis sample (Table I in the [Data Supplement](#)). The final sample included 35 571 participants (Figure 1). The study was approved by the human subjects review committee at each WHI participating institution, and all participants provided written informed consent.

### Outcomes of Interest

Participants were followed until development of the following outcomes: incident HF requiring hospitalization and all-cause mortality before or after developing HF. Data on incident HF was abstracted annually from medical records after self-report of hospitalizations. A trained committee adjudicated these hospitalizations as definite or probable HF based on symptoms, physical examination, clinical data, and therapy during a hospitalization, which has been described elsewhere.<sup>3,15</sup> All-cause mortality was collected during routine WHI follow-up by family report and death certificate.<sup>15</sup>



**Figure 1. Study profile.**

The final study sample excluded participants with missing covariates and races/ethnicities that did not include African-American, white, and Hispanic women. HF indicates heart failure; TIA, transient ischemic attack; and WHI, Women's Health Initiative.

## Explanatory Variables: RFs for HF

Established RFs for HF were defined per 2013 American College of Cardiology/American Heart Association Stage A classifications.<sup>3</sup> RFs for HF included having 1+ of the following risks in the absence of symptomatic HF: atherosclerosis (includes Stage B classifications of prior hospitalization for myocardial infarction because this is one of the largest etiologies of HF, prior percutaneous coronary intervention, prior coronary artery bypass graft surgery, history of carotid artery disease, stroke/transient ischemic attack, or peripheral vascular disease), diabetes mellitus (self-report of physician diagnosis and taking hypoglycemic medications), hypertension (self-report and taking antihypertensive medications, systolic blood pressure  $\geq 140$  mm Hg, or diastolic blood pressure  $\geq 90$  mm Hg by measurement on enrollment), obesity (body mass index  $\geq 30$  kg/m<sup>2</sup> by measurement on enrollment), and a recognized RFs for HF not included as Stage A: sedentary activity ( $< 500$  metabolic equivalent of task minute/week).<sup>16</sup> Metabolic syndrome was not included but can be inferred from the component RFs captured. Other established RFs for HF were excluded because they were unavailable in the WHI data set (cardiotoxin exposure and family history of cardiomyopathy). No baseline cardiac imaging was available for the population with RFs for HF.

## Statistical Analysis

Baseline patient characteristics were compared between race and ethnicities, using  $\chi^2$  tests for categorical variables and analysis of variance for continuous variables. We consider 3 outcomes: (1) time to HF from baseline, (2) time to death before HF, and (3) time to death after HF. For (1), time to HF from baseline was defined as the number of days from enrollment to the first occurrence of HF. A participant was censored at last contact. Death was modeled as a competing risk for HF using Fine and Gray method, where subdistribution hazard was estimated.<sup>17</sup> For (2), time to death before HF was defined as the number of days from enrollment to death. Follow-up for death was censored at last contact, and we restrict participants to those who did not have incident HF during the

follow-up. For (3), time to death after HF was defined as time from first incidence of HF to death, and participants were censored at last contact. Cox proportional hazard regression models were used for (2) and (3). Separate models were built for each outcome, and 3 sets of models were fitted: (1) menopausal hormone therapy control: where menopausal hormone therapy was adjusted given increased risk of cardiovascular disease with menopausal hormone therapy irrespective of race/ethnicity.<sup>18</sup>; (2) age+menopausal hormone therapy: where age was added to the model (1); and (3) socioeconomic status+age+menopausal hormone therapy: where socioeconomic status (education, income, and insurance) was added to the model (2), given known racial/ethnic differences in HF presentation.<sup>3</sup> First, models were fitted for all the participants with race/ethnicity as a covariate to estimate subdistribution hazard ratios or hazard ratios and 95% confidence interval (CI) for the number of baseline RFs (1, 2, or 3+), with 0 RF as reference for the outcomes of interest. Then interactions between race/ethnicity and number of baseline RFs were tested to determine whether risks varied by race/ethnicity. Finally, we built models within each race/ethnicity group to estimate subdistribution hazard ratios, hazard ratios, and 95% CI for the number of baseline RFs. Hispanic women were not assessed for all-cause mortality after HF because the event rate of incident HF was too low to yield precise estimates.

In the secondary analysis, associations between an individual RF and outcomes were performed using model (3), which is described above, and by adjusting for all other RFs. The same outcomes were chosen: HF, death before HF, and death after HF. Statistical analyses were performed using SAS 9.4 (Cary, NC), and the significance level was set at 0.05 for all tests.

