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## When the At-Risk Do Not Develop Heart Failure: Understanding Positive Deviance Among Postmenopausal African-American and Hispanic Women

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## Abstract

**Background:** African-American and Hispanic postmenopausal women have the highest risk for heart failure (HF) compared to other races, but HF prevalence is lower than expected in some national cohorts. It is unknown whether psychosocial factors are associated with lower risk of incident HF hospitalization (HFH) among high-risk postmenopausal minority women.

**Methods and Results:** Using the Women's Health Initiative Study, African-American and U.S. Hispanic women were classified as high-risk for incident HFH with 1 traditional HF risk factors and highest tertile HF genetic risk scores. Positive (optimism, social support, religion) and negative psychosocial factors (living alone, social strain, depressive symptoms) were measured using validated survey instruments at baseline. Adjusted sub-distribution hazard ratios (SHR) of developing HFH were determined with death as a competing risk. Positive deviance indicated not developing incident HFH with 1 risk factors and highest tertile for genetic risk. Among 7986 African-American women (16 years mean follow-up), 27.0% demonstrated positive deviance. Among high-risk African-American women, optimism was associated with modestly reduced risk of HFH [SHR 0.94(95%CI:0.91,0.99)], and social strain was associated with modestly increased risk of HFH [SHR 1.07(95%CI:1.02,1.12)] in initial models; however, no psychosocial factors were associated with HFH in fully-adjusted analyses. Among 3,341 Hispanic women, 25.1% demonstrated positive deviance. Among high-risk Hispanic women, living alone was associated with increased risk of HFH [SHR 1.97(95%CI:1.06,3.63)] in unadjusted analyses; however, no psychosocial factors were associated with HFH in fully-adjusted analyses.

**Conclusions:** Among post-menopausal African-American and Hispanic women, a significant proportion remained free from HFH despite having highest genetic risk profile and 1 traditional risk factors. No observed psychosocial factors were associated with incident HFH in high-risk African-Americans and Hispanics. Additional investigation is needed to understand protective factors among high-risk African-American and Hispanic women.

## Keywords

Heart failure; Racial disparities; Women

## INTRODUCTION

African-American and Hispanic women have the highest prevalence of risk factors for heart failure compared to women of other racial and ethnic groups.<sup>1</sup> Genetic polymorphisms contribute to racial and ethnic differences.<sup>2-4</sup> African-Americans develop heart failure at earlier ages than Whites.<sup>1</sup> However, in age-adjusted models from the national Women's Health Initiative (WHI) study, white women developed incident heart failure hospitalization at higher rates than African-American or Hispanic women.<sup>5,6</sup> This suggests that older

African-American and U.S. Hispanic WHI participants have protective factors that may delay the onset of incident heart failure despite having greater risk factors for the condition. In addition, traditional risk models may be missing pertinent factors for racial and ethnic subgroups since models are based upon U.S. White populations.<sup>7</sup> Understanding protective factors will further efforts to reduce racial and ethnic disparities in heart failure.

Factors protecting women of color from incident heart failure hospitalization may be related to psychosocial factors.<sup>5,8</sup> African-American and Hispanic WHI participants have greater college education and healthcare insurance coverage than the general population.<sup>5</sup> Individuals with higher socioeconomic position may be afforded better living conditions and social support. Social networks have been an independent predictor of heart failure in other smaller population studies.<sup>8</sup> In addition, social strain has been associated with multiple cardiovascular disease outcomes.<sup>9</sup> Psychosocial factors such as optimism and religiosity have both been associated with reduced cardiovascular events due to ideal behavior.<sup>10,11</sup> It is unknown whether psychosocial factors moderate the development of incident heart failure hospitalization in the highest risk population: African-American and Hispanic women with one or more heart failure risk factors and a high heart failure genetic risk score.

Positive deviance provides a useful framework for understanding the psychosocial factors that allow some disadvantaged individuals who share similar risks for disease to avoid heart failure while others in similar circumstances develop heart failure.<sup>12</sup> Positive deviance occurs when high-risk populations have unexpected positive outcomes rather than expected negative outcomes.<sup>13</sup> The validated positive deviance approach examines factors that lead to unexpected positive outcomes among high-risk populations.<sup>13</sup> Therefore, we examined the relationships between psychosocial factors among African-American and Hispanic women with the highest risk for heart failure who did and did not develop incident heart failure hospitalization. We hypothesized that high levels of protective psychosocial factors would independently reduce risk of incident heart failure hospitalization among those at high risk.

