ARIC Manuscript Proposal #3688

PC Reviewed: 8/11/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The Effect of Myocardial Infarction on Cognitive Decline: A Pooled Cohort Analysis of ARIC, CARDIA, CHS, FOS, MESA and NOMAS

b. Abbreviated Title (Length 26 characters): Myocardial Infarction and Cognitive Decline

2. Writing Group:

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This paper proposal will use data from the approved ARIC ancillary study called BP COG (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”)[1]

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __MCJ___ **[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 fall-winter 2020, final manuscript submission planned fall 2021

4. Rationale:

The importance of cognitive decline in the general population cannot be overstated. While the exact relationships remain to be defined, several mechanisms linking cardiac disease to dementia have been proposed.[2-4] Subclinical cerebral infarction, or "silent strokes" may occur in the setting of either a dilated heart or an arrhythmia, and thereby lead to cognitive decline.[5-8] Alternatively, or complementarily, shared risk factors between the two disease processes might alter clearance of cerebral toxins, resulting in accumulation of pathology necessary to cause dementia.[9,10] Prior work has focused on identifying the contribution risk factors for cardiac disease make to poor cognition, with the thought that with proper control of these risk factors, cognitive decline might be delayed, or avoided. However, the impact of a sudden cardiac event, such as that which occurs in an acute myocardial infarction (MI), on both cognition at the time of the event, and the cognitive trajectory of a patient remains poorly defined. Additionally, there is data to suggest that the impact of MI on cognition might differ between men and women, and between races. The presence of certain vascular risk factors appear to be more important for one sex versus the other in the development of vascular cognitive impairment.[11,12] Male sex was related to cognitive impairment in the REGARDS study and black race was a risk factor for the presence of brain amyloid on PET in the ARIC study.[12,13] Finally, it may be that there is a difference between those who have only had one MI event, versus those who had a second MI event and the literature to date has addressed only the cognitive sequela after the first event.

There are limitations in using one single prospective cohort to answer these questions given the potential limitations in 1) capturing repeated risk factor data in order to appropriately control for confounding, 2) defining the outcome, cognitive decline, in a way that is both accurate and generalizable, particularly to racial/ethnic minorities, and 3) having sufficient sample size and power to examine effect modification by race and sex. We propose to leverage six population-based cohorts of individuals with repeated measurements of important vascular risk factors, such

as blood pressure, and cognition in order to investigate the extent to which incident MI impacts participant cognition at the time of the event and cognitive trajectory after the event.

The main aim of this study is to determine if incident MI, among those without a prior history of MI, results in an acute decline in cognitive function at the time of the event as well as a faster rate of cognitive decline in the ensuing years when compared to those participants without the MI event controlling for risk factors and pre-MI cognitive trajectories. We will additionally examine whether the association between incident MI and cognitive decline varies by race and sex, as well as a sensitivity analysis where those with more than one MI event are included.

5. Main Hypothesis/Study Questions:
How does the trajectory of cognitive decline change at and after incident myocardial infarction (MI)? Does this trajectory differ among those with more than one MI event?
How is this post-MI cognitive trajectory modified by race (black race versus others) and sex?

We hypothesize that those participants with acute MI will have an acute decline at the time of the event as well as a faster rate of cognitive decline after the MI event, than those participants without an MI event over the years of follow up (time in study) controlling for pre-MI cognitive trajectories. We also hypothesize that the overall decline in cognition will be greater among those with more than one MI event compared to those with one MI event, and that the rate of change will be modified by race (worse for blacks) and sex (worse for males).

Relevance to approved ancillary study (BP COG):
Aim 1 of the cohort-approved NIH/NINDS-funded BP COG R01 study is examining the associations between race/ethnicity, BP, and cognitive decline in a pooled cohort of ARIC, CARDIA, CHS, FOS, MESA, and NOMAS.[1] This paper further examines a sequela of hypertension by specifically looking at the relationship between MI and cognitive decline. Aims 2 and 3 of the approved study proposal for NIH/NINDS-funded BP COG R01 involve simulation modeling of the association between BP, cognitive decline/incident dementia, and CVD events by race/ethnicity. We will examine inclusion of estimates of the association between BP and risk of CVD events from both RCTs involving selected patients and also the BP COG pooled cohort study involving unselected patients. The simulation model will be used to inform the design of RCTs including pragmatic trials of less selected patients. The knowledge gap is it is unclear how the trajectory of cognitive decline changes after incident MI in these participants. The proposed paper will address this knowledge gap, enable the BP COG simulation model and its results to be improved by including cognitive changes associated with incident MI, and also provide useful information for researchers and policymakers who work with simulation models. The simulation model in BP COG R01 Aims 2 and 3 will be used to inform trials and policies. The prediction models will be used for research purposes and not for clinical practice.