## RESULTS

### Baseline Characteristics

During the enrollment period of 1993 to 1998, 35571 women (34% African-American, 52% white, 14%

**Table 1. Baseline Characteristics**

Characteristics RF for HF, N	African-American, N (%) (11 996)	White, N (%) (18 479)	Hispanic, N (%) (5096)	P Value
Age, y, mean (SD)	61.4 (7.1)	64.0 (7.1)	60.2 (6.8)	<0.0001
No. of RFs				<0.0001
0	1315 (11.0)	4443 (24.0)	1062 (20.8)	
1	3301 (27.5)	6578 (35.6)	1872 (36.7)	
2	3859 (32.2)	4809 (26.0)	1387 (27.2)	
3+	3521 (29.4)	2649 (14.3)	775 (15.2)	
Comorbidities				
Atherosclerosis	1128 (9.4)	1102 (6.0)	316 (6.2)	<0.0001
Carotid disease	34 (0.3)	47 (0.3)	11 (0.2)	0.72
MI	341 (2.8)	358 (1.9)	48 (0.9)	<0.0001
PTCA/CABG	187 (1.6)	292 (1.6)	44 (0.9)	0.0005
PVD	383 (3.2)	273 (1.5)	121 (2.4)	<0.0001
Stroke/TIA	446 (3.7)	408 (2.2)	135 (2.6)	<0.0001
Treated diabetes mellitus	1364 (11.4)	820 (4.4)	356 (7.0)	<0.0001
Hypertension				<0.0001
Never hypertensive	5470 (45.6)	12 735 (68.9)	3598 (70.6)	
Current/untreated	1118 (9.3)	1591 (8.6)	464 (9.1)	
Current/treated	5408 (45.1)	4153 (22.5)	1034 (20.3)	
Obesity	6040 (50.4)	6729 (36.4)	1879 (36.9)	<0.0001
Sedentary activity	7473 (62.3)	10 259 (55.5)	3070 (60.2)	<0.0001
HT study arm				<0.0001
Not in HT	9769 (81.4)	0 (0.0)	3914 (76.8)	
HT	2227 (18.6)	18479 (100.0)	1182 (23.2)	
Socioeconomic variables				
Education				<0.0001
Less than HS	1289 (10.7)	911 (4.9)	1203 (23.6)	
HS/vocational	3121 (26.0)	6118 (33.1)	1502 (29.5)	
Some college	3251 (27.1)	5423 (29.3)	1248 (24.5)	
College graduate	4335 (36.1)	6027 (32.6)	1143 (22.4)	
Income				<0.0001
<\$35 000	6168 (51.3)	8799 (47.6)	2899 (56.9)	
\$35 000–<\$50 000	2145 (17.9)	3930 (21.3)	817 (16.0)	
\$50 000–<\$75 000	1994 (16.6)	3109 (16.8)	657 (12.9)	
≥\$75 000	1689 (14.1)	2641 (14.3)	723 (14.2)	
Any insurance	11 009 (91.8)	17 125 (92.7)	4137 (81.2)	<0.0001

CABG indicates coronary artery bypass graft surgery; HF, heart failure; HS, high school; HT, hormone therapy; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; PVD, peripheral vascular disease; RF, risk factor; and TIA, transient ischemic attack.

Hispanic) were followed for the development of HF (Table 1). Racial/ethnic minority women were younger than white women (African-American mean age, 61.4; white, 64.0; Hispanic, 60.2;  $P<0.0001$ ). The majority of patients had 1+ RFs at baseline across race and ethnicity, but African-Americans had the most RFs at baseline. College education levels were higher among African-Americans (63.2%) and whites (61.9%) than Hispanics (46.9%). Approximately

half of women from all race/ethnicities had an annual income of <\$35 000, and >80% of women from all race/ethnicities had some form of health insurance.

## Outcomes

Over an average 13 years of follow-up, 4.4% (n=524) African-American, 6.3% (n=1166) white women, and

