1.a. **Full Title**: Race differences in cardiovascular health in individuals with Mild Cognitive Impairment: The Atherosclerosis Risk in Communities Neurocognitive Study

b. **Abbreviated Title (Length 26 characters)**: Race Differences in CVH in individuals with MCI

2. **Writing Group**:
   Writing group members: Alvaro Alonso, Ambar Kulshreshtha, Ihab Hajjar, David Knopman, Thomas Mosley, Rebecca Gottesman

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

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3. **Timeline**: We will begin analysis on approval and have a manuscript draft ready in 5 months.

4. **Rationale**:
Race differences have been observed in the risk of different clinical and genetic etiologies of dementia, with vascular dementia and Alzheimer’s disease (AD) being more frequent in African Americans than whites.\textsuperscript{1,2,3} Despite the disproportionate burden of vascular and AD-type dementia in African Americans, research on Mild Cognitive Impairment (MCI), an intermediate step in the progression from normal cognition to dementia, in this population group has been limited. Research related to MCI can provide insight into risk factors, disease mechanisms, and strategies for prevention of dementia in general, and AD in particular, in specific racial subgroups.\textsuperscript{4}

Recent studies have shown that a 10-25\% reduction in selected key modifiable risk factors (including several CVD risk factors) could prevent 1.3 million AD cases globally.\textsuperscript{5} Converging evidence from large cardiovascular cohort studies have identified common modifiable risk factors that contribute towards both the CVD and Alzheimer’s Disease epidemic.\textsuperscript{6} Lower socio-economic status and poorly controlled CVD risk factors such as blood pressure and diabetes are more common in African Americans and probably account for some of the race differences in prevalence of AD-related dementia. However, there is very limited data on prevalence of CVD risk factors among African Americans individuals with MCI and how this compares with whites. As the proportion of African American population over the age of 65 years increases rapidly, risk modification strategies will be an important component for the long-term care of this population. Understanding the role of racial differences in prevalence and risk factors for cognitive impairment is thus critical to design health services that are more culturally tailored and can address the disparities prevalent in the US population.

In this study among participants of ARIC-NCS/visit 5, we propose to assess if Cardiovascular Health (CVH) metrics may mediate the association of race (African Americans and Whites) with Alzheimer’s Disease-related Mild Cognitive Impairment (AD-related MCI). The association between race and MCI is being currently addressed as part of MS #2120B (Knopman). The current proposal will serve as a follow-up to MS #2120B, exploring possible mechanisms of any racial differences. The availability of well-characterized data on CVD risk factors and biomarkers, together with the detailed cognitive phenotyping of the ARIC visit 5 participants, provides a unique opportunity to answer this important question. The advantage of ARIC-NCS over previous dementia studies in African Americans is that participants of both races were evaluated simultaneously using the same methods. The ARIC cohort comprising a large, representative, and racially diverse sample will facilitate the generalizability of our findings.

5. \textbf{Main Hypothesis/Study Questions:}

We propose the following specific aims:

1. Determine whether race differences in AD-related MCI prevalence are explained by differences in cardiovascular health metrics (i.e. American Heart Association’s life simple 7) or other cardiovascular risk factors.
2. Among ARIC-NCS participants with AD-related MCI, examine racial differences (African Americans and Whites) in cardiovascular risk factors profiles.
Among ARIC-NCS participants with AD-related MCI, we will describe the types of cognitive domains and assess the association of race differences with specific cognitive domains. We will determine the role of CVH metrics in mediating the association of race and specific cognitive domains.

We hypothesize that poorer cardiovascular health will mediate in part the association between race and AD-related MCI. We also hypothesize that among patients with AD-related MCI, African Americans have a higher prevalence of CVD risk factors and thus a poorer CVH profile compared with Whites and that cardiovascular health metrics will be associated with impairment in specific cognitive domains.

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 include individuals who attended ARIC visit 5. Participants who did not undergo cognitive assessment and those with missing values for relevant CVD covariates will be excluded, as well as those not meeting the usual ARIC race-center inclusion criteria (race other than white or black; non-whites in Minneapolis and Washington County).