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 population:

We will conduct a pooled cohort analysis using individual participant data from six well-characterized American prospective cohort studies with repeated measures of BP and cognition: 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 2017. To control for pre-MI cognitive function, we will require all participants to have an initial measurement of each outcome. We will require that participants with incident MI have at least one measurement of cognition after the incident MI event. Because cumulative mean BP is significantly associated with cognitive decline in this pooled cohort, we also require all cohort participants to have ≥1 measurement of BP at or before the first measurement of cognition. We will exclude participants with cohort-defined incident dementia at or before the first measurement of cognition. We will also exclude participants reporting a baseline history of MI and those with incident MI or cohort-defined MI at or before the first measurement of cognition (one measurement of cognition required before incident MI).

Outcomes:

The primary outcome will be change in global cognition. Secondary outcomes will be change in memory and executive function. Details about the harmonization of the cognitive measures across the cohorts have been reported elsewhere.[1] 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, we have co-calibrated available cognitive test items 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. In a pre-statistical harmonization phase, we have identified 153 test items from 34 cognitive instruments across the cohorts and determined shared items between cohorts. Expert neuropsychologists (EMB, BJG) have assigned each test item to a cognitive domain. In IRT, each test item is weighted based on its correlation with other items and empirically assigned a relative location along the latent trait (e.g., global cognition) corresponding to its estimated difficulty. We have computed factor scores from models for each domain using the regression-based method in Mplus version 8. Cognitive outcomes have been set to a t-score metric (mean 50, SD 10 at a participant's first cognitive assessment); a 1-point difference represents a 0.1 SD difference in the distribution of cognition across the 6 cohorts.

Covariates:

In this analysis, we will carefully consider covariates that could influence the relationship between incident MI and cognition. We will use covariate values from each cohort measured closest to, but not after the first cognitive assessment. Notably, covariates have been harmonized across cohorts by choosing common response categories for categorical variables and converting measurements to common units for continuous variables.

Covariates that will be considered are age (continuous), race/ethnicity (black, white, Hispanic), cohort (ARIC, CARDIA, CHS, FOS, MESA, NOMAS), education (eighth grade or less, grades 9-11, completed high school, some college but no degree, college graduate or more), 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 atrial fibrillation, fasting

glucose, low density lipoprotein cholesterol, cumulative mean systolic blood pressure and anti-hypertensive medication use. Of note, additional socioeconomic factors that might influence the relationship between MI 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.

Analysis:

Participant characteristics will be compared using Wilcoxon Rank Sum test or chi-squared tests as appropriate. To estimate the change in cognition among survivors of incident MI, controlling for their pre-morbid cognitive trajectories, we will used the methods of Levine DA et al. JAMA. 2015.[14] We will use linear mixed-effects models to estimate changes in each continuous cognitive outcome over time before and after incident MI. Models will include time since first cognitive assessment and baseline values (measured before or at time of first cognitive assessment) of sex, race, age, cohort study, years of school, cigarette smoking, body mass index, waist circumference, physical activity, hypertension treatment, fasting glucose, low density lipoprotein (LDL) cholesterol and history of atrial fibrillation. We will include time-varying cumulative mean systolic blood pressure (SBP), age* follow-up time, sex* follow-up time, race* follow-up time, time-varying cumulative mean SBP* follow-up time, and hypertension treatment*follow-up time, as well as subject-specific random effects for intercepts and slopes. Follow-up time will be treated as a continuous measure defined as years since first measurement of each cognitive outcome.

Model A will include a time-varying incident MI variable to estimate the effect of incident MI on the acute decline in cognitive function at the time of the event (the value changes from 0 to 1 on the date of the incident MI) because MI might be associated with an acute decline in cognitive function. The acute decline in cognitive function at the time of MI will be estimated based on the fitted model, which will include the first set of routinely administered cognitive function tests after the MI event as well as all other cognitive function tests administered before and after MI. For this study, the first cognitive assessment after MI will be considered the acute component or early/mid-stage recovery.

Model B will include the variables from Model A and add a follow-up time after incident MI variable to estimate the effect of incident MI on the decline in cognitive function over the years following the MI event. We will require that all participants with incident MI have at least one cognitive measure after MI to contribute sufficient time to the analysis. We will also assess for effect modification by sex and race with interaction terms as appropriate (e.g., race*MI*follow-up time interaction term and sex*MI*follow-up time interaction term).

For each outcome, all available cognitive observations will be used in the primary analysis except 1) observations after the time of first cohort-adjudicated incident stroke during follow-up because incident stroke alters the cognitive trajectory and 2) observations after the time of second cohort-adjudicated incident MI during follow-up.

