ARIC Manuscript Proposal #2856

PC Reviewed: 10/11/16	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Left Ventricular Hypertrophy and its Association with Cognitive Decline and Dementia Risk over 20 years: The ARIC Neurocognitive Study (ARIC-NCS)

b. Abbreviated Title (Length 26 characters): LVH and cognitive function

2. Writing Group:

Writing group members: Faye L. Norby, Lin Y. Chen, Elsayed Z. Soliman, Rebecca F. Gottesman, Thomas H. Mosley, Alvaro Alonso, others welcome.

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

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3. Timeline: Statistical analysis: 3 months
Manuscript preparation: 6 months
We expect to submit an abstract with preliminary results to the AHA Epi conference (submission deadline Oct 2016)

4. Rationale:

Left ventricular hypertrophy (LVH) is most commonly an indicator of target organ damage due to hypertension.[1] LVH is associated with cardiovascular morbidity and mortality, including myocardial infarction, coronary heart disease (CHD), sudden death, stroke, and congestive heart failure, independent of traditional cardiovascular risk factors.[2-5] Furthermore, LVH is more prevalent in blacks than in whites, and is an independent predictor of CHD / CVD survival in blacks beyond traditional risk factors.[6-8] LVH, measured by 12-lead ECG, may serve as a marker for chronicity and the degree of blood pressure elevation as an indicator of long-term burden of vascular risk factors.

An association between blood pressure and cognitive decline has been readily established,[9, 10] including an inverse relationship between the magnitude and duration of blood pressure elevation and cognitive performance.[11] Despite the extensive literature on the association of blood pressure and cognitive performance, few studies have looked at the association between LVH with cognitive function and dementia. In a cross-sectional study, LV mass (measured by echocardiography) was associated with lower global cognitive function and increased risk of dementia in the elderly, independent of risk factors including blood pressure.[12] In another cross-sectional study of stroke-free participants with an average age 57 years, LV mass was associated with cognitive performance after adjustment for blood pressure, but the association was attenuated after additional adjustment of CVD and risk factors, suggesting CVD risk factors play an important role in the relationship between LV mass and cognition.[13] In the Helsinki Aging Study, LV mass was associated with a 5-year decline in Mini-Mental State Examination scores for 160 elderly participants.[14]

In this study, we will examine the association of LVH with cognitive decline and dementia over time (approximately 20 years) in a bi-racial community sample. The ARIC study provides a large sample size and extensive follow-up time and covariate selection to evaluate whether these associations exist independent of risk factors.

5. Main Hypothesis/Study Questions:

Aim 1: Evaluate the association of LVH with cognitive change in ARIC participants

Aim 2: Evaluate the association of LVH with incident dementia in ARIC participants

Hypothesis: Participants with LVH will experience greater decline in cognitive function over the 20-year follow-up compared to those without LVH. In addition, LVH will be an independent risk factor for incident dementia.

If an association exists between LVH and lower cognitive performance or incident dementia, this could strengthen the hypothesis that long-term exposure to high blood pressure results in subclinical brain injury, which in turn, results in lower levels of cognitive performance.

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 – prospective

Study population

- Inclusion criteria: ARIC participants with ECG measures and cognitive data at visit 2.
- Exclusion criteria: Missing or indeterminate ECG measures at visit 2, prevalent stroke at visit 2, prevalent dementia at visit 2, race other than white or black and non-whites in the Minneapolis and Washington County field centers, those with major intraventricular conduction delay on ECG (including complete bundle branch blocks, Wolf Parkinson-White Syndrome and/or QRS duration >=120 ms) and those missing covariates.

Exposure

LVH will be derived from 12-lead ECG at visits 2, 3, 4 and 5. We will look at associations using the dichotomous (yes/no) gender-specific Cornell voltage criteria (SV3 + RaVL > 2.8mV for men, and >2.2mV for women).