**Table 2. Risk of Outcomes Based on Number of RFs Compared With Reference of 0 RFs**

	HF* Subdistribution, Hazard Ratio (95% CI)			All-Cause Mortality Before HF, Hazard Ratio (95% CI)			All-Cause Mortality After HF, Hazard Ratio (95% CI)		
	1 RF	2 RFs	3+ RFs	1 RF	2 RFs	3+ RFs	1 RF	2 RFs	3+ RFs
All									
MHT control	1.38 (1.16–1.66)†	2.26 (1.89–2.68)†	5.23 (4.42–6.19)†	1.25 (1.14–1.37)†	1.49 (1.36–1.64)†	2.23 (2.02–2.46)†	1.25 (1.14–1.37)†	1.49 (1.36–1.64)†	2.23 (2.02–2.46)†
Age+MHT	1.36 (1.14–1.63)†	2.24 (1.88–2.66)†	5.01 (4.23–5.94)†	1.24 (1.13–1.35)†	1.51 (1.37–1.66)†	2.18 (1.98–2.41)†	1.02 (0.78–1.33)	1.12 (0.86–1.44)	1.21 (0.94–1.55)
SES+Age+MHT	1.31 (1.09–1.57)†	2.11 (1.77–2.51)†	4.60 (3.88–5.46)†	1.20 (1.10–1.32)†	1.43 (1.30–1.57)†	2.02 (1.83–2.23)†	0.99 (0.76–1.29)	1.08 (0.84–1.40)	1.14 (0.89–1.47)
African-Americans									
MHT control	1.96 (1.10–3.48)†	3.72 (2.15–6.43)†	8.92 (5.22–15.24)†	1.41 (1.12–1.77)†	1.73 (1.39–2.16)†	2.77 (2.23–3.43)†	1.41 (1.12–1.77)†	1.73 (1.39–2.16)†	2.77 (2.23–3.43)†
Age+MHT	1.87 (1.05–3.32)†	3.46 (2.00–5.99)†	8.33 (4.87–14.25)†	1.34 (1.07–1.69)†	1.63 (1.31–2.04)†	2.61 (2.10–3.24)†	0.82 (0.34–1.98)	0.78 (0.34–1.81)	0.83 (0.37–1.89)
SES+Age+MHT	1.80 (1.01–3.20)†	3.19 (1.84–5.54)†	7.31 (4.26–12.56)†	1.30 (1.03–1.63)†	1.51 (1.21–1.89)†	2.34 (1.88–2.91)†	0.77 (0.32–1.87)	0.71 (0.30–1.65)	0.73 (0.32–1.67)
Whites									
MHT control	1.33 (1.10–1.62)†	2.03 (1.67–2.46)†	4.56 (3.78–5.52)†	1.23 (1.11–1.37)†	1.39 (1.24–1.55)†	1.92 (1.69–2.17)†	1.23 (1.11–1.37)†	1.39 (1.24–1.55)†	1.92 (1.69–2.17)†
Age+MHT	1.32 (1.08–1.60)†	2.06 (1.70–2.49)†	4.37 (3.61–5.28)†	1.22 (1.10–1.36)†	1.44 (1.28–1.61)†	1.89 (1.67–2.14)†	1.06 (0.80–1.42)	1.17 (0.89–1.55)	1.31 (1.00–1.72)
SES+Age+MHT	1.27 (1.04–1.54)†	1.95 (1.60–2.36)†	4.07 (3.36–4.93)†	1.19 (1.07–1.32)†	1.37 (1.23–1.54)†	1.78 (1.56–2.02)†	1.04 (0.78–1.38)	1.14 (0.86–1.51)	1.25 (0.95–1.65)
Hispanics									
MHT control	1.75 (0.70–4.39)†	4.10 (1.72–9.77)†	9.52 (4.03–22.50)†	1.24 (0.89–1.74)†	2.19 (1.57–3.04)†	3.24 (2.29–4.59)†	NA	NA	NA
Age+MHT	1.75 (0.70–4.40)†	4.08 (1.71–9.71)†	9.27 (3.91–21.95)†	1.24 (0.88–1.73)†	2.18 (1.57–3.03)†	3.09 (2.19–4.38)†	NA	NA	NA
SES+Age+MHT	1.72 (0.68–4.34)	3.87 (1.60–9.37)†	8.80 (3.62–21.42)†	1.22 (0.87–1.71)	2.11 (1.51–2.94)†	2.99 (2.10–4.24)†	NA	NA	NA

MHT control represents the unadjusted value because many patients were exposed to MHT, which has a known cardiovascular disease risk. Age+MHT and SES+age+MHT represent the adjusted models. Time to all-cause mortality after HF was not analyzed in Hispanics who had too few HF events. CI indicates confidence interval; MHT, menopausal hormone therapy; NA, not applicable; RF, risk factor; and SES, socioeconomic status.

\*Death was treated as a competing risk for the time to HF.

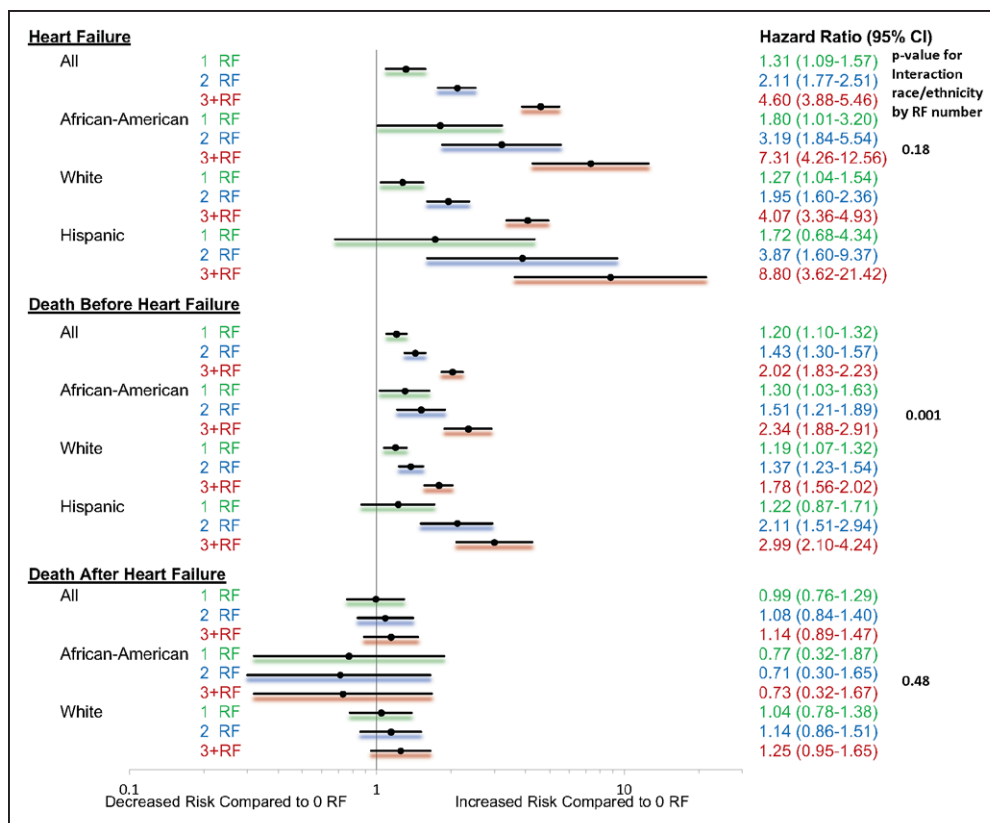
†Significant *P* value <0.0001.