For the secondary analysis examining whether cognitive decline is greater among those with more than one MI event compared to those with one MI event, we will include the observations after the time of second cohort-adjudicated incident MI during follow-up. We considered examining CABG as a potential mediator of the association between incident MI and long-term cognitive decline, however studies suggest that long-term cognitive decline in MI patients who undergo a CABG is similar to those who do not have the procedure.[15-17]

Statistical significance will be set as $P<0.05$ (2-sided).

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 account for this, we will compare baseline cognitive scores in those who do and do not drop out of the study and will determine whether the number of observations per person varies as a function of their baseline cognition.
We will also perform a sensitivity analysis excluding those with atrial fibrillation understanding that there is an association between atrial fibrillation and cognitive decline, and participants with MI are at increased risk for atrial fibrillation. It is of interest to understand how much of the effect is attenuated (hypothesis) when excluding those participants with atrial fibrillation either before or after the incident MI event.

References:

1. Levine DA, Gross AL, Briceno EM, et al. Association between blood pressure and later-life cognition among black and white individuals. *JAMA Neurol*. 2020.

2. Iadecola C. The pathobiology of vascular dementia. *Neuron*. 2013;80(4):844-866.

3. Deak F, Freeman WM, Ungvari Z, Csiszar A, Sonntag WE. Recent developments in understanding brain aging: Implications for alzheimer's disease and vascular cognitive impairment. *J Gerontol A Biol Sci Med Sci*. 2016;71(1):13-20.

4. Hooghiemstra AM, Bertens AS, Leeuwis AE, et al. The missing link in the pathophysiology of vascular cognitive impairment: Design of the heart-brain study. *Cerebrovasc Dis Extra*. 2017;7(3):140-152.

5. Elias MF, Sullivan LM, Elias PK, et al. Left ventricular mass, blood pressure, and lowered cognitive performance in the framingham offspring. *Hypertension*. 2007;49(3):439-445.

6. Ahn SH, Kim YH, Shin CH, et al. Cardiac vulnerability to cerebrogenic stress as a possible cause of troponin elevation in stroke. *J Am Heart Assoc*. 2016;5(10):e004135.

7. Bressler J, Knopman DS, Sharrett AR, et al. Incident heart failure and cognitive decline: The atherosclerosis risk in communities study. *J Card Fail*. 2017;23(1):47-55.

8. Cogswell RJ, Norby FL, Gottesman RF, et al. High prevalence of subclinical cerebral infarction in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2017.

9. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable alzheimer disease and mild cognitive impairment. *Ann Neurol*. 2009;66(2):200-208.

10. Jack CR,Jr, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *Lancet Neurol*. 2013;12(2):207-216.

11. Gottesman RF, Albert MS, Alonso A, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the atherosclerosis risk in communities (ARIC) cohort. *JAMA Neurol*. 2017;74(10):1246-1254.

12. Unverzagt FW, McClure LA, Wadley VG, et al. Vascular risk factors and cognitive impairment in a stroke-free cohort. *Neurology*. 2011;77(19):1729-1736.

13. Gottesman RF, Schneider AL, Zhou Y, et al. The ARIC-PET amyloid imaging study: Brain amyloid differences by age, race, sex, and APOE. *Neurology*. 2016;87(5):473-480.

14. Levine DA, Galecki AT, Langa KM, et al. Trajectory of cognitive decline after incident stroke. *JAMA*. 2015;314(1):41-51.

15. Selnes OA, Royall RM, Grega MA, Borowicz LM,Jr, Quaskey S, McKhann GM. Cognitive changes 5 years after coronary artery bypass grafting: Is there evidence of late decline? *Arch Neurol*. 2001;58(4):598-604.

16. Selnes OA, Grega MA, Borowicz LM,Jr, Barry S, Zeger S, McKhann GM. Self-reported memory symptoms with coronary artery disease: A prospective study of CABG patients and nonsurgical controls. *Cogn Behav Neurol*. 2004;17(3):148-156.

17. Selnes OA, Grega MA, Borowicz LM,Jr, et al. Cognitive outcomes three years after coronary artery bypass surgery: A comparison of on-pump coronary artery bypass graft surgery and nonsurgical controls. *Ann Thorac Surg*. 2005;79(4):1201-1209.

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)?

#2002; "Association of High Sensitivity Cardiac Troponin with Cognitive Function: the ARIC study"; #2334 "Troponin T and NT-proBNP and Cognitive Decline and Dementia in the ARIC 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

_x__ A. primarily the result of an ancillary study (list number* 2008.06, ARIC-NCS, PI Coresh/Gottesman**)**

___ 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.

This is understood.

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.