**Cardiovascular Health**
Individual CVD factors will be categorized as poor, intermediate, or ideal according to the AHA Life’s Simple 7 criteria. Ideal levels of health factors will be: nonsmoker or quit >1 year ago; body mass index <25 kg/m²; ≥150 minutes/week of physical activity; healthy diet score (data from Visit 3 in 1993-95); total cholesterol <200 mg/dL; blood pressure <120/80 mm Hg; and fasting blood glucose <100 mg/dL. Study participants treated to target levels for hypercholesterolemia, hypertension, or diabetes will be classified as intermediate for the respective health factor. The healthy diet score will be calculated as the sum of the scores for each of 5 individual components for which the recommended intake levels are: (1) ≥4.5 serving of fruits and vegetables per day; (2) ≥7 ounces of fish per week; (3) ≥3 ounces of fiber-rich whole grains per day (≥1.1 g of dietary fiber/10 g of carbohydrate per day); (4) <1500 mg of sodium per day; and (5) ≤36 ounces of sugar-sweetened beverages per week. The range is from 0 to 5, with a lower score being unhealthy (see Table 1 for AHA’s definition of cardiovascular health).

**Covariates of interest**
1. Socio-demographic variables: age, sex, race, education, income
2. Cardiovascular risk factors: diabetes, hypertension, BMI, smoking, dyslipidemia, physical activity and diet. (Components of Ideal Cardiovascular Health metric as defined by the American Heart Association)
3. Mood questionnaires: CES-D, Anxiety
4. Selected biomarkers: C-reactive protein, APOE genotype
5. Prevalent cardiovascular disease including past history of myocardial infarction, heart failure, or stroke.

Outcome of interest
Along with a Neuropsychology test battery, there are three ARIC cognitive instruments that have been administered in follow up visits: the Delayed Word Recall Task, Digit Symbol Substitution from the Wechsler Adult Intelligence Scale (WAIS-R) and a letter fluency task. Whenever available, imaging will supplement the diagnoses of cognitive impairment.

The primary endpoint will be a diagnosis of AD-related MCI as adjudicated by ARIC-NCS. The etiologic diagnosis of AD in ARIC-NCS is based on an algorithm using informant interviews, neurological examinations, neuropsychological tests and MRI –imaging (double review with neurologists or geriatrician) in the absence of convincing evidence of an alternative primary etiology.

Statistical analysis
For the first aim, we will compare demographic factors, CV risk factors among participants with normal cognition and those with AD-related MCI. Continuous variables and categorical variables will be expressed as mean ± SD and frequencies or percentages, respectively. We will exclude participants with prior history of stroke or dementia and missing covariate information. Binary logistic regression models including race and CVH metrics will be used to determine whether race differences in prevalence of AD-related MCI are explained by CVH. Initial models for each separate covariate in CVH will adjust for age, sex, center, income and education.

For aim 2, in the subset of patients with AD-related MCI, we will compare prevalence of CVH metrics between whites and African Americans. Each of the 7 CVH components (blood pressure, fasting glucose, total cholesterol, body mass index, physical activity, healthy diet, and smoking) will be given a point score of 0, 1, or 2 to represent poor, intermediate, or ideal health, respectively. A CVH summation score will be computed (range 0 to 14) and categorized as inadequate (0 to 4), average (5 to 9), or optimum (10 to 14) cardiovascular health.

Finally, we will assess race differences in the cognitive function of participants with AD-related MCI with multivariable linear models using race as the primary independent variable and domain specific cognitive scores as the outcome variable, separately for each cognitive domain. We will assess the role that CVH metrics have in explaining racial differences by including CVH variables in the multivariable models. We recognize the limitations and assumptions of this mediation analysis and will exert caution in its interpretation.

Limitations
The proposed analysis has few limitations:  
1. Cross-sectional design: temporal relationships between the CVD risk factor variables and prevalence of AD-related MCI cannot be determined.  
2. Despite the well-characterized ARIC data there is potential influence of residual confounding on the study results due to unmeasured and imprecisely measured confounders.
3. The dietary data will be used from Visit 3 (1993-95) with the assumption that participant’s diet is essentially unchanged over the last decade.
4. Despite the use of thorough algorithmic approach, the diagnosis of AD-related MCI will be imprecise in the absence of CSF-markers and Amyloid imaging.