1.8% (n=89) Hispanic women developed symptomatic HF requiring hospitalization. In the control which was adjusted for menopausal hormone therapy and fully adjusted models for age and socioeconomic status, having an additional RF was associated with a significantly higher risk of developing HF, compared with 0 RF (Table 2; Figure 2; subdistribution hazard ratios [95% CI]: 1 RF, 1.31 [1.09–1.57]; 2 RFs, 2.11 [1.77–2.51]; 3+ RFs, 4.60 [3.88–5.46]; *P*<0.0001). An increasing number of RFs increased the risk of HF irrespective of race/ethnicity (*P*=0.17 for interaction of race/ethnicity and number of RFs). Within each racial/ethnicity group, in the fully adjusted model, compared with 0 RF, subdistribution hazard ratios (95% CI) of developing HF in African-Americans for 1, 2, and 3+ RFs were 1.80 (1.01–3.20), 3.19 (1.84–5.54), and 7.31 (4.26–12.56), respectively. Among whites, 1 RF (1.27 [1.04–1.54]), 2 RFs (1.95 [1.60–2.36]), and 3+ RFs (4.07 [3.36–4.93]) demonstrated a higher hazard of developing HF com-

pared with 0 RF. Among Hispanics, 2 RFs (3.87 [1.60–9.37]) and 3+ RFs (8.80 [3.62–21.42]) were associated with a higher risk of developing HF, but 1 RF was not associated with risk of HF (1.72 [0.68–4.34]).

Prior to developing HF, death occurred in 12.0% (n=1376) African-American, 7.2% (n=358) Hispanic, and 15.3% (n=2656) white women. In the fully adjusted model, an additional RF modestly increased the risk of all-cause mortality prior to developing HF (Table 2; Figure 2; hazard ratios [95% CI]: 1 RF, 1.20 [1.10–1.32]; 2 RFs, 1.43 [1.30–1.57]; 3+ RFs, 2.02 [1.83–2.23]; *P*<0.0001). An increasing number of RFs increased the risk of death before HF differently based on race/ethnicity (*P*=0.001 for interaction of race/ethnicity and number of RFs). In the fully adjusted model, compared with 0 RF, 1 RF (1.30 [1.03–1.63]), 2 RFs (1.51 [1.21–1.89]), and 3+ RFs (2.34 [1.88–2.91]) were associated with all-cause mortality prior to developing HF in African-Americans. Among whites, 1 RF (1.19 [1.07–1.32]), 2





**Figure 2. Risk of outcomes based on number of risk factors (RF).**

The model is fully adjusted for menopausal hormone therapy status, age, and socioeconomic status. The reference is 0 RF. CI indicates confidence interval.

RFs (1.37 [1.23–1.54]), and 3+ RFs (1.78 [1.56–2.02]) were associated with all-cause mortality prior to developing HF. Similarly, among Hispanics, 2 RFs (2.11 [1.51–2.94]), and 3+ RFs (2.99 [2.10–4.24]) demonstrated an increased risk of HF compared with 0 RF, but 1 RF was not associated with mortality (1.22 [0.87–1.71]).

After developing HF, 49.4% (n=259) African-American, 37.1% (n=33) Hispanic, and 51.1% (n=596) white women died. An increasing number of RFs was not associated with risk of death after HF (Table 2; Figure 2; hazard ratios [95% CI]: 1 RF, 0.99 [0.76–1.29]; 2 RFs, 1.08 [0.84–1.40]; 3+ RFs, 1.14 [0.89–1.47]). This pattern occurred irrespective of race/ethnicity ( $P=0.48$  for interaction of race/ethnicity and number of RFs).

In the secondary analysis, adjusted for menopausal hormone therapy, age, socioeconomic status, and other RFs, each individual RFs was associated with increased risk of developing HF (Table 3). Diabetes mellitus was associated with significantly different risk of developing HF by race/ethnicity (African-American, 2.11 [1.71–2.61]; white, 2.78 [2.33–3.32]; Hispanic, 4.21 [2.52–7.02];  $P=0.04$  for interaction of diabetes mellitus with race/ethnicity; Table II in the [Data Supplement](#)). Each of the individual RFs was associated with death before HF with the exception of obesity, which was associated with different risk of death before HF across race/ethnicity (African-American, 1.08 [0.97–1.20]; white, 0.93 [0.85–1.01]; Hispanic, 1.67 [1.34–2.07];  $P<0.0001$  for interaction of obesity with race/ethnicity). After HF, only atherosclerosis

and diabetes mellitus were associated with increased risk of death. Obesity was associated with reduced risk of death after HF (0.85 [0.74–0.99]). There were no significant differences in risk of death after HF with individual RF across race/ethnicity (Table II in the [Data Supplement](#)).

