ARIC Manuscript Proposal #3434

PC Reviewed: 7/9/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Psychological conditions and subsequent risk of peripheral artery disease: The Atherosclerosis Risk in Communities (ARIC)

b. Abbreviated Title (Length 26 characters): Psychological Stress and PAD

2. Writing Group:

Writing group members: Yasuyuki Honda, Yejin Mok, Lena Matthews, Jeremy Van`t Hof, Gail Daumit, Kucharska-Newton Anna, Elizabeth Selvin, Thomas Mosley, Josef Coresh, Kunihiro Matsushita

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _Y.H._ **[please confirm with your initials electronically or in writing]**

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3. Timeline: Data to be used in this proposal are available. Analyses and manuscript preparation will be performed over the next 12 months.

4. Rationale:

Psychological conditions/disorders have been associated with increased risk of cardiovascular disease (CVD), including coronary artery disease and cardiovascular mortality.[1, 2] For example, several systematic reviews showed depression as a risk factor for the development of CVD.[3-5] In addition, a few studies have reported the link of trait anger to increased risk of CVD outcomes.[6-8] Social isolation, a condition closely related to depression, has also been associated with the risk of CVD.[9]

There are several plausible mechanisms linking psychological conditions to the increased risk of CVD. For example, biological factors such as autonomic nervous system dysfunction, hypothalamic-pituitary-adrenal axis dysregulation, inflammation, and increased platelet reactivity are considered to be associated with psychological conditions[1-5]. Additionally, behavioral mechanisms including poor adherence to medical treatment, smoking, high-fat diet, and lack of physical exercise are substantially involved in the relation between psychological conditions and the development of CVD.[1-5]

Despite a number of epidemiological studies about psychological conditions and CVD, data regarding psychological conditions and the risk of peripheral artery disease (PAD) are sparse. To our knowledge, only one prospective study has reported positive associations of anger trait and depression with the risk of PAD.[10] Since risk factor profile is not consistent across different atherosclerotic CVD (ASCVD) subtypes (e.g., lipids strongly related to coronary disease, blood pressure to stroke, and diabetes to PAD), it is important to comprehensively evaluate the associations of psychological conditions with PAD.

Therefore, we propose to investigate the association of psychological conditions assessed at visits 2 and 5 (e.g., depression, anger trait, and social isolation) with the risk of PAD in a bi-racial community-based cohort, the ARIC Study. With a long follow-up, we will be able to uniquely assess the most severe type of PAD, critical limb ischemia (CLI), as an outcome as well.

5. Main Hypothesis/Study Questions:

Aim 1) To examine the association of psychological conditions with a long-term risk of PAD and CLI.

Aim 2) To contrast the associations of psychological conditions with PAD, CLI, and other ASCVDs (i.e., coronary heart disease and stroke). Although the associations of psychological conditions with coronary disease and stroke have been reported, since risk factor profiles are not consistent across PAD and other ASCVDs, it would be informative to contrast these associations in a single study population.

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 methodologic limitations or challenges if present).

Inclusions:

All black and white ARIC subjects

Exclusions:

-Missing exposures of psychological conditions at visit 2
-Participants with prevalent PAD, coronary heart disease, or stroke at visit 2
-As detailed below, we will conduct secondary analysis using visit 5 exposure of the 11-item version of Center for Epidemiologic Studies Depression Scale (CES-D). For that secondary analysis, we will apply basically the same exclusion criteria at visit 5

Exposures:
Primary exposures at visit 2 with long follow-up:

In ARIC, psychological conditions at visit 2 (i.e., depression, anger trait, and social isolation) were measured by Health and Life Profile: Part A (HPA), Health and Life Profile: Part B (HPB), and Health and Life Profile: Part C (HPC). These questionnaires were basically self-administered, but participants were able to receive support by interviewers as needed.

The HPA questionnaire is designed to measure social relationships. This form includes a Short-Form of the Interpersonal Support Evaluation List (ISEL-SF) and the Lubben Social Network Scale (LSNS), two scales evaluating the quantity of social networks.[11, 12] The ISEL-SF consists of 16 questions on a 0-3 rating scale[13] (HPA question 3-18) assessing perceived social support with 4 subscales (1) appraisal support (e.g., There is at least one person I know whose advice I really trust.), (2) tangible assets support (e.g., If I were sick, I could easily find someone to help me with my daily chores.), (3) belonging support (e.g., When I feel lonely, there are several people I can talk to.), and (4) self-esteem (e.g., Most of my friends are more interesting than I am.). Each item has response choices from definitely false to definitely true. An established threshold does not exist for ISEL-SF, so we will categorize total scores into quartiles. The LSNS consisting of 10 questions on a 0-5 rating scale (HPA question 19-29) assessing the size of the participant's active social network of family, friends, and neighbors (e.g., How many relatives do you see or hear from at least once a month?). It is ranging from 0 point to 50 point. According to a previous study, the LSNS will be categorized as: socially isolated (score: ≤ 20); high risk for isolation (score: 21-25); moderate risk for isolation (score: 26-30); and low risk for isolation (score: ≥ 31).[14]

The HPB questionnaire is designed to measure symptoms of fatigue and depression using the Maastricht Vital Exhaustion Questionnaire (MQ).[15, 16] This questionnaire consists of 21 questions on a 0-2 rating scale and has questions for fatigue symptoms (Question1.4.5.6.8.9.11.14.15.17.20.21; e.g., Do you often feel tired?) and depressive symptoms (Question2.3.7.10.16.18.19; e.g., Have you experienced a feeling of

hopelessness recently?).[17] Responses to the questionnaire are coded as: Yes = 2, Don't know = 1, No = 0. Questions 9 and 14 are reversed coded: Yes = 0, Don't know = 1, No = 2. Due to lack of established cut-off value for the MQ, we will categorize total scores into quartile.

