ARIC Manuscript Proposal #1973

PC Reviewed:  8/14/12  
SC Reviewed: _________  

Status:  A  
Priority:  2

1.a. Full Title: Cardiovascular exposures, cognitive decline and depression in whites and blacks

b. Abbreviated Title (Length 26 characters): CV risk and cognition

2. Writing Group: Adina Zeki Al Hazzouri, PhD; Mary N Haan, DrPH; Kristine Yaffe, MD; Thomas H Mosley, PhD; David S Knopman, MD

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

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3. Timeline:

Data analysis and manuscript preparation: September 2013 till September 2014

4. Rationale:

Cardiovascular (CV) disease and its risk factors plague 1 in 3 American adults and remain the most common causes of morbidity and mortality in the United States. Individual cardiovascular risk factors are not uniformly distributed across the population. For example, African Americans have higher prevalence of hypertension and high blood pressure than non-Hispanic whites. Among those being treated, the rate of blood pressure control is lower for African Americans than non-Hispanic whites. Differences in the age at exposure may result in longer duration of CV exposure in African Americans than non-Hispanic whites. Thus,
understanding cumulative long-term trajectories of CV risk factors over the adult life span is of utmost importance to our targeted interventions aimed at preventing or decreasing CV-related health outcomes and disparities.

Cognitive function\textsuperscript{20-22} and depressive symptoms\textsuperscript{23} are an essential component of healthy aging, a major public health goal. Cognitive function and depressive symptoms share many cardiovascular origins and constitute processes that likely unfold over the lifespan. Establishing the extent to which long-term trajectories of CV risk factors (CVRF) can impact change in cognitive function and depressive symptoms is necessary for identifying critical points of intervention and guiding public health efforts. Yet, the evidence to date of whether long-term cumulative CV exposure impacts trajectories of cognitive decline and depressive symptoms is quite small. The majority of prior investigations has focused on CVRFs and CV-related outcomes in restricted age frames such as young adulthood, middle age or old age. Using advanced epidemiological techniques will provide strong tools to overcome methodological biases and better estimate the causal relationship between CV exposures and CV-related health outcomes.

This paper proposal is part of my K99/R00 which will examine the link between long-term trajectories of CVRFs and cognitive decline and depressive symptoms over the \textit{adult life span}, comparing non-Hispanic whites and African Americans. While I will examine trajectories of individual CVRFs separately, I will also examine trajectories of a cardiovascular summary score. To this end, the proposed work will \textit{combine five cohorts} conducted over the past 30 years with data on CV exposures and cognition and depressive symptoms over the adult life span (Figure 1): (1) early adulthood, (2) middle-age and (3) old age. These include: the Coronary Artery Risk Development in Young Adults (CARDIA), Atherosclerosis Risk in Communities (ARIC), Multi Ethnic Study of Atherosclerosis (MESA), Cardiovascular Health Study (CHS) and Health, Aging and Body Composition study (Health ABC). I will use all 5 cohorts to estimate our measure of long-term cumulative cardiovascular exposure. For \textit{cognitive decline as the outcome}, I will combine ARIC, CHS and Health ABC. CARDIA and MESA do not provide repeated measures of cognitive function. For \textit{depressive symptoms as the outcome}, I will combine CARDIA, MESA, CHS and Health ABC. ARIC does not provide repeated measures of depressive symptoms. Accordingly, \textbf{from ARIC}, I will be using cardiovascular and cognitive data as discussed in the methods section below. ARIC study is optimal since it includes a middle-age cohort and has long follow-up time with repeated measures of cognitive function and cardiovascular risk factors.

5. Main Hypothesis/Study Questions that incorporate ARIC data:

\textbf{Aim 1}: To determine long-term trajectories of exposure to each CV risk factor (CVRF) separately for whites and blacks.
Hypothesis 1.1: long-term cumulative trajectories of exposure to CVRF (Blood pressure, diabetes, lipids, anthropometry, and smoking) will be higher risk for blacks than whites.
Hypothesis 1.2: Age will modify the association between Race and CVRF trajectories. The race difference will diminish with increasing age.

Aim 2 (This will combine ARIC, CHS and health ABC): To determine the associations of long-term trajectories of exposure to CVRF with cognitive decline, in whites and blacks.

Hypothesis 2.1: higher risk long-term trajectories of exposure to CVRF will be associated with greater cognitive decline. Race will modify the association between CVRF and cognitive decline such that blacks will experience greater cognitive decline than whites for a given CVRF level. Age may modify this further (age*Race*CVRF).

