SUPPLEMENTAL MATERIAL

Supplemental Table 1. Distribution of Events by Stress and Depressive Symptoms Group, REGARDS (N = 4,487).

	Low stress and low depressive symptoms (n =3,613)	High stress and low depressive symptoms (n =253)	Low stress and high depressive symptoms (n =347)	High stress and high depressive symptoms (n =274)	p-value
First 2.5 years of follow-up					
MYOCARDIAL INFARCTION OR DEATH					
Number of events	361	25	41	47	-
Person-years at risk	8,443	592	798	606	-
Incidence rate per 1,000 person-years	42.8	42.2	51.4	77.5	0.004
MYOCARDIAL INFARCTION					
Number of events	198	14	18	21	-
Person-years at risk	8,443	592	798	606	-
Incidence rate per 1,000 person-years	23.5	23.6	22.5	34.6	0.44
DEATH					
Number of events	245	20	32	34	-
Person-years at risk	8,594	601	808	628	-
Incidence rate per 1,000 person-years	28.5	33.3	39.6	54.1	0.006
> 2.5 years of follow-up					
MYOCARDIAL INFARCTION OR DEATH					
Number of events	694	54	70	45	-
Person-years at risk	11,071	674	934	660	-
Incidence rate per 1,000 person-years	62.7	80.2	74.9	68.2	0.21
MYOCARDIAL INFARCTION					
Number of events	299	22	23	19	-
Person-years at risk	11,071	674	934	660	-
Incidence rate per 1,000 person-years	27.0	32.7	24.6	28.8	0.80
DEATH					
Number of events	612	48	63	40	-
Person-years at risk	11,777	707	985	709	-
Incidence rate per 1,000 person-years	52.0	67.9	63.9	56.4	0.17

Supplemental Table 2. Association of concurrent stress and depressive symptoms with myocardial infarction or death, REGARDS (N = 4,487). Sensitivity analysis for the first 2 years of follow-up.

	Hazard ratio (95% confidence interval)		
	Model 1	Model 2	Model 3
First 2 years of follow-up			
Low stress and low depressive symptoms	1 (ref)	1 (ref)	1 (ref)
High stress and low depressive symptoms	0.87 (0.56-1.36)	0.88 (0.57-1.38)	0.90 (0.58-1.41)
Low stress and high depressive symptoms	0.88 (0.59-1.29)	0.83 (0.56-1.23)	0.79 (0.53-1.16)
High stress and high depressive symptoms	1.54 (1.08-2.20)	1.45 (1.02-2.07)	1.39 (0.97-1.98)
p-value for interaction	0.03	0.04	0.05
> 2 years of follow-up			
Low stress and low depressive symptoms	1 (ref)	1 (ref)	1 (ref)
High stress and low depressive symptoms	1.04 (0.79-1.37)	1.04 (0.80-1.37)	1.06 (0.81-1.39)
Low stress and high depressive symptoms	1.07 (0.84-1.34)	1.00 (0.79-1.26)	0.96 (0.76-1.21)
High stress and high depressive symptoms	1.09 (0.82-1.44)	1.02 (0.77-1.36)	0.99 (0.74-1.32)
p-value for interaction	0.93	0.92	0.92

Model 1 adjusted for race, age, sex, region of residence, body mass index, income, education, marital status, general self-rated health, hypertension, diabetes, history of myocardial infarction and stroke.
Model 2 adjusted for all covariates in Model 1 and use of statins, beta blockers, aspirin, antidepressants, clopidogrel and renin angiotensin system inhibitors.
Model 3 adjusted for all in Model 1 and Model 2 and physical activity, alcohol consumption, cigarette smoking, and medication adherence.
REGARDS (Reason for Geographic and Racial Differences in Stroke).

Supplemental Table 3. Association of concurrent stress and depressive symptoms with myocardial infarction or death, REGARDS (N = 4,487). Sensitivity analysis for the first 3 years of follow-up.