The HPC questionnaire is designed to measure trait anger using the 10-item Spielberger Trait Anger Scale (STAS).[18] On this scale, respondents rated their typical experience with anger (e.g., When I get angry, I say nasty things.) on a 4-point anchor: Almost Never = 1, Sometimes = 2, Often = 3, and Almost Always = 4. It is ranging from 10 point to 40 point. In accordance with a previous ARIC study, anger proneness will be categorized as: low anger (score: 10-14); moderate anger (score: 15-21); and high anger (score: 22-40).[6]

Secondary exposures at visit 5 with shorter follow-up:

In ARIC, the CES-D was measured at visit 5 between 2011 and 2013. The CES-D is a scale of depressive symptoms.[19] This scale is based on a 0-2 rating scale and ranging from 0 point to 22 point. According to a previous study, we will define depressive symptoms as a score ≥ 9.[20]

Outcome variables:

-PAD and CLI

Peripheral artery disease events will be identified from hospitalizations on the basis of International Classification of Diseases Code, Ninth Revision (ICD-9) diagnosis codes for peripheral artery disease (440.2, 440.3, 440.4) or ICD-9 procedure codes for leg revascularization (38.18, 39.25, 39.29, 39.50).[21]

Of PAD cases, those with ulcer, gangrene, resting pain, or amputations will be considered as having CLI.

-Other ASCVDs

Coronary heart disease will be defined as adjudicated myocardial infarction and fatal coronary heart disease as well as a coronary revascularization hospitalization.[22, 23]

Stroke will be defined as definite or probable ischemic stroke adjudicated by a physician panel.[22, 23]

Other variables of interest and covariates:

Sociodemographics: age, race, gender, education, marital status, and health insurance
Physical information: body mass index, systolic and diastolic blood pressure.
Lifestyles: smoking status/amount and alcohol habit
Comorbidities: diabetes, dyslipidemia, hypertension, kidney function
Medications: use of antihypertensive, anti-depressant, and statin medication.
Laboratory examinations: low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, glucose, hemoglobin A1c, estimated glomerular filtration rate.
Echographic variable: carotid intima-media thickness

Statistical analysis plan:

1) Baseline characteristics will be compared across each of psychological condition category (i.e., depression, anger trait, and social isolation) at visit 2, and summarized as mean (SD) for continuous variables (median [interquartile interval] if skewed distribution), and number (proportion) for category variables.

2) We will use the Kaplan Meier method to evaluate cumulative incidence of PAD and CLI (as well as the other ASCVDs) according to each of psychological condition.

3) We will use Cox proportional hazards models to quantify the independent association between psychological conditions (depression, anger trait, and social isolation, in turn) with PAD and a composite coronary heart disease and stroke. Vital exhaustion assessed using the MQ will be treated as categorical (quartiles) and trait anger assessed using STAS will be treated as categorical according to the previous study (as described above).[6] Social isolation assessed using the ISEL-SF will be treated as categorical (quartiles) and that using the LSNS will be treated as categorical according to the previous study (as described above).[14] We will implement three models to evaluate the impact of potential confounders for relationship. Model 1 will be crude. Model 2 will be adjusted for demographic variables (age, gender, and race-center). Model 3 will further adjust for education levels, marital status, smoking, alcohol habit, diabetes, lipids, blood pressure, antidepressant medication, kidney function, and other comorbidities listed above.

4) We will conduct subgroup analysis by key demographic and clinical factors (e.g., race, gender, hypertension, dyslipidemia, diabetes, body mass index, and smoking status). The interaction will be tested by log-likelihood ratio test.

5) We will conduct a sensitive analysis accounting for time-varying covariates (e.g., hypertension, dyslipidemia, diabetes, body mass index, smoking status, and alcohols status).

6) We will conduct a sensitive analysis using only depressive part of the MQ (as described above).[17]

7) We will repeat the analysis above using CES-D at visit 5. It is unlikely that we will have enough CLI cases after visit 5, but we will explore just in case.

7.a. 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

8.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)?

The most relevant proposal would be MP#920 by Wattanakit exploring the associations of psychological conditions at visit 2 with the risk of PAD. However, the final results from this proposal have been already published in 2005,[10] and the current proposal will be able to evaluate more PAD cases during longer follow-up. Also, the current proposal will uniquely evaluate CLI as an outcome.

There are other proposals investigating coronary disease and stroke individually (as summarized below). However, most of them have been already published and in the current proposal ASCVD will be presented as a composite endpoint and a contrast to PAD. Also, there are no existing proposals studying psychological conditions at visit 5 and subsequent risk of ASCVD.

<u>Proposals exploring other ASCVD events in the context of psychological conditions</u>

MP#508: Anger and the occurrence of CHD events
MP#538: The Relationship of Social Support to Incident Myocardial Infarction and Ischemic Stroke

MP#621: Does vital exhaustion increase the risk of stroke?
MP#625: Does vital exhaustion increase CHD risk?
MP#640: Convergence of trait anger and exhaustion and incident CHD risk
MP#854: Components of trait anger and incident stroke risk: The ARIC Study
MP#877: The association of depression and risk factors for stroke: Findings from the ARIC study.
MP#878: The association of depression and risk factors for coronary heart disease: Findings from the ARIC study.
MP#1181: Vital Exhaustion and incident coronary heart disease
MP#1755: Anger proneness, heart failure risk, and hospital useMP#2139: Social Isolation, Social Support, and the Risk of Incident Stroke: the Atherosclerosis Risk in Communities Study

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

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* 2014.05)

___ 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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