## DISCUSSION

In one of the largest studies of a diverse racial and ethnic population of women, we found that an additional established RFs for HF was associated with significantly increased risk of HF and death prior to developing HF among African-American, Hispanic, and white women. Conversely, additional RFs for HF were not associated with increased risk of death after HF in either African-American or white women.

Our study supports findings from smaller studies that address racial/ethnic differences in risk of HF based on the number of ideal RF.<sup>11,19</sup> In the Jackson Heart Study of African-Americans (n=4195), a progressively reduced risk of incident HF was demonstrated with an increased number of Life's Simple 7 ideal RF, including ideal blood pressure, glucose, lipids, weight, daily exercise, balanced meals, and tobacco-free lifestyle.<sup>11</sup> Similarly, in the Multi-Ethnic Study of Atherosclerosis (n=6506), an increased number of ideal RF was associated with a trend toward reduced incidence of HF in African-Americans, whites, and Hispanics.<sup>19</sup> African-Americans and Hispanics demonstrated the greatest benefit with each additional ideal RFs.<sup>19</sup>

**Table 3. Risk of Outcomes Based on Individual RFs**

	HF Subdistribution, Hazard Ratio (95% CI)	All-Cause Mortality Before HF, Hazard Ratio (95% CI)	All-Cause Mortality After HF, Hazard Ratio (95% CI)
All			
Atherosclerosis	2.05 (1.80–2.34)*	1.56 (1.42–1.72)*	1.22 (1.03–1.45)*
Treated diabetes	2.54 (2.23–2.90)*	2.03 (1.84–2.24)*	1.22 (1.03–1.45)*
Hypertension	1.72 (1.56–1.91)*	1.30 (1.23–1.38)*	0.98 (0.84–1.14)
Obesity	1.44 (1.30–1.59)*	1.03 (0.96–1.24)	0.85 (0.74–0.99)*
Sedentary activity	1.24 (1.12–1.37)*	1.17 (1.10–1.24)*	1.15 (0.99–1.34)
African-Americans			
Atherosclerosis	1.94 (1.55–2.43)*	1.58 (1.36–1.84)*	1.16 (0.87–1.55)
Treated diabetes mellitus	2.11 (1.71–2.61)*	1.97 (1.71–2.26)*	1.20 (0.92–1.57)
Hypertension	2.10 (1.69–2.60)*	1.30 (1.16–1.45)*	0.96 (0.70–1.30)
Obesity	1.58 (1.31–1.90)*	1.08 (0.97–1.20)	0.81 (0.62–1.06)
Sedentary activity	1.30 (1.07–1.58)*	1.21 (1.08–1.35)*	0.95 (0.72–1.25)
Whites			
Atherosclerosis	2.13 (1.81–2.52)*	1.48 (1.30–1.70)*	1.26 (1.02–1.55)*
Treated diabetes mellitus	2.78 (2.33–3.32)*	1.96 (1.68–2.30)*	1.23 (0.98–1.54)
Hypertension	1.58 (1.39–1.78)*	1.35 (1.24–1.46)*	0.99 (0.84–1.17)
Obesity	1.38 (1.22–1.56)*	0.93 (0.85–1.01)	0.87 (0.73–1.04)
Sedentary activity	1.20 (1.06–1.36)*	1.14(1.05–1.23)*	1.22 (1.02–1.46)*
Hispanics			
Atherosclerosis	1.87 (0.99–3.52)	1.99 (1.45–2.74)*	NA
Treated diabetes mellitus	4.21 (2.52–7.02)*	2.56 (1.89–3.46)*	NA
Hypertension	2.13 (1.36–3.34)*	1.08 (0.86–1.35)	NA
Obesity	1.52 (0.98–2.37)	1.67 (1.34–2.07)*	NA
Sedentary activity	1.46 (0.91–2.33)	1.35 (1.08–1.68)*	NA

Results are fully adjusted for menopausal hormone therapy, age, socioeconomic status, and other risk factors. All-cause mortality after HF was not applicable in Hispanics who had too few HF events to detect death after HF. CI indicates confidence interval; HF, heart failure; NA, not applicable; and RF, risk factor.

\**P* value <0.05.

The decreased risk of death with more ideal RF has been demonstrated in a survey study that does not address racial/ethnic differences.<sup>20</sup> In the National Health and Nutrition Examination Survey (N=44 959), a higher number of Life's Simple 7 ideal RF was associated with reduced risk of all-cause death.<sup>20</sup> However, associations between the number of RF and risk of death after HF are less described in diverse racial/ethnic populations. Numerous studies have developed calculators to predict the risk of death after developing HF, but most assess risk based on specific types of RF, not the number of RF.<sup>3</sup>

The WHI study is unique by demonstrating the risk of HF and death before or after HF based on the number of baseline RFs. Most studies have not addressed this combination of progressive events within the same population or within diverse racial/ethnic groups. Our study and the Life's Simple 7 literature suggest that preventing established RFs and pursuing ideal management of RFs may reduce racial/ethnic disparities in HF incidence and

death prior to HF.<sup>11,19,20</sup> However, there is a noteworthy distinction. The lack of an association between the number of RF and risk of death after HF in African-Americans and whites implies that the preventative RF target should occur before HF develops. Additional study is warranted in a larger population of Hispanic women to determine if the same conclusion applies.