	Hazard ratio (95% confidence interval)		
	Model 1	Model 2	Model 3
First 3 years of follow-up			
Low stress and low depressive symptoms	1 (ref)	1 (ref)	1 (ref)
High stress and low depressive symptoms	0.91 (0.63-1.29)	0.92 (0.64-1.32)	0.94 (0.66-1.34)
Low stress and high depressive symptoms	1.09 (0.82-1.46)	1.04 (0.78-1.38)	0.98 (0.74-1.31)
High stress and high depressive symptoms	1.58 (1.18-2.12)	1.49 (1.11-2.00)	1.42 (1.06-1.91)
p-value for interaction	0.08	0.09	0.10
> 3 years of follow-up			
Low stress and low depressive symptoms	1 (ref)	1 (ref)	1 (ref)
High stress and low depressive symptoms	1.06 (0.78-1.44)	1.06 (0.78-1.44)	1.08 (0.79-1.46)
Low stress and high depressive symptoms	0.94 (0.72-1.24)	0.88 (0.67-1.16)	0.85 (0.64-1.12)
High stress and high depressive symptoms	0.93 (0.67-1.31)	0.87 (0.62-1.23)	0.85 (0.61-1.20)
p-value for interaction	0.79	0.77	0.81

Model 1 adjusted for race, age, sex, region of residence, body mass index, income, education, marital status, general self-rated health, hypertension, diabetes, history of myocardial infarction and stroke.
Model 2 adjusted for all covariates in Model 1 and use of statins, beta blockers, aspirin, antidepressants, clopidogrel and renin angiotensin system inhibitors.
Model 3 adjusted for all in Model 1 and Model 2 and physical activity, alcohol consumption, cigarette smoking, and medication adherence.
REGARDS (Reason for Geographic and Racial Differences in Stroke).

Supplemental Table 4. Association of high stress and depressive symptoms evaluated separately on myocardial infarction, REGARDS (N = 4,487).

	Hazard ratio (95% confidence interval)		
	Model 1	Model 2	Model 3
First 2.5 years of follow-up			
High stress versus low stress	1.12 (0.77 – 1.61)	1.09 (0.76 – 1.58)	1.07 (0.74 – 1.55)
High depressive symptoms versus low depressive symptoms	1.05 (0.74 – 1.49)	0.96 (0.68 – 1.37)	0.91 (0.64 – 1.30)
> 2.5 years of follow-up			
High stress versus low stress	1.02 (0.73 – 1.43)	0.99 (0.71 – 1.39)	0.98 (0.70 – 1.37)
High depressive symptoms versus low depressive symptoms	0.83 (0.60 – 1.16)	0.75 (0.54 – 1.06)	0.72 (0.52 – 1.01)

Model 1 adjusted for race, age, sex, region of residence, body mass index, income, education, marital status, general self-rated health, hypertension, diabetes, history of myocardial infarction and stroke.
Model 2 adjusted for all covariates in Model 1 and use of statins, beta blockers, aspirin, antidepressants, clopidogrel and renin angiotensin system inhibitors.
Model 3 adjusted for all in Model 1 and Model 2 and physical activity, alcohol consumption, cigarette smoking, and medication adherence.

Supplemental Table 5. Association of concurrent high stress and depressive symptoms on myocardial infarction, REGARDS (N = 4,487).

	Hazard ratio (95% confidence interval)		
	Model 1	Model 2	Model 3
First 2.5 years of follow-up			
Low stress and low depressive symptoms	1 (ref)	1 (ref)	1 (ref)
High stress and low depressive symptoms	0.87 (0.50 – 1.50)	0.89 (0.52 – 1.54)	0.89 (0.52 – 1.55)
Low stress and high depressive symptoms	0.84 (0.52 – 1.38)	0.78 (0.48 – 1.28)	0.74 (0.46 – 1.21)
High stress and high depressive symptoms	1.31 (0.82 – 2.08)	1.19 (0.75 – 1.90)	1.12 (0.70 – 1.79)
p-value for interaction	0.17	0.21	0.22
> 2.5 years of follow-up			
Low stress and low depressive symptoms	1 (ref)	1 (ref)	1 (ref)
High stress and low depressive symptoms	1.06 (0.68 – 1.64)	1.06 (0.69 – 1.65)	1.06 (0.68 – 1.64)
Low stress and high depressive symptoms	0.78 (0.51 – 1.20)	0.71 (0.46 – 1.09)	0.68 (0.44 – 1.04)
High stress and high depressive symptoms	0.92 (0.57 – 1.49)	0.84 (0.52 – 1.36)	0.81 (0.50 – 1.31)
p-value for interaction	0.77	0.78	0.76

