1. **Full Title:** Cardiovascular and metabolic risk, Cognition and Dementia in a Life Course Pooled Cohort

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

3. **Writing Group:** Adina Zeki Al Hazzouri, PhD; Kristine Yaffe, MD; Eric Vittinghoff, PhD; Thomas H Mosley, PhD; David S Knopman, MD

4. **Timeline:**
   - As soon as data is available

5. **Rationale:**
   - This is a request for ARIC data from the ARIC-MRI visit and earlier; as described below, it is being sought to perform an analysis across the age spectrum using CARDIA, MESA and CHS data, within which ARIC fits.
   - Cardiometabolic 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 cardiometabolic exposure in African Americans than non-Hispanic whites. Thus, understanding cumulative long-term trajectories of cardiometabolic risk factors over the adult life span is of utmost importance to our targeted interventions aimed at preventing or decreasing cardiometabolic related health outcomes and disparities.

Cognitive function is an essential component of healthy aging and shares many cardiometabolic origins and constitute processes that likely unfold over the lifespan. Establishing the extent to which long-term trajectories of cardiometabolic risk factors can impact change in cognitive function is necessary for identifying critical points of intervention and guiding public health efforts. Yet, the evidence to date of whether long-term cumulative cardiometabolic exposure impacts trajectories of cognitive decline is quite small. The majority of prior investigations has focused on relationships 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 cardiometabolic exposures and related cognitive outcomes.

This proposal will examine the link between long-term trajectories of cardiometabolic and cognitive decline over the adult life span, comparing non-Hispanic whites and African Americans. The proposed work will combine four cohorts conducted over the past 30 years with data on cardiometabolic exposures and cognition 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), and Cardiovascular Health Study (CHS). We will use all 4 cohorts together to estimate our measure of long-term cumulative cardiometabolic exposure. From ARIC, we will be using cardiometabolic, cognitive and neuroimaging data as discussed in the methods section below. We will not be performing analyses restricted to ARIC data only. All analyses will be solely conducted on the pooled cohort. ARIC study is optimal since it includes a middle-age cohort and has long follow-up time with repeated measures of cognitive function and cardiometabolic risk factors.

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

Aim 1: To determine long-term trajectories of cardiometabolic exposure separately for whites and blacks, in the pooled cohort.
Hypothesis 1: long-term cumulative trajectories of cardiometabolic risk factors (Blood pressure, diabetes, obesity, lipids, anthropometry, and smoking) will be higher risk for blacks than whites.

Aim 2: To determine the associations of long-term trajectories of cardiometabolic risk factors with cognitive decline and structural brain markers, in whites and blacks in the pooled cohort.

Hypothesis 2.1: greater cumulative cardiometabolic burden will be associated with greater cognitive decline and worse brain markers. Race will modify the association such that blacks will experience greater cognitive decline than whites for a given cardiometabolic risk factor level. Age may modify this further.

6. Design and analysis.

Here we layout the variables we will request from the ARIC study. We will not use the ARIC data as a stand-alone 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. Structural brain MRI markers.

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 cardiometabolic risk factor. ARIC study participants can contribute cardiometabolic 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 cardiometabolic trajectories later in life will be obtained by including participants from ARIC, MESA, and CHS. Using the 4 cohorts combined will allow us to estimate the **overall distribution of each cardiometabolic 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 cardiometabolic risk factors. 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 cardiometabolic risk factor 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, and CHS data.

In a next step, based on the fixed and random component estimates obtained from the fitted overall model for each cardiometabolic risk factor over the adult lifespan, we will estimate the *person-specific trajectories of exposure to each cardiometabolic risk factor* by so-called best linear unbiased predictions.

**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 cardiometabolic risk factor in the pooled cohort with repeated cognitive function (CF) measurements. In order to avoid potential bias from reverse causation, we will lag the person-specific risk factor trajectories by 3-5 years. 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. As an exploratory analysis, we will explore similar associations with brain markers as the outcome.

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

As an analysis conducted across several multicenter studies and moreover uses data from ARIC MRI and earlier, the current approach is novel and does not overlap with any current ARIC-NCS analyses.

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)?

This is a pooled cohort project and there are no related manuscript proposals in ARIC. The closest ARIC mss would be: Knopman DS, Mosley TH, Catellier DJ, et al. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. Alzheimers Dement. 2009;5(3):207-14

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

_____ Yes  ___X__ No

11.b. If yes, is the proposal

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

___x__ 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 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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