## METHODS

### Data Source

WHI is one of the largest U.S. population studies of women.<sup>14</sup> WHI followed 161,808 postmenopausal women for the epidemiological development of cardiovascular disease, cancer, and osteoporosis over 20 years.<sup>15</sup> Participant data was collected through self-report in surveys and interviews and through WHI study team collection of anthropometric data and medical record adjudication.<sup>14</sup>

### Study Cohort

A cohort of 44,174 postmenopausal women from WHI underwent annual assessment for heart failure adjudication from baseline enrollment (1993–1998) through March 2018.<sup>16</sup> The heart failure adjudication cohort included all participants randomized to the WHI hormone therapy trial (n=27,347) and an over-sampling of self-identified races and ethnicities in order to include all non-hormone trial non-Hispanic African-Americans (n=11,880) and U.S. Hispanics (n=4,947). All WHI African-American and Hispanic women were eligible for

inclusion in the WHI Single Nucleotide Protein (SNP) Health Association Resource study (SHARe), which included 12,080 African-American and Hispanic women.<sup>17</sup> After joint imputation in the WHI Imputed Genome Wide Association Study (GWAS), 11,992 African-American and Hispanic women remained in this study after extensive quality control.<sup>18</sup> In order to study positive deviance among high traditional and genetic risk African-American and Hispanic women, participants in the WHI GWAS were excluded due to missing risk factors (n=15 diabetes, n=361 hypertension, n=114 sedentary) and baseline presence of heart failure (n=175), resulting in a final study sample of 11,327 women (n=7,986 African-American; n=3,341 Hispanic). Other observations with missing values of the following variables were excluded for respective analyses (African-American and Hispanics: body mass index n=101; menopausal hormone therapy ever n=55; education n=149; income n=797; insurance n=280; positive psychosocial factors: optimism construct n=625, social support n=513; negative psychosocial factors: live alone n=1875, social strain construct n=698, presence of depressive symptoms n=599.)

The study was approved by the human subjects review committee at each WHI participating institution, and all participants provided written informed consent. This study was also approved by the University of Arizona Institutional Review Board.

### Outcome of Interest

Participants were followed for incident heart failure hospitalization. Adjudication for heart failure hospitalization was based upon annual review of medical records and self-report of hospitalizations. WHI defined incident heart failure hospitalization as definite or probable according to symptoms, physical exam, clinical data, and medical therapy provided during hospitalizations, as previously reported.<sup>19,20</sup>

### Variables

Risk factors for incident heart failure hospitalization were defined according to American College of Cardiology/American Heart Association Stage A classifications.<sup>20</sup> As previously described,<sup>5</sup> risk factors included baseline atherosclerosis (includes Stage B history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, carotid artery disease, stroke/transient ischemic attack, and peripheral vascular disease), diabetes mellitus (self-report or usage of hypoglycemic medications or insulin), hypertension (self-report or usage of antihypertensive medications, systolic blood pressure 140 mmHg, or diastolic blood pressure 90 mmHg at baseline), obesity (body mass index 30 kg/m<sup>2</sup> at baseline), and a recognized risk factor for heart failure not included as Stage A: sedentary (<500 metabolic equivalent of task minute/week).

SNP coverage was evaluated for candidate SNPs previously identified in GWAS of heart failure which reached or nearly reached genome-wide significance ( $5 \times 10^{-8}$ ) (Supplemental Table 1, Supplemental References). Missing SNPs were previously imputed.<sup>18</sup> The genetic risk score was developed from established SNPs from prior GWAS analyses.<sup>18</sup> Univariate logistic regression models were used to estimate individual SNP associations within African-American and Hispanic women in this data set. Associations were considered important with a *P*-value <0.10, and those SNPs were included in the genetic risk score,

which was generated by summing the logit coefficients from the regression models. Among each race/ethnic group, the distribution was characterized in tertiles: high, medium, and low-risk.