Model 1 adjusted for race, age, sex, region of residence, body mass index, income, education, marital status, general self-rated health, hypertension, diabetes, history of myocardial infarction and stroke.
Model 2 adjusted for all covariates in Model 1 and use of statins, beta blockers, aspirin, antidepressants, clopidogrel and renin angiotensin system inhibitors.
Model 3 adjusted for all in Model 1 and Model 2 and physical activity, alcohol consumption, cigarette smoking, and medication adherence.

Supplemental Table 6. Association of high stress and depressive symptoms evaluated separately on death, REGARDS (N = 4,487).

	Hazard ratio (95% confidence interval)		
	Model 1	Model 2	Model 3
First 2.5 years of follow-up			
High stress versus low stress	1.30 (0.96 – 1.74)	1.28 (0.95 – 1.72)	1.28 (0.95 – 1.73)
High depressive symptoms versus low depressive symptoms	1.37 (1.04 – 1.81)	1.29 (0.98 – 1.71)	1.22 (0.93 – 1.62)
> 2.5 years of follow-up			
High stress versus low stress	1.03 (0.82 – 1.30)	1.01 (0.80 – 1.28)	1.02 (0.81 – 1.28)
High depressive symptoms versus low depressive symptoms	0.96 (0.78 – 1.20)	0.91 (0.73 – 1.13)	0.87 (0.70 – 1.08)

Model 1 adjusted for race, age, sex, region of residence, body mass index, income, education, marital status, general self-rated health, hypertension, diabetes, history of myocardial infarction and stroke.
Model 2 adjusted for all covariates in Model 1 and use of statins, beta blockers, aspirin, antidepressants, clopidogrel and renin angiotensin system inhibitors.
Model 3 adjusted for all in Model 1 and Model 2 and physical activity, alcohol consumption, cigarette smoking, and medication adherence.

Supplemental Table 7. Association of concurrent high stress and depressive symptoms on death, REGARDS (N = 4,487).

	Hazard ratio (95% confidence interval)		
	Model 1	Model 2	Model 3
First 2.5 years of follow-up			
Low stress and low depressive symptoms	1 (ref)	1 (ref)	1 (ref)
High stress and low depressive symptoms	0.97 (0.61 – 1.53)	0.98 (0.62 – 1.55)	1.01 (0.64 – 1.59)
Low stress and high depressive symptoms	1.15 (0.79 – 1.67)	1.09 (0.75 – 1.59)	1.02 (0.71 – 1.49)
High stress and high depressive symptoms	1.68 (1.16 – 2.43)	1.58 (1.09 – 2.28)	1.52 (1.05 – 2.21)
p-value for interaction	0.22	0.26	0.25
> 2.5 years of follow-up			
Low stress and low depressive symptoms	1 (ref)	1 (ref)	1 (ref)
High stress and low depressive symptoms	1.11 (0.82 – 1.49)	1.11 (0.82 – 1.50)	1.13 (0.83 – 1.52)
Low stress and high depressive symptoms	0.99 (0.76 – 1.28)	0.93 (0.71 – 1.21)	0.88 (0.67 – 1.15)
High stress and high depressive symptoms	0.96 (0.69 – 1.33)	0.90 (0.64 – 1.26)	0.88 (0.63 – 1.23)
p-value for interaction	0.60	0.59	0.65

Model 1 adjusted for race, age, sex, region of residence, body mass index, income, education, marital status, general self-rated health, hypertension, diabetes, history of myocardial infarction and stroke.
Model 2 adjusted for all covariates in Model 1 and use of statins, beta blockers, aspirin, antidepressants, clopidogrel and renin angiotensin system inhibitors.
Model 3 adjusted for all in Model 1 and Model 2 and physical activity, alcohol consumption, cigarette smoking, and medication adherence.