LVH will be also be explored as a continuous variable using Cornell voltage, as the association between LVH measures with most CVD is linear. Using ECG LVH criteria as a continuous variable is becoming more common with the emerging shift of using these criteria for prediction rather than diagnosis of anatomical LVH.

Outcomes

Cognitive function (measured at visit 2, visit 4, and visit 5)

Z-scores of 3 neuropsychological tests: Delayed Word Recall Test (DWRT), Digit Symbol Substitution Test (DSST), and Word Fluency Test (WFT); and a global cognitive score will be used to assess cognitive function and determine cognitive decline.

Dementia: All-cause dementia (without information about reviewer classification of dementia etiology). Dementia diagnosis will be defined as diagnosis level 3 (per MS#2020 (Gottesman et al).

Covariates

Variables measured at one-time only: sex, race/study center, educational level, occupation, APOE genotype

Variables measured at each visits 2, 4 and 5: Age, smoking, body mass index, systolic and diastolic blood pressure, use of antihypertensive medication, total cholesterol, diabetes.

Variables ascertained yearly: coronary heart disease, heart failure, atrial fibrillation, stroke.

Statistical analysis

Aim1:

To test the association between LVH and cognitive decline rate, we will follow recommendations from the ARIC-NCS Analysis Committee. Specifically, we will use linear regression models fit with generalized estimating equations to evaluate associations with cognitive performance trajectories using robust variance and an unstructured correlation matrix. Models will include time modeled using a linear spline with a knot at 6 years (visit 4) and interactions between follow-up time and covariates will be explored as appropriate. Separate models will be run for each cognitive test (DWR, DSS, and WF) and a global cognitive score.

The models will adjust for the following covariates (and if necessary, interaction of these covariates with time):

- Model 1 is adjusted for age, race/center, and sex

- Model 2 is adjusted for adjusted for model 1, education, occupation, APOE genotype, smoking (not current vs. current), body mass index, total cholesterol, diabetes, systolic and diastolic blood pressure, use of antihypertensive medication, coronary heart disease, and heart failure
- Model 3 is adjusted for model 2 plus time-dependent atrial fibrillation and stroke

We will first look at the association of LVH measured at visit 2 with cognitive decline, and then proceed with additional analysis in which we use time-dependent LVH and covariates from visits 4 and 5.
Additionally, to account for attrition during follow-up, we will conduct this analysis using multiple imputation chained equations (MICE) to impute cognitive scores and covariates for participants who did not attend follow-up visits. This will most likely be the primary analysis, and the analysis not using MICE will be presented as a sensitivity analysis.

Aim 2:

The association of LVH with dementia incidence will be assessed using a Cox proportional hazards model. We will use the 3 models listed above. Time will be from visit 2 until dementia, death, or at the end of follow-up. We will first look at the association of LVH measured at visit 2 with incident dementia, and then proceed with additional analysis in which we use time-dependent LVH and covariates from visits 3, 4 and 5.

Both:

For both aims, interactions by age, race and sex will be explored through stratified analysis and including multiplicative terms in the models.
Sensitivity analysis: We will consider the following:

- Aim 1: To mitigate possible floor effects, we will exclude participants scoring the in the bottom 5^{th} percentile of race/sex-based cognitive scores at baseline.
- Aim 1: The un-weighted results, before applying MICE
- Aim 2: we will also define incident dementia using only hospitalization with an ICD-9 code of dementia.

- Aim 2: because of clustering of dementia diagnosis around visit 5, we will also consider discrete time alternatives to Cox regression.

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)?
There are no similar manuscripts exploring the association of LVH with cognitive decline or dementia. Similar manuscripts include:
#2829: Orthostatic hypotension and cognitive outcomes – Rawlings
#2358: Postural BP and cerebral infarcts – Poon
#2175: Hypertension and cognitive change – Gottesman
#2405: Atrial fibrillation and Cognitive Decline – Chen

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.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.

References:

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