6. Design and analysis.

Study design: 14-year longitudinal study

Inclusion: ARIC participants who participated in the ARIC MRI and Neurocognitive Longitudinal Study.

Exclusion: None

Outcome: Cognitive data from ARIC study visits 2, 3, 4 and Brain MRI study (which is post ARIC study visit 4). Cognitive outcomes include: Delayed Word Recall Test, Digit Symbol Substitutions Test, and Word Fluency Test

Exposure variables: from all ARIC study visits (V1, V2, V3, V4) and from the Brain MRI study.
1) Blood pressure/hypertension (all exams): systolic and diastolic BP, antihypertensive medication use
2) Type-2 diabetes (all exams): fasting plasma glucose levels, plasma insulin levels, anti-diabetic medication use
3) Lipids (all exams): HDL, LDL, total cholesterol and total triglycerides
4) Anthropometry (all exams): standing height, weight, BMI, waist circumference
5) Cigarette smoking status (all exams).

Covariates: age at cognitive assessments (as well as at visit 1); DOB (to calculate age at each visit) (exam 1); date of each visit (to calculate age at each visit) (all exams); gender (exam 1); race (exam 1); educational attainment (exam 1); alcohol intake (all exams); physical activity level (all exams); inflammatory biomarkers (Interleukin-6 and C-reactive protein) (all exams); vascular disease (stroke and stroke subtype, myocardial infarction, angina pectoris, intermittent claudication, congestive heart failure, peripheral arterial disease, ankle-brachial index, carotid intima-medial thickness) (prevalent at baseline and incident throughout study period).

Summary of data analysis:

For aim 1, the objective is to estimate person-specific long-term trajectories of exposure to each CVRF. ARIC study participants can contribute CVRF information beginning at ages 45+. We will use data from the CARDIA Study to provide information on early adulthood levels from age
18 forward. Additional information on the shape and determinants of the CVRF trajectories later in life will be obtained by including participants from ARIC, MESA, CHS, and Health ABC. Using the 5 study cohorts combined will allow us to estimate the **overall distribution of each CVRF over the adult lifespan**. To do that, we will use generalized linear mixed models (GLMMs), as appropriate to the distribution of the CVRF, modeling the effect of increasing age as a 3- or 4-knot restricted cubic spline, with random intercepts and 1 or more random spline components to account for within-subject correlation of the repeated CVRF. The influence of other fixed factors on the CVRF trajectories, in particular, race, will be modeled by interactions with the age spline components. In combined analyses, study source will be included as a fixed effect, to capture potential systematic differences in CVRF calibration/measurement; in model validation, we will assess evidence for interactions between cohort and age, which might invalidate the backward extrapolation of the trajectories for participants in the ARIC, based on CARDIA as well as MESA, CHS, and HABC data.

In a next step, based on the fixed and random component estimates obtained from the fitted overall model for each CVRF over the adult lifespan, we will estimate the **person-specific trajectories of exposure to each CVRF** by so-called best linear unbiased predictions. In result, each ARIC participant will have a person-specific trajectory of exposure to each CVRF from age 18 forward till the participant’s death or end of follow-up.

**For aim 2**, again using generalized linear mixed models (GLMMs) we will assess the independent associations of the person-specific trajectories of exposure to each CVRF, in ARIC, CHS and Health ABC combined, with repeated cognitive function (CF) measurements within the same studies. In order to avoid potential bias from reverse causation, we will lag the person-specific CVRF trajectories by 3-5 years. For example in ARIC, with a lag of 3 years, we would use combined estimated CVRF trajectories from age 18 to ages 45, 50, 55, and 60 as predictors of ARIC cognitive scores obtained at ages 48, 53, 58, and 63, respectively. If some CF outcomes cannot be adequately transformed to meet the assumptions of the linear mixed model, we will use Poisson, negative binomial, or gamma GLMMs, which accommodate skewed distributions.

7.a. Will the data be used for non-CVD analysis in this manuscript?
_____ x__ 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?
_____ x__ 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  ____ 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)?

Most related manuscript proposals in ARIC:

Most related publications in ARIC: For the first 3 publications, cognitive decline was based on 2 assessments. In the last publication listed below, cognitive function was assessed using all available exams from the ARIC MRI Study they have only used baseline cardiovascular exposures.


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

_____x____ Yes    _____ No

11b. If yes, is the proposal

_____X____ 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)* _1999.01_ __________ __________)

*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

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