ARIC Manuscript Proposal #3971

PC Reviewed: 12/14/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority:**

1.a.Full Title: The Association Between Depression and Elevated Cardiac Biomarkers: Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title: Depression and Cardiac Biomarkers

2. Writing Group:

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3. Timeline: Analysis is anticipated to begin as soon as approval is obtained. The manuscript is to be prepared as soon as analyses are available. Both the analysis and manuscript preparation are anticipated to take place within one year of approval of the proposal.

4. Rationale:

A large and growing body of evidence has demonstrated an important association between mental health and cardiovascular disease (CVD) (1). Several mental health disorders have been identified as risk factors for the development of CVD including mood disorders, anxiety disorders, post-traumatic stress disorder, and chronic stress. Multiple studies have shown that depression is an independent risk factor for CVD (2). Depression affects approximately 10% of the population in the United States (3), but is two or three times more common among patients with CVD (4). In addition to depression, other forms of psychological stress such as vital exhaustion, anger, and inadequate social support have also been identified as risk factors for atherosclerotic cardiovascular disease and heart failure(5-7). Mental stress has been shown to be associated with reversible coronary ischemia in patients with coronary heart disease (CHD) (8). Although the association between poor mental health and CVD is well established and bidirectional, the exact mechanisms remain incompletely understood.

Several pathophysiologic mechanisms have been implicated linking depression (or depressive symptoms) to the development of CVD including neurohormonal disruptions, inflammation and endothelial dysfunction, autonomic dysfunction, and maladaptive lifestyles (9). Neurohormonal changes in depression involve alterations in the hypothalamic-pituitary axis resulting in enhanced adrenal responses to adrenocorticotropic hormone (ACTH) and elevated cortisol levels (10). Depression has been associated with prolonged state of inflammation and oxidative stress with elevations in C-reactive protein (CRP), TNF-alpha, and IL-6 (11). Elevated cortisol levels and inflammation can cause endothelial dysfunction through decreased nitric oxide bioavailability, increased platelet activation and thrombosis (12). Autonomic dysfunction in depression involves low heart rate variability (HRV) and elevated cardiac sympathetic tone, which are predictive for CHD and mortality (13). While several studies have identified links between depression and elevations in inflammatory biomarkers, few studies have looked for an association between stress, anxiety, and depression with biomarkers of myocardial injury (high-sensitivity troponin I (HsTnI), high-sensitivity troponin T (hsTnT) or stretch [N-terminal pro-brain natriuretic peptide (NT-proBNP)].

The ARIC study provides a unique platform to further assess the association between mental stress and biomarkers of myocardial injury/myocardial stretch among those with and without clinical CVD. Psychometric evaluation was performed using the “Health and Life Profile” during visit 2, and the Center for Epidemiologic Studies Depression (CES-D) scale during visits 5 and 6. The Health and Life Profile consisted of 3 components: (1) the Maastricht vital exhaustion questionnaire (MVEQ) for assessment of vital exhaustion, (2) the Spielberger Trait Anger Scale (STAS) for measurement of anger burden, and (3) the Interpersonal Support Evaluation List-Short Form (ISEL-SF) and Lubben Social Network Scale (LSNS) for evaluation of psychosocial support. The MVEQ is a 21-item questionnaire that assesses the presence and severity of vital exhaustion, which is defined as a maladaptive response to chronic stress characterized by excessive fatigue, irritability, and feelings of demoralization (14). Several studies have demonstrated a strong correlation between vital exhaustion and other depression screening measures (15). However, unlike depression, vital exhaustion is not associated with depressed mood, feelings of guilt, or low self-esteem. Several studies from the ARIC cohort have demonstrated that symptoms of vital exhaustion (measured by increasing scores on the MVEQ) are independently associated with the development of CVD (5-7,16). Previous studies have also shown that anger proneness and poor social support are also associated with increased risk for CVD (6,17-19). However, no studies have compared MVEQ scores with levels of cardiac biomarkers.

During visits 5 and 6, current depressive symptoms were assessed using the CES-D. The CES-D form is an 11-item questionnaire that is well validated as a screening tool for identifying clinical depression with excellent positive predictive value (20). Depressive symptoms determined by higher scores on the CES-D form have been shown to be predictive of all-cause and CVD mortality after adjustment for demographic factors and comorbidities (21). In the ARIC cohort, current depressive symptoms, measured using the CES-D during visit 5, were twice as prevalent in participants with diabetes compared to those without diabetes (22). Additionally, a study by Sonsin-Diaz et al found that chronically elevated CRP levels were associated with an increased risk for clinically significant depressive symptoms independent of related diseases or risk factors (23).

