ARIC Manuscript Proposal #4151

PC Reviewed: 11/8/22 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Association Between Incident Congestive Heart Failure and Cognitive Decline

b. Abbreviated Title (Length 26 characters): Heart Failure and Cognition

This is an ancillary study of the ARIC-approved BP COG ancillary study (PI Levine Deborah) (#2016.07 "Blood Pressure over the Life Course and Later-life Cognition in Hispanics and Whites (BP-COG): A Pooled Cohort Analysis").

2. Writing Group:

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

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3. Timeline: 1 year, data acquisition and statistical analysis first few months, planned interim abstract submission winter 2022, final manuscript submission planned spring 2023

4. Rationale: Heart Failure (HF) is a chronic, irreversible condition that imposes a high burden of disabling symptoms on afflicted individuals, associated caregivers, health care systems and society.[1,2] Contemporary data estimate that HF is prevalent in 6.2 million American adults.[3] These estimates are projected to rise in the next several years as the population continues to age. Previous studies note an association between HF and prevalent cognitive impairment that further complicates burden associated with HF.[4-6] However, there is limited data on the trajectory of cognitive change after incident HF. Existing studies are limited by small cohort size, have a short follow-up duration, use claims data to identify HF which is of uncertain accuracy in identifying the true incident event or lack repeated measures of cognitive function (for example: occurrence of dementia).[7-10]

It is unclear how HF influences cognition both at the onset of the disease and longitudinally during the disease course given irreversibility of the condition. Understanding how cognition changes after onset of HF is key from both a clinical practice and health policy standpoint as managing HF is complex, needing significant care coordination associated with a large economic burden.[11] We propose conducting a pooled cohort study of individuals with repeated objective measures of cognition and data on incident HF by leveraging an existing pooled cohort of six population-based cohorts, one of which is ARIC. Other cohorts will include Coronary Artery Risk Development in Young Adults Study (CARDIA), Cardiovascular Health Study (CHS), Framingham Offspring Study (FOS), Multi-Ethnic Study of Atherosclerosis (MESA) and Northern Manhattan Study (NOMAS). We aim to determine if incident CHF is associated with an acute decline in cognition with disease diagnosis, and a faster rate of cognitive decline in the years following CHF diagnosis.

5. Main Hypothesis/Study Questions:

Study question: What is the magnitude of change in cognitive function acutely at the time of incident HF diagnosis and longitudinally over the course of the condition?

Hypothesis: Incident HF is associated with acute cognitive decline and persistent, accelerated decline over follow-up, compared to individuals without HF

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 and population: We will conduct a pooled cohort analysis using individual participant data from six well-characterized American prospective cohort studies with repeated measures of cognition and physician-adjudicated incident HF: Atherosclerosis Risk in Communities Study (ARIC), Coronary Artery Risk Development in Young Adults Study (CARDIA), Cardiovascular Health Study (CHS), Framingham Offspring Study (FOS), Multi-Ethnic Study of Atherosclerosis (MESA) and Northern Manhattan Study (NOMAS) for years 1971 to 2021.

Inclusion/Exclusions: We will exclude all participants with HF, stroke or dementia at cohort baseline and prior to each cohort's first cognitive assessment. Stroke has been associated with cognitive decline and hence presence prior to first cognitive assessment will confound our findings.[12] All included participants need at least one cognitive assessment but participants with cohort-defined incident HF event need to have at least one measurement of cognition prior to onset of HF, to control for pre-HF cognitive levels, and at least one measurement of cognition after onset of HF. Follow-up will be censored after incident stroke if it occurred during follow-up.

Exposure Variable: Incident HF adjudicated by a team of experts in each of the 6 cohorts will be used.

Outcomes and variables to be used: The primary outcome is change in global cognitive performance and secondary outcomes are changes in executive function and memory. These have been used in previous work by our group.[13] Each outcome will be treated as a continuous variable to better detect intraindividual changes. To make inferences about cognitive domains instead of individual cognitive test items, and to resolve the challenge of different cognitive tests administered across the cohorts, available cognitive test items have been co-calibrated into factors representing global cognition (global cognitive performance), memory (learning and delayed recall/recognition), and executive function (complex and/or speeded cognitive functions) using item response theory (IRT) methods that leverage all available cognitive information in common across cohorts and test items unique to particular cohorts.[14,15,16]

Covariates: Covariates included are factors that could influence association between HF and cognition and are available in all the cohorts prior to first cognitive assessment. We will use covariate values measured closest to, but not after, the first cognitive assessment. We will use harmonized covariates across cohorts by choosing common response categories for categorical variables and converting measurements to common units for continuous variables.

- Demographics: age (continuous), race/ethnicity (self-reported as Black, White, Hispanic [any race]), sex, education (eighth grade or less, grades 9-11, completed high school, some college but no degree, college graduate or more), study cohort (ARIC, CARDIA, CHS, FOS, MESA, NOMAS).
- Clinical variables: use of alcoholic drinks per week (none, one to six, seven to thirteen, fourteen or more), current cigarette smoking, any physical activity, body mass index, waist circumference, history of myocardial infarction (MI), history of atrial fibrillation, fasting glucose, low density cholesterol (LDL), glomerular filtration rate (GFR), use of antihypertensive medications and cumulative mean systolic blood pressure. We will assess for presence of MI and atrial fibrillation at any point from cohort enrollment until the first cognitive assessment.

Brief analysis plan and methods

We will compare baseline characteristics between patients with and without incident HF during follow-up using 2-sample *t*-test for continuous variables or χ^2 tests for categorical variables. Each

outcome measuring cognitive function will be assessed as a continuous variable. Incident HF will be treated as a time-dependent covariate. The association of baseline covariates with cognitive function will be assessed using linear mixed effects models adjusted for years since baseline.