Supplemental Table 8. Association of concurrent high stress and depressive symptoms with myocardial infarction or death, REGARDS (N = 4,487). Sensitivity analysis (high stress was defined by Cohen's Perceived Stress Scale score ≥ 7).†

	Hazard ratio (95% confidence interval)		
	Model 1	Model 2	Model 3
First 2.5 years of follow-up			
Low stress and low depressive symptoms	1 (ref)	1 (ref)	1 (ref)
High stress and low depressive symptoms	0.88 (0.63 – 1.22)	0.88 (0.63 – 1.22)	0.89 (0.64 – 1.23)
Low stress and high depressive symptoms	1.02 (0.71 – 1.46)	0.97 (0.67 – 1.39)	0.91 (0.63 – 1.30)
High stress and high depressive symptoms	1.51 (1.13 – 2.03)	1.41 (1.05 – 1.90)	1.36 (1.01 – 1.83)
p-value for interaction	0.06	0.06	0.06
> 2.5 years of follow-up			
Low stress and low depressive symptoms	1 (ref)	1 (ref)	1 (ref)
High stress and low depressive symptoms	1.10 (0.87 – 1.38)	1.10 (0.87 – 1.38)	1.09 (0.87 – 1.38)
Low stress and high depressive symptoms	1.07 (0.82 – 1.41)	1.01 (0.77 – 1.32)	0.96 (0.73 – 1.25)
High stress and high depressive symptoms	0.92 (0.69 – 1.22)	0.85 (0.64 – 1.14)	0.84 (0.63 – 1.12)
p-value for interaction	0.26	0.24	0.31

† The analysis includes 3,465 (77.2%) participants with low stress and low depressive symptoms, 401 (8.9%) participants with high stress and low depressive symptoms, 281 (6.3%) participants with low stress and high depressive symptoms and 340 (7.6%) participants with high stress and high depressive symptoms.
Model 1 adjusted for race, age, sex, region of residence, body mass index, income, education, marital status, general self-rated health, hypertension, diabetes, history of myocardial infarction and stroke.
Model 2 adjusted for all covariates in Model 1 and use of statins, beta blockers, aspirin, antidepressants, clopidogrel and renin angiotensin system inhibitors.
Model 3 adjusted for all in Model 1 and Model 2 and physical activity, alcohol consumption, cigarette smoking, and medication adherence.

Supplemental Table 9. Association of concurrent high stress and depressive symptoms with myocardial infarction or death, REGARDS. Sensitivity analysis using multiple imputation (N = 5,205).

	Hazard ratio (95% confidence interval)		
	Model 1	Model 2	Model 3
First 2.5 years of follow-up			
Low stress and low depressive symptoms	1 (ref)	1 (ref)	1 (ref)
High stress and low depressive symptoms	0.98 (0.69 – 1.40)	0.99 (0.70 – 1.41)	1.01 (0.71 – 1.44)
Low stress and high depressive symptoms	1.07 (0.79 – 1.45)	1.02 (0.75 – 1.38)	0.97 (0.72 – 1.32)
High stress and high depressive symptoms	1.63 (1.22 – 2.17)	1.54 (1.15 – 2.05)	1.46 (1.09 – 1.95)
p-value for interaction	0.10	0.12	0.14
> 2.5 years of follow-up			
Low stress and low depressive symptoms	1 (ref)	1 (ref)	1 (ref)
High stress and low depressive symptoms	1.07 (0.82 – 1.39)	1.06 (0.82 – 1.38)	1.08 (0.83 – 1.41)
Low stress and high depressive symptoms	1.05 (0.83 – 1.33)	0.99 (0.79 – 1.25)	0.95 (0.75 – 1.20)
High stress and high depressive symptoms	1.02 (0.77 – 1.36)	0.95 (0.71 – 1.27)	0.92 (0.69 – 1.23)
p-value for interaction	0.66	0.64	0.61

