

ARIC Manuscript Proposal # 3371

PC Reviewed: 4/12/19
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Effects of depressive symptoms on cardiac structure and function and risk of incident HFpEF and HFrEF in late-life

b. Abbreviated Title (Length 26 characters):

Depression, echo, and heart failure phenotype

2. Writing Group:

Writing group members: Katja Vu, Amil M. Shah, Brian Claggett, Hicham Skali, Scott Solomon, Jenine John, Janice E. Williams, Anna Kucharska-Newton, Thomas Mosley, Tor Biering-Sørensen, OTHERS WELCOME

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline: Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 6 months.

4. Rationale:

Depression is an established risk factor for coronary heart disease, possibly mediated via inflammation which has been shown to be increased in depression¹. Depression has also been associated with heart failure (HF), although the existing data are more limited. The prevalence of depression is higher among persons with versus without HF, and co-morbid depression is a predictor of mortality and morbidity in HF, including rehospitalization.² Depression is also a risk factor for incident HF, independent of coronary heart disease. In one large population-based study, depression was an independent risk factor for incident HF over a mean follow-up of 11.3 years³. Similar independent associations between prevalent depression and incident HF have been observed in smaller studies in patients with isolated hypertension,⁴ elderly women and men^{5,6}, patients who reported poor health at baseline,⁷ and veterans.⁸ However, there are limited data regarding the prevalence of depression amongst HF sub-groups based on LVEF (i.e. HFpEF vs HFrEF),⁹⁻¹¹ and the prognostic relevance of depressive symptoms for incident HFpEF versus HFrEF. In addition, limited data exist regarding mechanisms linking depression to HF risk, and antecedent alterations in cardiac structure and function specifically, although heightened systemic inflammation has been proposed as inflammatory markers are elevated in both conditions^{12,13}. Depressive symptoms have been associated with worse Tissue Doppler Imaging E', an echocardiographic measure of diastolic function,^{14,15} although little is known about the relationship between depressive symptoms and contemporary echocardiographic measures of cardiac structure and function^{14,15}, or the extent to which these associations account for the potential relationships between depression and either HFpEF or HFrEF. We recognize that this proposal is thematically related to Dr Janice E. Williams' MP#2233 "Depression and incident heart failure: A prospective analysis from the ARIC Study". We have discussed this with Dr Williams, who is a member of the writing group for this proposal, and have agreed that focusing on incident HF phenotype (HFpEF vs HFrEF) as opposed to HF overall in this proposal will avoid overlap.

5. Main Hypothesis/Study Questions:

Study aims:

Aim 1: Determine prevalence of depression and severity of depressive symptoms in HFpEF and HFrEF compared to HF-free people in late life.

Aim 2: Among persons free of HF, determine the extent to which depression associates with impairments in cardiac structure and function.

Aim 3: Determine the extent to which depression in late life predicts HF phenotype (i.e. LVEF $\geq 50\%$ vs $< 50\%$), and determine the degree to which these associations (if present) are accounted for by associated impairments in cardiac function as defined in Aim 2.

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).

Study design:

Aims 1 and 2 will be cross-sectional in nature, using data at Visit 5. Aim 3 will assess the relationship between depressive symptoms at Visit 5 and incident HF phenotype post-Visit 5.

Exclusion

All aims: absent or incomplete response on CES-D; missing data on prevalent or previous HF

Aims 2 and 3 only: Prevalent HF at Visit 5

Aim 2 only: missing echocardiographic data at Visit 5

Key variables of interest:

1. Primary exposure: Depression scale, CES-D-11 (visit 5)
2. Anthropometrics (visit 5): height, weight, BMI
3. Echocardiographic variables (visit 5 echo): 1) LV structure (LV end-diastolic and end-systolic volumes and dimensions, wall thickness, and mass); 2) LV diastolic function (E wave, A wave, TDI E', and LAVi); 3) LV systolic function (LVEF and longitudinal strain)
4. Demographics: gender, ethnicity, age, education, income, field center
5. Clinical covariates (visit 5): heart rate, history of hypertension, history of diabetes, prevalent coronary artery disease, prior MI, prior stroke, prevalent heart failure, eGFR, physical activity
6. Outcomes: Incident adjudicated HF phenotype (HFpEF, HFrEF) post-Visit 5, incident CHD post-Visit 5, death

Data analysis:

Aim 1: We will compare the prevalence of depression among the following Visit 5 participants: those with prevalent HFpEF; those with prevalent HF with LVEF <50%; and those free of HF. Depression will be defined using the cut-off value of ≥ 9 of the individual total CES-D score. To compare severity of depressive symptoms between HF phenotypes and the HF-free group, adjusted median regression will be performed given the skewed distribution of CES-D score.

Aim 2: The relationship between depressive symptoms based on CES-D score and echocardiographic measures at Visit 5 will be assessed using multivariable linear regression. Depression, the primary predictor, will be modeled in 2 different ways in separate analyses. First, depression will be dichotomized (depressed/non-depressed), while in a second analysis raw CES-D score will be employed as a continuous variable.

Aim 3: The risk of incident heart failure with LVEF \geq versus <50% (i.e. HFpEF versus HFrEF) post-Visit 5, associated with depression at Visit 5, will be estimated using multivariable Cox proportional hazard regression. We will include the following covariates in additive multivariable models: 1) demographics [age, sex, race, field center, education, income]; 2)

cardiovascular risk factors [BMI, hypertension, diabetes, CHD, stroke, AF, prior MI, physical activity, cigarette, and alcohol use]; 3) echocardiographic parameters significantly associated with depression in Aim 2. We will consider adding inflammation marker CRP to the model to examine possible pathophysiological mechanisms contributing to the risk of incident heart failure phenotype among the depressed population.

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes 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 ICTDER03 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 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.csc.unc.edu/ARIC/search.php>
 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)?

ARIC Manuscript Proposal # 879: Depression and mortality in the ARIC study (2002)

Dirk M. Dhossche, M.D.

This proposal uses Depression as measured by Maastricht Questionnaire at visit 2, while we use CES-D 11 at visit 5. While this proposal assesses the risk of mortality, our proposal focuses on heart failure.

ARIC MS #1276: Exhaustion and risk for congestive heart failure: The Atherosclerosis Risk in Communities (ARIC) Study (2007)

Janice E. Williams

Our proposal will employ a different exposure, namely depression, assessed at a different time (Visit 5).

ARIC Manuscript Proposal # 1770: Clinical outcomes in depression and heart failure (2011)

Janice E. Williams

This analysis employed depression assessed by the Maastricht Questionnaire at Visit 2, and assessed different outcomes (rehospitalization, all-cause mortality).

ARIC Manuscript Proposal #2233: Depression and incident heart failure: A prospective analysis from the ARIC Study (2013)

Janice E. Williams

This proposal assesses the relationship between depression assessed at Visit 5 and incident HF. In contrast, we aim to determine the extent to which the relationship between depression and echocardiographic measures accounts for the association of depression with HF, and whether this is differential between incident HFpEF and HFrEF.

ARIC Manuscript Proposal #2837: Association between Arterial Stiffness and Pressure Pulsatility with Depressive Symptoms: A Cross-Sectional Study of The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) (2016)

Jingkai Wei

We are assessing the relationship of depression with echocardiographic, as opposed to PWV, measures. We will use depression as the primary exposure, as opposed to outcome.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

___ Yes No

11.b. If yes, is the proposal

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

___ **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.csc.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.csc.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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