Prospective studies in MCI are needed to further define the relationship between CVD risk factors and incident MCI with intervention studies are needed to determine if reduction of the risk factors will indeed decrease in the incidence of AD.

Table 1: Life’s Simple Seven as a measure of Cardiovascular Health

<table>
<thead>
<tr>
<th>Health Metric</th>
<th>Levels</th>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>Ideal</td>
<td>2</td>
<td>&lt;200 mg/dl, without lipid lowering medication</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>1</td>
<td>200-239 mg/dl or treated to &lt;200 mg/dl</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>0</td>
<td>≥240 mg/dl</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Ideal</td>
<td>2</td>
<td>SBP 120–139 or DBP 80–89 mm Hg or treated with antihypertensive medication</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>1</td>
<td>SBP ≥140 or DBP ≥90 mm Hg</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>0</td>
<td>&lt;120/&lt;80 mm Hg, without antihypertensive medication</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>Ideal</td>
<td>2</td>
<td>&lt;100 mg/dl, without diabetes medication</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>1</td>
<td>100–125 mg/dl or treated with diabetes medications to &lt;100 mg/dl</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>0</td>
<td>≥126 mg/dl</td>
</tr>
<tr>
<td>Physical activity*</td>
<td>Ideal</td>
<td>2</td>
<td>&gt;150 min/week moderate or &gt;75 min/week vigorous or &gt;150 min/week moderate + vigorous</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>1</td>
<td>1-149 min/week moderate or 1-74 min/week vigorous or 1-149 min/week moderate + vigorous</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>0</td>
<td>No physical activity</td>
</tr>
<tr>
<td>Healthy diet score†</td>
<td>Ideal</td>
<td>2</td>
<td>4–5 components</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>1</td>
<td>2–3 components</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>0</td>
<td>0–1 components</td>
</tr>
<tr>
<td>Smoking</td>
<td>Ideal</td>
<td>2</td>
<td>Never or quit &gt;12 months</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>1</td>
<td>Former, quit ≤12 months</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>0</td>
<td>Current</td>
</tr>
<tr>
<td>Body mass index</td>
<td>Ideal</td>
<td>2</td>
<td>&lt;25 kg/m²</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>1</td>
<td>25–29.99 kg/m²</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>0</td>
<td>≥30 kg/m²</td>
</tr>
</tbody>
</table>

Per Lloyd-Jones et al.
† The five components are:
- Fruits and vegetables: >4.5 cup per day.
- Fish: >two 3.5 oz servings per week (preferably oily fish).
- Fiber-rich whole grains (>1.1 g of fiber/10 g of carbohydrate): >three 1-oz servings per day.
- Sodium: <1500 mg per day.
- Sugar-sweetened beverages: <450 kcal (36 oz) per week.

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? __X__ Yes (APOE genotype) ____ 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”? _X_ 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)?

MS#1898 Life’s simple 7 of neurocognitive health (González) – This manuscript explores the association between baseline cardiovascular health in ARIC and cognitive decline over 22 years, while the current proposal focuses on the impact of cardiovascular health to explain racial differences in MCI prevalence at visit 5.

MS #2120B: MCI and Midlife Vascular Risk Factors (Knopman) – This manuscript looks at midlife vascular risk factors (prior to Visit 5) and risk of prevalent MCI. Our current proposal includes Lifestyle factors (such as diet and physical activity) as part of the American Heart Association – Ideal Cardiovascular Health (CVH) definition and the assessment of these factors at visit 5. Further, the analyses we propose looks specifically at the association of race with AD-MCI and assesses if CVH factors mediates this association rather than an exploration of race as an interaction. Dr. Knopman is included as a co-author of our manuscript proposal and we will work with him to avoid any overlaps.

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)_)
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/](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/](http://publicaccess.nih.gov/) are posted in [http://www.cscc.unc.edu/aric/index.php](http://www.cscc.unc.edu/aric/index.php), under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit_process_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

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