Model 1 adjusted for race, age, sex, region of residence, body mass index, income, education, marital status, general self-rated health, hypertension, diabetes, history of myocardial infarction and stroke.
Model 2 adjusted for all covariates in Model 1 and use of statins, beta blockers, aspirin, antidepressants, clopidogrel and renin angiotensin system inhibitors.
Model 3 adjusted for all in Model 1 and Model 2 and physical activity, alcohol consumption, cigarette smoking, and medication adherence.

Supplemental Table 10. Association of concurrent high stress and depressive symptoms on CVD death, REGARDS (N = 4,487).

	Hazard ratio (95% confidence interval)		
	Model 1	Model 2	Model 3
First 2.5 years of follow-up			
Low stress and low depressive symptoms	1 (ref)	1 (ref)	1 (ref)
High stress and low depressive symptoms	1.10 (0.59 – 2.05)	1.13 (0.61 – 2.11)	1.14 (0.61 – 2.13)
Low stress and high depressive symptoms	1.03 (0.59 – 1.80)	0.95 (0.54 – 1.67)	0.89 (0.51 – 1.56)
High stress and high depressive symptoms	1.57 (0.92 – 2.69)	1.44 (0.84 – 2.46)	1.38 (0.80 – 2.36)
p-value for interaction	0.50	0.55	0.53
> 2.5 years of follow-up			
Low stress and low depressive symptoms	1 (ref)	1 (ref)	1 (ref)
High stress and low depressive symptoms	1.25 (0.83 – 1.90)	1.27 (0.84 – 1.93)	1.26 (0.83 – 1.92)
Low stress and high depressive symptoms	1.01 (0.68 – 1.48)	0.93 (0.63 – 1.37)	0.86 (0.58 – 1.27)
High stress and high depressive symptoms	0.75 (0.44 – 1.28)	0.69 (0.40 – 1.19)	0.68 (0.39 – 1.16)
p-value for interaction	0.17	0.16	0.22

Model 1 adjusted for race, age, sex, region of residence, body mass index, income, education, marital status, general self-rated health, hypertension, diabetes, history of myocardial infarction and stroke.
Model 2 adjusted for all covariates in Model 1 and use of statins, beta blockers, aspirin, antidepressants, clopidogrel and renin angiotensin system inhibitors.
Model 3 adjusted for all in Model 1 and Model 2 and physical activity, alcohol consumption, cigarette smoking, and medication adherence.

REGARDS MANUSCRIPT PROPOSAL FORM

Please read REGARDS P&P Policies, available from regards_admin@ms.soph.uab.edu before completing this form.

Date of submission: 01/17/13

WRITING CHAIR NAME: Carmela Alcántara, Ph.D.

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(If this is your first REGARDS proposal, please include a letter of introduction from a REGARDS investigator.)

REGARDS Investigator/Sponsor: Paul Muntner, Ph.D.

PROPOSAL TITLE: The synergistic effect of stress and depression on recurrent coronary heart disease morbidity and mortality

Abbreviated title: Stress, depression, and recurrent CHD

Co-authors: (The REGARDS Executive Committee may nominate additional authors if special expertise for interpreting REGARDS data is needed. For all locally analyzed papers, please justify use of each co-author; if the paper is from a multisite ancillary study, co-authors from contributing units of REGARDS should be involved.)

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Have all co-authors reviewed and approved this document? X Yes (required)

Has lead author checked for overlap with other REGARDS manuscripts? X Yes (required)
Please confirm that this manuscript has been checked for overlap. Check with the REGARDS administrator at **regards_admin@ms.soph.uab.edu**). Yes, no overlap.
If possible overlap exists, please explain and describe resolution here:

1. **Type of study: _____ Main ____X_ Ancillary (select only one)**

   If Ancillary Study, please list Study Title & PI: REGARDS MI (Safford)

2. **Type of data (select one):[X Events] [_____ Longitudinal] [_____ Cross-sectional] [_____ Methods]**

2a. If cross-sectional: Complete participants only: ____
Partial participants included also: ____
(Partial participants are those who only completed baseline but did not have in-person exam component.)