In this study, we will analyze the association between symptoms of vital exhaustion (visit 2) and depression (visit 5 and 6) with biomarkers of systemic inflammation, myocardial injury, and neurohormonal stress.

5. Main Hypothesis/Study Questions:

Hypothesis:

1. Depressive symptoms in older age, as measured using the CES-D questionnaire during visit 5 (mean age 75.8 ± 5.3), are associated with markers of systemic inflammation (hsCRP), subclinical myocardial injury (hsTnT, hsTnI), and neurohormonal stress (NT-proBNP). We hypothesize that higher scores on the CES-D will be independently associated with higher levels of circulating biomarkers during visit 5.
2. High levels of baseline depressive symptoms are associated with increasing levels of biomarkers of systemic inflammation (hsCRP), subclinical myocardial injury (hsTnT, hsTnI), and neurohormonal stress (NT-proBNP) over time. We hypothesize that participants with higher baseline CES-D scores during visit 5 will have increasing levels of biomarkers between visits 5 and 6.
3. Symptoms of vital exhaustion during middle age, as measured using the MVEQ during visit 2 (mean age 57.0 ± 5.7) are associated with markers of systemic inflammation (hsCRP), subclinical myocardial injury (hsTnT), and neurohormonal stress (NT-proBNP). We hypothesize that higher scores on the MVEQ will be independently associated with higher levels of circulating biomarkers during visit 2.

Study Aims:

Aim 1: Assess the association between current depressive symptoms (exposure) and circulating hsCRP, hsTnT, hsTnI, and NT-proBNP levels (outcome) at visit 5 using cross-sectional analysis.

Aim 2: Assess the association between depressive symptoms at visit 5 (exposure) and changes in biomarker levels between visits 5 and 6 (outcome).

Aim 3: Assess the association between current symptoms of vital exhaustion (exposure) and circulating hsCRP, hsTnT, and NT-proBNP levels (outcome) at visit 2 using cross-sectional analysis.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodological limitations or challenges if present).

Aim 1:

Study design:

We will perform a cross-sectional analysis of the association between current depressive symptoms (measured by CES-D scores) and biomarker levels (hsCRP, hsTnT, hsTnI, and NT-proBNP) during visit 5.

Participants who completed the CES-D questionnaire will be included. Participants will be excluded if they meet any of the following criteria: (1) did not complete CES-D during visit 5; (2) missing biomarker data at visit 5; (3) missing covariate information; (4) race other than black or white (due to small numbers).

Exposure variables:

Current depressive symptoms measured using the CES-D questionnaire during visit 5 will be modeled as both continuous and categorical variables, with current depressive symptoms defined as a score ≥ 9 (22).

Outcome variables:

Biomarker levels (hsCRP, hsTnT, hsTnI, and NT-proBNP) measured at visit 5 will be modeled as continuous and categorical variables. Categorical variables will be stratified based on previous studies:

- hsTnT: < 6, 6 to <13, and ≥ 13 ng/L.
- hsTnI: <6, 6 to <12, and ≥12 ng/L.
- NT-proBNP: <125, ≥125 pg/mL.
- hsCRP: < 2 mg/L, ≥2 mg/L.

Statistical analysis:

Multivariable logistic regression analysis will be performed to estimate the odds ratios for each biomarker outcome as a categorical variable. We will also perform multivariable linear regression analysis with biomarkers modeled as a continuous variable.

Analysis will include 2 adjustment models. Model 1 will include age, sex, and race. Model 2 will include variables from model 1 plus level of education, physical activity level, smoking status, alcohol use, body mass index (BMI), systolic and diastolic blood pressure, total cholesterol levels, plasma LDL-cholesterol, and plasma HDL-cholesterol, hypertension, diabetes, CKD (eGFR of less than 60 ml/min/1.73m^2), and lipid-lowering therapy.

We will perform stratified analysis of patients with and without prevalent cardiovascular disease (CHD, CHF, or stroke). Stratified analysis will be performed based on sex/gender. We will perform sensitivity analysis in a model that include use of antidepressant medications in order to see if any effects seen are driven by antidepressants. For NT-proBNP levels, sensitivity analysis will be performed to account for variability caused by differences in BMI.

Aim 2:

Study design:

To assess whether depressive symptoms are associated with changes in biomarker levels over time, we will correlate changes in CES-D scores with that of biomarker levels between visits 5 and 6.