Multiple observational studies have demonstrated the obesity paradox in HF, as demonstrated in this study.<sup>21,22</sup> Obesity was associated with increased risk of HF irrespective of race/ethnicity and increased risk of death before HF in Hispanics. However, obesity was protective for death after HF. Exercise is recommended in obese patients with HF because exercise is associated with improved exercise capacity and quality of life.<sup>3,23</sup> The definitive trial has not been performed to determine if purposeful weight loss causes increased mortality among obese HF patients.

This study is subject to several limitations. First, RFs for HF did not include family history of cardiomy-



opathy and metabolic syndrome. However, metabolic syndrome should be represented with the capture of diabetes mellitus, hypertension, and obesity. Also, an interdependent relationship of the individual RF may influence HF outcomes. For this reason, we also assessed the risk of each outcome for each individual RF. Second, some of the patients may have structural heart disease without symptoms of HF because WHI participants had no imaging at baseline, and patients with prior myocardial infarction were not excluded. Systolic dysfunction at baseline was likely low given small rates of myocardial infarction at baseline, but the presence of left ventricular hypertrophy was likely missed given high baseline prevalence of hypertension.<sup>24</sup> Third, incident HF only included hospitalized events and may underreport development of symptomatic HF. However, the population that is hospitalized is at the highest risk for death<sup>25</sup> and thus a key group for study. Fourth, the socioeconomic status of participants demonstrate a nonrepresentative sample of the US racial/ethnic minorities, but this is one of the largest population studies of diverse racial/ethnic women. Finally, the exact time of development of baseline RFs prior to WHI enrollment is not well captured for all RFs, and new development of some RFs during follow-up were not collected. However, the risk of long-term events after baseline provides important data that may inform public health targets.

## CONCLUSIONS

Among the WHI population of postmenopausal women, compared with 0 RF, each additional RF was associated with an increased risk of HF and death before HF among African-American, Hispanic, and white women. However, additional RFs for HF were not associated with increased risk of death after HF diagnosis among either African-American or white women. Racial/ethnic disparities in HF may be reduced by seeking RF prevention. Further study of RF prevention interventions in longitudinal populations is warranted.

## ARTICLE INFORMATION

Received October 6, 2017; accepted March 30, 2018.

Guest Editor for this article was Jay N. Cohn, MD.

The Data Supplement is available at <http://circheartfailure.ahajournals.org/lookup/suppl/doi:10.1161/CIRCHEARTFAILURE.117.004642/-DC1>.

## Correspondence

Khadajah Breathett, MD, MS, Division of Cardiovascular Medicine, Sarver Heart Center, University of Arizona College of Medicine—Tucson, 1501 N Campbell Ave, Tucson, AZ 85724. E-mail [kbreathett@shc.arizona.edu](mailto:kbreathett@shc.arizona.edu)

## Affiliations

Division of Cardiovascular Medicine, Sarver Heart Center, University of Arizona, Tucson (K.B.). Department of Biostatistical Sciences, Wake Forest School

of Medicine, Winston-Salem, NC (I.L.). Institute for Informatics, Washington University in St Louis School of Medicine, MO (R.E.F.). Division of Cardiovascular Medicine, The Ohio State University Wexner Medical Center, Columbus (W.T.A.). Division of Public Health Sciences, Wake Forest School of Medicine, Social Sciences and Health Policy, Winston-Salem, NC (L.C., S.S.). Wayne State University, Detroit, MI (K.E.W.). Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (J.E.M.). Department of Family Medicine, Alpert Medical School of Brown University and Department of Epidemiology, School of Public Health of Brown University, Center for Primary Care and Prevention, Pawtucket, RI (C.B.E.). MedStar Health Research Institute and Georgetown/Howard Universities Center for Clinical and Translational Science, Washington, DC (B.V.H.). Division of Cardiology, Altru Health System, Grand Forks, ND (N.I.). Division of General Internal Medicine, University of North Carolina-Chapel Hill (C.W.C.). Division of Cardiology, George Washington University, Washington, DC (L.W.M.). Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis (K.C.J.). Division of Cardiology, University of California San Francisco (L.K.).

## Acknowledgments

We have gratitude for the WHI participants, clinical sites, investigators, and staff of which otherwise this study would not be possible.

## Sources of Funding

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C. Dr Breathett received support from the National Institute of Health (NIH) L60 MD010857 and the University of Arizona Health Sciences, Strategic Priorities Faculty Initiative Grant.

## Disclosures

None.