Psychosocial factors were characterized by positive and negative psychosocial factors using validated surveys from WHI, where higher value indicated increased level of factor (Supplemental Table 2, Supplemental References).<sup>21</sup> Positive psychosocial factors included the following constructs: optimism (score 6–30),<sup>22</sup> social support (score 9–45),<sup>23</sup> and religious support (binary: a great deal or none/a little).<sup>24</sup> Negative psychosocial factors included: living alone (binary),<sup>21</sup> social strain construct (score 4–20),<sup>25</sup> and depressive symptoms (binary).<sup>26</sup>

## Statistical Analyses

All analyses were stratified within race and ethnic group. Baseline characteristics were evaluated using descriptive statistics. Using the Fine and Gray method, time to first occurrence of heart failure hospitalization from enrollment was modelled with death as a competing risk for incident heart failure hospitalization (identified via annual follow-up and death certificate), with adjustment for age, participation in observational study or clinical trial, receipt of menopausal hormone therapy ever, tobacco smoking (never, past, current), education or income (choosing socioeconomic covariate with most significant p value), and 10 principal components of ancestry in order to address admixture and differences between self-reported race, ethnicity and genetic profile. The sub-distribution hazard ratio for incident heart failure hospitalization was estimated according to the individual number of risk factors and genetic risk score tertile. The prevalence of participants who developed and did not develop incident heart failure hospitalization were categorized by presence of risk factors and genetic risk (<1 risk factors with highest genetic risk tertile; 1+ risk factors with lowest heart failure genetic risk tertile; <1 risk factor with highest heart failure genetic risk tertile; <1 risk factor with lowest heart failure genetic risk tertile).

According to the positive deviance approach,<sup>12</sup> African-American and Hispanic women with the highest risk, women with 1+ risk factors and highest genetic risk score tertile, were isolated for assessment. Among the high-risk population, the sub-distribution hazard ratio for developing incident heart failure hospitalization used the same Fine and Gray method as above for the unadjusted and adjusted models. Covariates that had a p value <0.10 were included in the adjusted models. Statistical analyses were performed using Stata 16.1 (College Station, TX).

## RESULTS

### Baseline Characteristics

Among WHI participants, 7986 African-American women and 3341 Hispanic women had not developed heart failure and were in their seventh decade of life [mean age 61.6 years (SD 7.0) African-American and 60.3 years (SD 6.7) Hispanic] at study entry (Table 1). The majority of women had 1 or more traditional risk factors for heart failure (88% African-American, 78% Hispanic). The mean genetic risk score was 0.18 (SD 0.01) in African-

Americans and 0.19 (SD 0.02) in Hispanics. The majority of African-Americans (76.3%) and Hispanics (61.7%) had some level of college education, and a majority also had an annual household income of <\$35,000 (52.3% African-Americans, 57.5% Hispanics). Both African-American and Hispanic participants had low levels of self-rated negative psychosocial factors. Both African-Americans and Hispanics had higher levels of self-rated positive psychosocial factors.

## Outcomes

**Heart Failure Risk and Phenotype Deviance**—Compared to 0–1 risk factors, an increasing number of traditional risk factors were independently associated with increased risk of incident heart failure hospitalization in African-American and Hispanic women (Table 2). Compared to low tertile genetic risk scores, moderate and high-risk tertile genetic risk scores were independently associated with higher risk of incident heart failure hospitalization in African-American and Hispanic women (Table 2). Over 16 years of follow-up, 27.0% of African-Americans and 25.1% of Hispanics exhibited positive deviance by not developing incident heart failure hospitalization despite having 1+ risk factors and highest tertile of genetic risk (Table 3). Over 16 years of follow-up, 0.06% of African-Americans and 0.06% of Hispanics exhibited negative deviance by having incident heart failure hospitalization despite having <1 risk factor and lowest tertile of genetic risk.

**Psychosocial Factors Association with Heart Failure in High-risk Women**—Among high-risk African-American women with 1+ risk factor and high genetic risk, a positive psychosocial factor, optimism [SHR 0.94(95%CI: 0.91,0.99)], and a negative psychosocial factor, social strain [SHR 1.07(95%CI:1.02,1.12)], were modestly associated with risk of incident heart failure hospitalization in initial models (Table 4). No psychosocial factors were associated with incident heart failure hospitalization among African-Americans in the fully-adjusted analysis [including 10 principal components of ancestry and variables with  $p < 0.1$  in unadjusted analyses of African-Americans (age, participation in observational study or clinical trial, menopausal hormone therapy, current smoking, college education, optimism, religion, social strain; Table 4, Supplemental Table 3)]. Among Hispanics with 1+ risk factor and high genetic risk, only living alone was significantly associated with higher risk of incident heart failure hospitalization in unadjusted models [SHR 1.97(95%CI: 1.06,3.63)]. No psychosocial factors were significantly associated with risk of heart failure in high-risk Hispanic women in the fully-adjusted analysis [including 10 principal components of ancestry and variables with  $p < 0.1$  in unadjusted analyses of Hispanics (age, participation in observational study or clinical trial, menopausal hormone therapy, income, living alone; Table 4, Supplemental Table 3)].