3. **Location of analysis: __X__ Central (by UAB Statistical and Data Coordinating Center staff)**
   _____ Local (Site) – additional details are required – see P&P Policies and Procedures for instructions and supplemental information to be provided.

4. **Key words:** cardiovascular disease, stress, depression

5. **Genetic Information:**

Do you propose use of data from participants' DNA? __X__ No _____ Yes
If yes, is the paper addressing vascular-related conditions? __X__ No _____ Yes
If no, REGARDS participants did not provide consent for uses of DNA for diseases unrelated to vascular problems. Please refer to the Coordinating Center for guidance.

6. Conflict of Interest:

a. Are these analyses to involve a for-profit corporation? __X__ No _____ Yes

b. Do you or any member of your Writing Group intend to patent any process, aspect or outcome of these analyses? __X__ No _____ Yes

c. If the answer to a or b is yes, the involvement includes (check one):

___ An unrestricted educational or research grant

___ Hypothesis development and/or data analysis (results require verification by the Coordinating Center)

PART I (*The following should produce no more than approximately 2-3 pages):*

Introduction [Rationale and background]:

Despite significant improvements in cardiology care, depression remains an independent risk factor for major adverse cardiac events and/or all-cause mortality after an acute coronary syndrome (ACS) (1-4). Several biological and behavioral mechanisms have been postulated and tested to explain the excess risk, but the evidence has been inconsistent (5-7). Thus, the specific mechanism or mechanisms that drive the elevated risk for poor prognosis among depressed patients remain elusive. The inconsistent findings in the depression – coronary heart disease (CHD) research literature might be attributable to confounding due to stress. Most prior work has been conducted under the assumption that there are main effect differences between depressed and non-depressed patients (*Main effects model*), without considering that depression might function as an underlying vulnerability or diathesis, and that only under circumstances of stress exposure does the vulnerability lead to differences in cardiac event recurrence and mortality (*Perfect storm model*) (8). The *Perfect storm* is a recent model of ACS events reminding us that events are not caused by a single or a few factors, but rather result from the unfortunate confluence of certain situations and underlying risk factors (8). Just as depressive symptoms alone are insufficient to allow accurate prediction of who will die or reinfarct after ACS, many other established CHD risk factors such as dyslipidemia or diabetes are similarly insufficient to single-handedly identify who is at risk (9). Recent studies have also documented that exposure to acutely stressful situations are associated with immediate increases in ACS recurrence/mortality risk, although again, such exposure alone is also insufficient allow accurate prediction (10). The objective of the proposed manuscript is to conduct a formal test of the applicability of the *Perfect storm* model for heart health by examining whether stress modifies the association of depression to CHD morbidity and all-cause mortality in participants with CHD, and whether behavioral mechanisms (smoking, heavy alcohol consumption, physical inactivity, and low medication adherence) account for a substantial portion of this excess risk.

Research Hypothesis:

In REGARDS study participants with a history of CHD at baseline:

1) Stress will modify the association between depression and behavioral risk factors including heavy alcohol use, smoking status, physical inactivity, and low medication adherence, after adjustment for socio-demographics, such that depressed participants with high stress will exhibit worse behaviors when compared to their depressed counterparts with low stress, non-depressed counterparts with high stress and non-depressed counterparts with low stress.
2) Stress will modify the association between depression and recurrent CHD events, defined as a definite or probable myocardial infarction or death after adjustment for socio-demographics, medication use, and co-morbid conditions such that depressed participants with high stress will exhibit a higher hazard ratio (HR) for recurrent CHD events/ACM when compared to their

counterparts with low stress, non-depressed counterparts with high stress, with non-depressed low stress participants serving as a referent group. All-cause mortality (ACM) and CHD will be investigated separately in a secondary analysis.