For this analysis, participants who completed the CES-D score at visit 5 and completed visit 5 and 6 will be included. Participants will be excluded if they meet any of the following criteria: (1) did not complete CES-D during visits 5; (2) missing biomarker data at visits 5 or 6, (3) missing covariate information; (4) race other than black or white (due to small numbers).

Exposure variables:

Current depressive symptoms measured using the CES-D questionnaire during visit 5 will be modeled as both continuous and categorical variables, with current depressive symptoms are defined as a score ≥ 9.

We will then assess if depressive symptoms at visit 5 (based on the CES-D) is associated with changes in biomarker level between visit 5 and 6 (stable levels will be = +/- 25% change; increase->25% while decrease <25%)

If there is an association between depressive symptoms and increasing biomarkers over time, we will then analyze whether there is an association between changes in depressive symptoms scores according to the following criteria:

Depressive symptom category	CES-D score visit 5	CES-D score visit 6
Sustained depression symptoms	≥ 9	≥ 9
New Depressive symptoms	<9	≥9
Improved depressive symptoms	≥9	<9
Low or absent depressive symptoms	<9	<9

Outcome variables:

Change in biomarker levels (hsCRP, hsTnT, hsTnI, and NT-proBNP) between vists 5 and 6 will be modeled as categorical variables defined by the following:

- >25% increase from visit 5 to visit 6.
- >25% decrease from visit 5 to visit 6
- ≤25% (+or -) change between visits (stable)

Statistical analysis:

Multivariable logistic regression analysis will be used to analyze the association between changes in depressive symptoms and biomarker levels over time.

Analysis will include 2 adjustment models with the same covariates listed for Aim 1. For aim 2, absolute and percent changes in covariates will be included for analysis. We will use inverse probability weighting to account for attrition, CV events, and death between visits 5 and 6.

Aim 3:

Study design:

We will perform a cross-sectional analysis of the association between current symptoms of vital exhaustion (measured by MVEQ scores) and biomarker levels (hsCRP, hsTnT, NT-proBNP) during visit 2.

For analysis of current vital exhaustion symptoms at visit 2, participants who completed the "Health and Life Profile" will be included. Participants will be excluded if they meet any of the following criteria: (1) did not complete MVEQ during visit 2; (2) missing biomarker data at visit 2; (3) missing covariate information; (4) race other than black or white (due to small numbers).

Exposure variables:

Current symptoms of vital exhaustion measured using the MVEQ scores during visit 2 will be modeled as both continuous and categorical variables. For categorical analysis, MVEQ results will be approximated into 4 quartiles based on previous studies: (1) 0-4 (low); (2) 5-8; (3) 9-15; (4) 16-42 (high) (7).

We will also perform exploratory analysis on the relationship between the STAS, ISEL-SF, and LSNS scores with levels of circulating biomarkers. These questionnaires were administered in conjunction with the MVEQ as part of the ARIC study's "Health and Life Profile" during visit 2.

Outcome variables:

Biomarker levels (hsTnT, NT-proBNP, and hsCRP) measured at visits 2 and 5 will be modeled as continuous and categorical variables. Categorical variables will be stratified based on previous studies:

- hsTnT: < 6, 6 to <13, and ≥ 13 ng/L.
- NT-proBNP: <125, ≥125 pg/mL.
- hsCRP: < 2 mg/L, ≥2 mg/L.

Statistical analysis:

Statistical analysis for Aim 3 will be similar to methods described for Aim 1.

Limitations/Major Challenges:

1. The MVEQ and the CES-D may not be as commonly used in clinical practice such as other depression tools, such as the Patient Health Questionnaire-2 (PHQ-2) and Patient Health Questionnaire-9 (PHQ-9). This may affect the generalizability of our results.
2. Levels of attrition, CV events, and death between visits 5 and 6 may complicate interpretation of change analysis.

7a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used?____ Yes ____ No

(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8 a. Will the DNA data be used in this manuscript? ____ Yes __X_ No

b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

___X__ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

Manuscript 1: Vital Exhaustion as a Risk Factor for Adverse Cardiac Events (From the Atherosclerosis Risk in Communities [ARIC] Study)

Abstract 1: Depressive Symptoms, Cardiac Function, and Risk of Heart Failure With Preserved or Reduced Ejection Fraction in Late Life: The Atherosclerosis Risk in Communities (ARIC) Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?_____ Yes __X__ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study *

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

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