## DISCUSSION

In a large national sample of postmenopausal women, 27.0% of African-American and 25.1% of Hispanic women with high-risk features, 1+ traditional risk factors and highest tertile genetic risk, did not develop heart failure hospitalization over an average 16 years of follow-up. The majority of African-American and Hispanic women had higher levels of positive psychosocial risk factors (optimism, social support, religion) and lower levels of



negative psychosocial factors (living alone, social strain, and depression). Observed positive and negative psychosocial factors were not significantly associated with the risk of incident heart failure hospitalization in high-risk African-American and Hispanic women in fully-adjusted analyses. This work suggests a need to identify additional pathways contributing to this clinical paradox.

This study is unique for using a positive deviance approach to study why some high-risk populations do not develop heart failure. Thus, the highest risk population of postmenopausal African-American and Hispanic women were evaluated for psychosocial factors that moderate genetic and traditional risk factors which predispose to heart failure. These women were the ideal women to study since they had survived into their 7<sup>th</sup> decade without developing heart failure. Although trial study participants are known to not be representative of the general population due to younger age, better health<sup>27</sup> and higher education, this knowledge can be used advantageously for positive deviance studies.

African-American and Hispanic women in the WHI have different heart failure prevalence than the general population. The general population of women have a heart failure prevalence of 5% by their 7<sup>th</sup> decade;<sup>1</sup> the prevalence of baseline heart failure at full WHI study adjudication represented less than 2% of the cohort.<sup>5</sup> African-American and Hispanic women have higher prevalence of heart failure than White women.<sup>1</sup>

It remains unclear whether the best psychosocial questions are being used to understand why high-risk African-American and particularly Hispanic women are not developing heart failure. The WHI psychosocial survey constructs have individually been validated across many populations.<sup>21–26</sup> However, the cultural application of positive and negative psychosocial factors is complex.<sup>28</sup> For example, resilience is thought to be an explanation for the Hispanic paradox, which confers lower risk of cardiovascular disease despite high prevalence of multiple traditional risk factors.<sup>28</sup> Resilience was not assessed at baseline in WHI. In addition, forms of discrimination such as racism<sup>29,30</sup> and xenophobia<sup>31</sup> were not evaluated and have been associated with health outcomes. This is particularly important for many of the WHI participants who have experienced the Civil Rights Movement of 1950–1960s and the current Time's Up Movement. These women may have developed a complex system for maintaining their well-being that is not measured through traditional scales that are normalized to White Americans.<sup>7</sup>

This may be a prime opportunity for engaging in qualitative research with high-risk participants who have not developed heart failure. In the era of patient-centered decision-making, ethnographic research would help detail everyday life for participants, and qualitative interviews and focus groups may highlight pertinent protective psychosocial factors. Qualitative research may reveal that traditional risk factors are missing important risk factors that are more relevant to specific racial and ethnic subgroups and individuals. Until a clear understanding of the protective factors for both African-Americans and Hispanics is available, it will be difficult to implement approaches that prevent heart failure in these high-risk groups.

## Limitations

This study is subject to several limitations. First, genetic polymorphisms for heart failure are understudied in African-Americans and Hispanics; there may be unknown polymorphisms contributing to disease burden that may better stratify patients into risk categories. Second, time-varying covariates were not assessed and could contribute to results. For example, most psychosocial factors were assessed once during this study. Although psychosocial factors can be dynamic, a single evaluation has been predictive in assessing risk of incident heart failure in multiple longitudinal studies.<sup>8</sup> Third, WHI was not adjudicated for incident outpatient heart failure rather incident heart failure requiring hospitalization. This is a strength since the risk of death rises incrementally with heart failure hospitalization in the general public and aides in the study focus of a high-risk population.<sup>1</sup> Fourth, low power may contribute to the null findings. Last, as in any observational study, unmeasured confounders may contribute to results.