Exploratory Aim) The HR for recurrent CHD events/ACM associated with depression and high stress will be attenuated after adjusting for the above behavioral risk factors

Data [Variables to be used, sample inclusions/exclusions]:

Population:	All REGARDS participants with baseline CHD (N~4,676). History of CHD at baseline will be defined as a self-reported history of myocardial infarction or coronary revascularization procedure. We considered including individuals whose only evidence of CHD was based on the study electrocardiogram but chose to limit the analysis to participants aware of their disease history.
Primary Outcome:	The pooled outcome of recurrent CHD events (definite/probable myocardial infarction) or ACM
Secondary Outcomes:	ACM and recurrent CHD evaluated separately
Primary Predictors:	Participants' depressive symptoms, as measured using the 4 item Center for Epidemiologic Studies Depression Scale (CES-D) and participants' perceived stress, as measured using the 4 item Cohen's Perceived Stress Scale, will be used to create four groups: (1) not depressed and low stress; (2) not depressed and high stress; (3) depressed and low stress; and (4) depressed and high stress. Depressed will be defined as a CES-D score ≥ 4 and high stress will be defined as a Stress scale score ≥ 7. The "not depressed and low stress" group will serve as the referent group.
Covariates:	Baseline demographic covariates, including age, race, sex, region of residence, income, education level, and body mass index (BMI); baseline comorbid conditions, including hypertension, MI, stroke, and diabetes mellitus; baseline medication use, including aspirin, beta blocker, thienopyridines, ace-inhibitors / angiotensin receptor blockers, statins, and anti-depressants
Behavioral risk factors:	baseline behavioral risk factors, including alcohol use, smoking status, self-reported physical activity, and self-reported low medication adherence, as determined through the 4-item Morisky scale

Brief analysis plan and methods:

Using the 4-item CES-D score ≥ 4 to define the presence of depression and a perceived stress score ≥ 7 to define high stress, four groups will be created: (1) not depressed and low stress; (2) not depressed and high stress; (3) depressed and low stress; and (4) depressed and high stress. Baseline characteristics of REGARDS participants will be calculated for participants in each of the four groups. The prevalence of behavioral risk factors will also be calculated for these four groups. We will calculate the odds ratio for each of the behavioral risk factors associated with each of the four depressed by stress groups with participants in the "not depressed and low stress" group serving as the reference category. Next, Cox proportional hazards models will be constructed using time to the first new CHD event or mortality as the dependent variable and the four depressed by stress groups as the independent variable of interest with participants in the "not depressed and low stress" group serving as the reference category. For both the logistic and Cox regression models, two levels of adjustment will be performed. First, adjustment will be made for baseline socio-demographic covariates including age, sex, race, region of residence, income, and education level. Second, a model will include covariates in model 1, with further addition of baseline

comorbidities including hypertension, MI, stroke, and diabetes mellitus, baseline medication use including aspirin, beta blocker, thienopyridines, ace-inhibitors / angiotensin receptor blockers, and statins.

Next, the change in effect size for the depressed x stress groups on outcomes (e.g., the pooled outcome of CHD and ACM) will be calculated as the percent change of the log of HR as compared to that in model 1 described above. We will evaluate the attenuation in the HR associated with comorbidities, medication use and health behaviors. Using a 1,000 iteration bootstrap, empirical confidence intervals will be constructed around the percent change in the log HR. A secondary analysis will be performed in the same manner using all-cause mortality only and CHD only as the outcomes.

Summary/conclusion:

The proposed analysis of REGARDS will allow us to test a conceptual model (i.e., the *Perfect Storm* model) for the recurrence of CHD that focuses on the synergistic effect of stress and depression on CHD and all-cause mortality. By identifying the specific conditions under which depressed people exhibit poor cardiac prognosis, we might be better able to identify the modifiable mechanisms (biological, psychological, social, and environmental) by which depression increases risk of CHD and create targeted interventions to mitigate the excess risk.

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