Two sequential, linear mixed-effects models will be used to estimate the effect of HF on cognitive function, both acutely (model A) and over long-term (model B), after adjusting for covariates including baseline cognitive score. The models will include random effects for intercept and slope to accommodate correlation of cognitive measures within participants over time and to allow participant specific rates of cognitive change. Models will include age*time, sex*time, and race/ethnicity*time interaction terms based on our prior research.[13,17] Each outcome will be censored at incident stroke, death, loss of follow-up or end of follow-up. Time will be expressed as the years from date of first assessment of cognitive outcome. For all three cognitive domains, we will assume that the cognitive score in individuals without HF followed a linear time function and will check this assumption using visual plots and examining residuals and non-linear functions (e.g., time squared).

Model A will include a time-varying incident HF variable (changed from 0 to 1 on the date of the first incident HF diagnosis) to estimate the effect of incident HF on cognitive function acutely (Equation 1). Acute decline in the cognitive function at the time of incident HF will be estimated based on the fitted model that will include the first assessment of cognitive function after incident HF event and other cognitive function tests administered before the incident HF event.

In Model B, we will add a time after HF covariate to Model A to determine if incident HF results in a faster rate of cognitive decline in the years following the incident diagnosis (Equation 2). For each individual with HF, this time after HF variable will be 0 before their first HF diagnosis and will remain at 0 for all other individuals. This coefficient will quantify the slope and represent the effect of incident HF on the rate of decline in cognitive function. Variables that will be forced in will include age, sex, race, education, cohort and baseline cognitive function and other variables that approach statistical significance ($p<0.05$) in Model A will be retained.

Statistical significance for all analyses will be set as $P<0.05$ (2-sided). All analyses will be performed using SAS version 9.4 (SAS Institute, Cary, NC).

Equation 1: $E(Y_{ij}|b_i) = \beta_0+\beta_1 T_{ij}+\beta_2 CHF_{ij}+\beta_{cov}^{T} Covariates_{ij}+b_{i1}+b_{i2}T_{ij}$

Equation 2: $E(Y_{ij}|b_i) = \beta_0+\beta_1 T_{ij}+\beta_2 CHF_{ij}+\beta_3 CHF_{ij}(T_{ij}-Tchf_{ij})+ \beta_{cov}^{T} Covariates_{ij}+b_{i1}+b_{i2}T_{ij}$

Legend: $Tchf_{ij}$ is the time at index CHF diagnosis. $\beta_2\ CHF_{ij}$: cognitive function at the time of CHF diagnosis. $\beta_3 CHF_{ij}(T_{ij}-Tchf_{ij})$: longitudinal change in cognitive function with CHF diagnosis. b_{i1} is random intercept and b_{i2} is random slope

Sensitivity Analyses:

We understand that there may be a selection bias in who remains in the study versus those who drop out early in the study, and that poor cognition might result in early study drop out.

To assess for attrition bias, we will examine the number (%) of participants who died during follow-up, the number (%) of participants with 2 or more cognitive tests and repeat analyses above with individuals who have 2 or more cognitive assessments.

To explore whether the association of incident HF with cognitive decline differs based on age of HF onset, we will add the following interaction terms of incident HF with age as fixed effects: incident HF X age, incident HF X age squared, time elapse since incident HF diagnosis X age and time elapsed since incident HF diagnosis X age squared. Similar analyses will be performed to assess for effect modification by sex and race.

We will also perform a secondary analysis examining whether cognitive decline is associated with recurrent hospitalizations for acute on chronic HF exacerbations. We will add the number of hospitalizations for acute on chronic HF exacerbations as a time dependent covariate to model B

We will perform additional analyses using MI, atrial fibrillation and cumulative mean systolic blood pressure updated at each sequential cognitive assessment as time varying covariates instead of treating them as fixed covariates as described in previous BP COG study analyses. An interaction term of cumulative mean systolic blood pressure X time will also be added. These additional analyses are proposed to account for any additional changes in exposure to these variables after first cognitive assessment as they have previously been associated with a cognitive decline and are on the causal pathway with HF and cognitive decline.[13,18,19]

Limitations: Heart failure typically has an insidious onset and diagnosis may be delayed until progression of symptoms. Participants are also likely to delay their cohort visit until they feel better following a diagnosis of HF. Accordingly, assessment of cognitive change at the time of first HF diagnosis as we propose would delay capturing changes in cognitive function associated with the disease. However, this is likely to bias our findings towards underestimating cognitive decline rather than overestimate it. We propose using linear, mixed effects models that are robust to sparse data, using all available cognitive measurements prior to diagnosis of HF. This would also allow us to compare trajectory in cognitive change prior to patients receiving a diagnosis of HF.

We are unable to control for severity of HF as variables such as NYHA class and 6-minute walk tests are lacking for all cohorts.
We are unable to account for HF subtype (reduced vs. preserved ejection fraction) as this variable has not been harmonized across the six cohorts by our group.
Additional socioeconomic factors that might influence the relationship between HF and cognition, such as literacy, quality of education, occupation, and socioeconomic status, cannot be included because they are either unavailable for all cohorts or occur after the first cognitive assessment.
Depressive symptoms were not captured in all cohorts at or before the first cognitive assessment and we are unable to account for this as a confounder.

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/mantrack/maintain/search/dtSearch.html

__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)? Association Between Blood Pressure and Later-Life Cognition Among Black and White Individuals.

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
__x_ A. primarily the result of an ancillary study (list number* 2016.07**)**
___ 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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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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