## CONCLUSIONS

In a national study of high-risk post-menopausal women with 1 traditional risk factors and high genetic risk, no measured psychosocial factors were associated with lower risk of incident heart failure hospitalization in African-American or Hispanics. A significant proportion of African-American and Hispanic women exhibited positive deviance by not developing heart failure despite high traditional risk and high genetic risk. Additional investigation is needed to understand what hidden protective factors may reduce risk of heart failure in high-risk African-American and Hispanic women.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1.****Baseline Characteristics of Women with Risk Factors and Polymorphisms for Heart Failure**

	<b>African-American N=7986</b>	<b>Hispanic N=3341</b>
Age years, Mean (SD)	61.6 (7.0)	60.3 (6.7)
Study		
Observational Study	3678 (46.1)	1701 (50.9)
Clinical Trial	4308 (53.9)	1640 (49.1)
Menopausal Hormone Therapy Ever	4265 (53.6)	2034 (61.3)
Risk Factors		
0 Risk Factors	920 (11.5)	720 (21.6)
1 Risk Factors	2168 (27.2)	1274 (38.1)
2 Risk Factors	2590 (32.4)	885 (26.5)
3+ Risk Factors	2308 (28.9)	462 (13.8)
Atherosclerosis	306 (3.8)	52 (1.6)
Diabetes	1077 (13.5)	277 (8.3)
Hypertension	4411 (55.2)	985 (29.5)
Body mass index (kg/m <sup>2</sup> )	31.1 (6.6)	28.9 (5.8)
Sedentary (<500 MET-min/week)	4960 (62.1)	1971 (59.0)
Smoking Status		
Never smoker	3868 (48.4)	2080 (62.5)
Past smoker	3209 (40.1)	1021 (30.7)
Current smoker	920 (11.5)	227 (6.8)
Socioeconomic Factors		
Education High School	1869 (23.7)	1261 (38.4)
Some College	3069 (38.9)	1251 (38.1)
College Graduate	2952 (37.4)	776 (23.6)
Income < \$35,000	3916 (52.3)	1752 (57.5)
\$35,000–<\$50,000	1370 (18.3)	527 (17.3)
\$50,000–<\$75,000	1324 (17.7)	443 (14.5)
\$75,000	874 (11.7)	324 (10.6)
Insurance	7227 (92.6)	2658 (82.1)
Positive Psychosocial Factors, Mean (SD)		
Optimism Construct, 6–30*	23.3 (3.4)	22.3 (3.5)
Social Support Construct, 9–45*	35.1 (7.8)	34.2 (9.0)
Negative Psychosocial Factors, Mean (SD)		
Live Alone, binary	2450 (36.2)	612 (22.9)
Social Strain Construct, 4–20*	7.4 (3.0)	7.2 (2.9)
Presence of depressive symptoms	991(13.0)	574 (18.4)

\* denotes validated survey construct score range; Kg/m<sup>2</sup>, kilograms per meter squared. Higher values denote higher level of the factor. Continuous variables are described by mean (standard deviation (SD)) and remaining variables are categorical with frequency (%). Missing values include: body mass index n=101; menopausal hormone therapy ever n=55; education n=149; income n=797; insurance n=280; positive psychosocial factors:

optimism construct n=625; social support n=513; and negative psychosocial factors: live alone n=1875; social strain construct n=698; presence of depressive symptoms n=599.

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**Table 2.** Heart Failure Phenotypes Based Upon Number of Risk Factors and Ethnic-Specific Genetic Risk Score

Risk Status	African-American Women N=7817		Hispanic Women N=3280	
	n events	Sub-Hazard Ratio (95% CI)	n events	Sub-Hazard Ratio (95% CI)
Risk Factors				
0-1 Risk Factors	70	Ref	25	Ref
2 Risk Factors	125	<b>2.18 (1.61, 2.95)*</b>	27	<b>2.32 (1.32, 4.06)*</b>
3+ Risk Factors	272	<b>5.50 (4.20, 7.22)*</b>	39	<b>6.76 (4.01, 11.39)*</b>
Genetic Risk Score				
Tertile (median; interquartile range)				
Low (0.17; 0.09-0.17)	124	Ref	11	Ref
Moderate (0.18; 0.17-0.18)	179	<b>1.35 (1.06, 1.71)*</b>	28	<b>2.31 (1.14, 4.68)*</b>
High (0.18; 0.18-0.18)	164	<b>1.33 (1.05, 1.70)*</b>	50	<b>4.21 (2.18, 8.13)*</b>

This table includes only complete case analysis of participants with all variables. This study includes only Single Nucleotide Proteins (SNPs) significantly associated with heart failure ( $P < 0.1$ ). Risk factors include diabetes, atherosclerosis, hypertension, obesity, sedentary. Risk factor reference category collapses 0-1 risk factors due to small number of events in women with 0 risk factors (African-American: n=16; Hispanic: n=9). Analyses were fully-adjusted for age, observational study or clinical trial, menopausal hormone therapy ever, smoking status, and 10 principal components of ancestry. Death was treated as a competing risk.