## APPENDIX: A SHORT LIST OF WOMEN'S HEALTH INITIATIVE INVESTIGATORS

Program Office: Jacques Rossouw, Shari Ludlam, Dale Burwen, Joan McGowan, Leslie Ford, and Nancy Geller (National Heart, Lung, and Blood Institute, Bethesda, Maryland). Clinical Coordinating Center: Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg (Fred Hutchinson Cancer Research Center, Seattle, WA). Investigators and Academic Centers: JoAnn E. Manson (Brigham and Women's Hospital, Harvard Medical School, Boston, MA); Barbara V. Howard (MedStar Health Research Institute/Howard University, Washington, DC); Marcia L. Stefanick (Stanford Prevention Research Center, Stanford, CA); Rebecca Jackson (The Ohio State University, Columbus, OH); Cynthia A. Thomson (University of Arizona, Tucson/Phoenix, AZ); Jean Wactawski-Wende (University at Buffalo, Buffalo, NY); Marian Limacher (University of Florida, Gainesville/Jacksonville, FL); Robert Wallace (University of Iowa, Iowa City/Davenport, IA); Lewis Kuller (University of Pittsburgh, Pittsburgh, PA); Sally Shumaker (Wake Forest University School of Medicine, Winston-Salem, NC). Women's Health Initiative Memory Study: Sally Shumaker (Wake Forest University School of Medicine, Winston-Salem, NC).

## REFERENCES

- Centers for Disease Control and Prevention. Heart Failure Fact Sheet. Data & Statistics[DHDSP]CDC. [http://www.cdc.gov/dhdsp/data\\_statistics/fact\\_sheets/fs\\_heart\\_failure.htm](http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_heart_failure.htm). Accessed October 10, 2013.
- Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statis-