\* denotes  $P < 0.05$ .

**Table 3.**

Heart Failure Phenotype Deviance Over 16 Years of Follow-up

Risk Status	African-American Women (n=7986)			Hispanic Women (n=3341)			Total
	Heart Failure Absent n (% of 7986)	Heart Failure Present n (% of 7986)	Total	Heart Failure Absent n (% of 3341)	Heart Failure Present n (% of 3341)	Total	
I Risk Factors, Highest Tertile of Genetic Risk	<b>Positive Deviance</b> <b>2155 (27.0)</b>	Normative pattern 162 (2.0)	2317 (29.0)	<b>Positive Deviance</b> <b>838 (25.1)</b>	Normative pattern 47 (1.4)	885 (26.5)	
I Risk Factors, Lowest Tertile of Genetic Risk	Probable Positive Deviance 2205 (27.6)	Probable Negative Deviance 119 (1.5)	2324 (29.1)	Probable Positive Deviance 846 (25.3)	Probable Negative Deviance 9 (0.3)	855 (25.6)	
<I Risk Factor, Highest Tertile of Genetic Risk	Probable Positive Deviance 286 (3.6)	Probable Negative Deviance 2 (0.03)	288 (3.6)	Probable Positive Deviance 225 (6.7)	Probable Negative Deviance 3 (0.09)	228 (6.8)	
<I Risk Factor, Lowest Tertile of Genetic Risk	Normative pattern 333 (4.2)	<b>Negative Deviance</b> 5 (0.06)	338 (4.2)	Normative pattern 257 (7.7)	<b>Negative Deviance</b> 2 (0.06)	259 (7.8)	

High-risk population includes women with I traditional risk factors and highest tertile of genetic risk. Positive deviance is indicated by high-risk populations (I traditional risk factors and highest tertile of genetic risk) who do not develop heart failure; probable positive deviance, moderate high-risk populations (either I traditional risk factors or highest tertile of genetic risk) who do not develop heart failure; probable negative deviance, moderate low-risk population (either <I traditional risk factor or lowest tertile of genetic risk) who develop heart failure; negative deviance, low-risk populations (<I traditional risk factor and lowest tertile of genetic risk) who develop heart failure. Note: percentages do not add up to 100 as women in the second tertile of genetic risk were not included in this table.



**Table 4.** Hazard Ratio of Developing Heart Failure Among Women with 1 or More Risk Factor and Highest Genetic Risk Score

Psychosocial Factors	Sub-distribution Hazard Ratio (95% CI)								
	African-American				Hispanic				
	n	Unadjusted Models	P-value	Adjusted Model (n=2034)	P-value	n	Unadjusted Models	Adjusted Model (n=645)	P-value
Positive Psychosocial									
Optimism	2198	<b>0.94 (0.91, 0.99)</b>	<b>0.01*</b>	0.97 (0.93, 1.02)	0.28	835	1.01 (0.93, 1.10)		0.85
Social Support	2215	1.00 (0.98, 1.02)	0.75			838	1.00 (0.97, 1.03)		<1.00
Religion	2306					880			
A Great Deal		Ref		Ref			Ref		
None/A Little		0.55 (0.29, 1.05)	0.07#	0.64 (0.32, 1.26)	0.19		1.37 (0.71, 2.63)		0.35
Negative Psychosocial									
Living Alone	1965	1.03 (0.73, 1.45)	0.86			710	<b>1.97 (1.06, 3.63)</b>		<b>0.03*</b>
Social Strain	2183	<b>1.07 (1.02, 1.12)</b>	<b>0.01*</b>	1.05 (0.99, 1.10)	0.07	808	1.00 (0.91, 1.09)		0.91
Depression	2195	0.81 (0.49, 1.34)	0.41			823	1.07 (0.51, 2.24)		0.86

This is subsample of WHI women with highest genetic risk tertile and 1 risk factors. Death was treated as a competing risk. Unadjusted models indicate univariate testing with each covariate. The adjusted model for African-American women (n=2034) includes age, participation in observational study or clinical trial, menopausal hormone therapy, smoking status, education, optimism construct, religion, social strain construct, and principal components of ancestry. The adjusted model for Hispanic women (n=645) includes age, participation in observational study or clinical trial, menopausal hormone therapy, income, living alone, and principal components of ancestry.

Bold\* denotes  $P < 0.05$

# inclusion in adjusted model for  $P < 0.10$ .