- tics-2017 update: a report from the American Heart Association. *Circulation*. 2017;135:e146–e603. doi: 10.1161/CIR.0000000000000485.
3. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128:1810–1852. doi: 10.1161/CIR.0b013e31829e8807.
  4. Heidenreich PA, Trogon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, Finkelstein EA, Hong Y, Johnston SC, Khera A, Lloyd-Jones DM, Nelson SA, Nichol G, Orenstein D, Wilson PW, Woo YJ; American Heart Association Advocacy Coordinating Committee; Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Cardiopulmonary; Critical Care; Perioperative and Resuscitation; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease; Council on Cardiovascular Surgery and Anesthesia, and Interdisciplinary Council on Quality of Care and Outcomes Research. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. 2011;123:933–944. doi: 10.1161/CIR.0b013e31820a55f5.
  5. Eaton CB, Abdulkali AM, Margolis KL, Manson JE, Limacher M, Klein L, Allison MA, Robinson JG, Curb JD, Martin LA, Liu S, Howard BV. Racial and ethnic differences in incident hospitalized heart failure in postmenopausal women: the Women's Health Initiative. *Circulation*. 2012;126:688–696. doi: 10.1161/CIRCULATIONAHA.111.066688.
  6. Eaton CB, Pettinger M, Rossouw J, Martin LW, Foraker R, Quddus A, Liu S, Wampler NS, Hank Wu W-C, Manson JE, Margolis K, Johnson KC, Allison M, Corbie-Smith G, Rosamond W, Breathett K, Klein L. Risk factors for incident hospitalized heart failure with preserved versus reduced ejection fraction in a multiracial cohort of postmenopausal women. *Circ Heart Fail*. 2016;9:e002883. doi: 10.1161/CIRCHEARTFAILURE.115.002883.
  7. Breathett K, Baliga RR, Capers Q. Review of heart failure management in African-Americans. In: Baliga RR, Haas GJ, eds. *Management of Heart Failure*. London: Springer; 2015:277–286.
  8. Franciosa JA, Ferdinand KC, Yancy CW; Consensus Statement on Heart Failure in African Americans Writing Group. Treatment of heart failure in African Americans: a consensus statement. *Congest Heart Fail*. 2010;16:27–38. doi: 10.1111/j.1751-7133.2009.00118.x.
  9. Maas AHEM, van der Schouw YT, Regitz-Zagrosek V, Swahn E, Appelman YE, Pasterkamp G, Ten Cate H, Nilsson PM, Huisman MV, Stam HCG, Eize-ma K, Stramba-Badiale M. Red alert for women's heart: the urgent need for more research and knowledge on cardiovascular disease in women: proceedings of the workshop held in Brussels on gender differences in cardiovascular disease, 29 September 2010. *Eur Heart J*. 2011;32:1362–1368.
  10. Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. *Circ Heart Fail*. 2012;5:720–726. doi: 10.1161/CIRCHEARTFAILURE.111.966366.
  11. Spahillari A, Talegawkar S, Correa A, Carr JJ, Terry JG, Lima J, Freedman JE, Das S, Kociol R, de Ferranti S, Mohebbali D, Mwasongwe S, Tucker KL, Murthy VL, Shah RV. Ideal cardiovascular health, cardiovascular remodeling, and heart failure in blacks: The Jackson Heart Study. *Circ Heart Fail*. 2017;10:e003682. doi: 10.1161/CIRCHEARTFAILURE.116.003682.
  12. Kalogeropoulos A, Georgiopoulos V, Kritchevsky SB, Psaty BM, Smith NL, Newman AB, Rodondi N, Satterfield S, Bauer DC, Bibbins-Domingo K, Smith AL, Wilson PW, Vasani RS, Harris TB, Butler J. Epidemiology of incident heart failure in a contemporary elderly cohort: the health, aging, and body composition study. *Arch Intern Med*. 2009;169:708–715. doi: 10.1001/archinternmed.2009.40.
  13. Women's Health Initiative. About WHI. <https://www.whi.org/about/SitePages/About%20WHI.aspx>. Accessed September 1, 2017.
  14. Anderson GL, Manson J, Wallace R, Lund B, Hall D, Davis S, Shumaker S, Wang CY, Stein E, Prentice RL. Implementation of the Women's Health Initiative study design. *Ann Epidemiol*. 2003;13(9 Suppl):S5–S17.
  15. Heckbert SR, Kooperberg C, Safford MM, Psaty BM, Hsia J, McTiernan A, Gaziano JM, Frishman WH, Curb JD. Comparison of self-report, hospital discharge codes, and adjudication of cardiovascular events in the Women's Health Initiative. *Am J Epidemiol*. 2004;160:1152–1158. doi: 10.1093/aje/kw011.
  16. Pandey A, LaMonte M, Klein L, Ayers C, Psaty BM, Eaton CB, Allen NB, de Lemos JA, Carnethon M, Greenland P, Berry JD. Relationship between physical activity, body mass index, and risk of heart failure. *J Am Coll Cardiol*. 2017;69:1129–1142. doi: 10.1016/j.jacc.2016.11.081.
  17. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.
  18. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, Ko M, LaCroix AZ, Margolis KL, Stefanick ML. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*. 2007;297:1465–1477. doi: 10.1001/jama.297.13.1465.
  19. Ogunmoroti O, Oni E, Michos ED, Spatz ES, Allen NB, Rana JS, Virani SS, Blankstein R, Aronis KN, Blumenthal RS, Veledar E, Szklo M, Blaha MJ, Nasir K. Life's simple 7 and incident heart failure: the multi-ethnic study of atherosclerosis. *J Am Heart Assoc*. 2017;6:e005180. doi: 10.1161/JAHA.116.005180.
  20. Yang Q, Cogswell ME, Flanders WD, Hong Y, Zhang Z, Loustalot F, Gillespie C, Merritt R, Hu FB. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. *JAMA*. 2012;307:1273–1283. doi: 10.1001/jama.2012.339.
  21. Curtis JP, Selter JG, Wang Y, Rathore SS, Jovin IS, Jadbabaie F, Kosiborod M, Portnay EL, Sokol SI, Bader F, Krumholz HM. The obesity paradox: body mass index and outcomes in patients with heart failure. *Arch Intern Med*. 2005;165:55–61. doi: 10.1001/archinte.165.1.55.
  22. Powell-Wiley TM, Ngwa J, Kebede S, Lu D, Schulte PJ, Bhatt DL, Yancy C, Fonarow GC, Albert MA. Impact of body mass index on heart failure by race/ethnicity from the Get With The Guidelines-Heart Failure (GWTG-HF) Registry. *JACC Heart Fail*. 2018;6:233–242. doi: 10.1016/j.jchf.2017.11.011.
  23. Horwich TB, Broderick S, Chen L, McCullough PA, Strzelczyk T, Kitzman DW, Fletcher G, Safford RE, Ewald G, Fine LJ, Ellis SJ, Fonarow GC. Relation between body mass index, exercise training, and outcomes in chronic systolic heart failure. *Am J Cardiol*. 2011;108:1754–1759. doi: 10.1016/j.amjcard.2011.07.051.
  24. Cuspidi C, Sala C, Negri F, Mancia G, Morganti A; Italian Society of Hypertension. Prevalence of left-ventricular hypertrophy in hypertension: an updated review of echocardiographic studies. *J Hum Hypertens*. 2012;26:343–349. doi: 10.1038/jhh.2011.104.
  25. Shahar E, Lee S, Kim J, Duval S, Barber C, Luepker RV. Hospitalized heart failure: rates and long-term mortality. *J Card Fail*. 2004;10:374–379.

**SUPPLEMENTAL MATERIAL****Supplemental Table 1. Comparison of Participants with Complete and Missing Covariates**

Characteristics	Complete covariates (N = 35,571)	Missing covariates (N = 6,768)	P-value
Age	62.6 (7.2)	62.3 (7.2)	0.002
HF incidence	1,779 (5.0)	330 (4.9)	0.66
Death	5,278 (14.8)	1,056 (15.6)	0.11
Race/Ethnicity			<0.0001
Black	11,996 (33.7)	2,159 (31.9)	
Hispanic	5,096 (14.3)	1,284 (19.0)	
Caucasian	18,479 (52.0)	3,325 (49.1)	
HT Study Arm	21,888 (61.5)	4,108 (60.7)	0.20



**Supplemental Table 2. P-value for Interaction of Race/Ethnicity and Individual RF**

RF	HF	All-cause Mortality Before HF	All-cause Mortality after HF
Atherosclerosis	0.56	0.20	0.70
Treated Diabetes	0.04	0.35	0.89
Hypertension	0.10	0.38	0.81
Obesity	0.25	<0.0001	0.58
Sedentary Activity	0.50	0.45	0.19