

ARIC Manuscript Proposal # 2120B

PC Reviewed: 4/14/15
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Mid-life vascular risk factors for Mild Cognitive Impairment in the ARIC NCS Study

b. Abbreviated Title (Length 26 characters): MCI and Midlife Vascular Risk Factors

2. Writing Group: Knopman, Mosley, Sharrett, Wruck, Albert, Schneider, Coker, Gottesman, Windham

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: **Knopman**

Address: same as above

3. Timeline: now....complete in 6 months

4. Rationale: With the completion of the case adjudication for MCI and dementia in ARIC-NCS, there are several foundational manuscripts to be written. The first is on the methodology of ascertainment of cognitive status and presumed etiology. That will be the first paper written under ARIC MS proposal #2120 by this same writing team. That manuscript will also include descriptions of dementia and MCI prevalence by age, race and sex. Because of concerns that the simple presentation of prevalence of dementia would not be newsworthy and therefore not merit publication in first or second tier journals, manuscript proposal #2120, as first proposed, also included evaluation of vascular risk factors, both midlife and at the time of ARIC-NCS visit. At the same time, the basic mission of #2120 must be completed in order to lay a foundation for all other ARIC-NCS manuscripts based on the clinical diagnoses made in ARIC-NCS. Thus, manuscript #2120, as now conceived, will focus only on methodology and basic prevalence data.

There is still a need for an initial “global” vascular risk factor analysis of persons diagnosed as MCI or dementia in ARIC-NCS. Upon further reflection, linkage of midlife vascular risk factors with surviving demented individuals is highly likely to be biased by survivorship. We have plans, therefore, to submit an additional manuscript proposal that includes both the dementia cases prevalent at the time of ARIC-NCS and all dementia cases enumerated prior to the start of ARIC-NCS in 2011.

In contrast, our inability to detect MCI in any other context except the in-person assessments of ARIC-NCS made the exercise of linking midlife vascular risk factors and MCI an essential analysis. The manuscript being proposed in here is to perform the vascular risk factor analysis proposed in #2120 but to restrict it to MCI as detected at ARIC NCS examination. The risk factors cited in #2120 were diabetes and hypertension only, but we would also expand that list to include elevated cholesterol levels, incident and prevalent stroke, smoking and BMI. APOE genotype will be examined as a risk factor as well. We will use only single “summary” measures of these risk factors, leaving more detailed subclassifications, eg treated versus untreated hypertension, to future analyses by other authors.

5. Main Hypothesis/Study Questions:

- A. Midlife (ARIC V1) diabetes, hypertension, elevated plasma cholesterol, BMI and smoking history, independent of APOE genotype and stroke prior to Visit 5, are related to risk for prevalent MCI. This holds for MCI regardless of etiology as well as both MCI attributed to AD and to CVD.
- Mid-life diabetes mellitus and hypertension will be major vascular risk factors, independent of APOE genotype
 - These associations will remain in people who never had a stroke prior to Visit 5.
 - There will be no interaction of vascular risk factors with sex or race.
 - Vascular risk factors will show stronger associations in apoE4 carriers

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).

Analysis population: Participants who attended the baseline visit (V1)

Definition of MCI:

- Main analysis: Level 1 MCI diagnosis at Visit 5, defined as
 - Reviewer diagnosis if available,
 - Otherwise algorithmic diagnosis
- Secondary analysis: Level 1 MCI or dementia diagnosis (collapsed) at Visit 5

Definition of syndrome / etiology combined:

- Collapse current categories:
 - Normal
 - MCI with AD primary
 - MCI with AD primary/CVD secondary
 - MCI with CVD primary
 - MCI with Other Etiology
 - MCI with Unknown Etiology
 - Dementia (because we will not be testing hypotheses associated with dementia, etiology will not be modeled separately)

Covariates:

- Race: use derived variable for self-reported race included in DERIVE13
- Gender: use derived variable for self-reported gender included in DERIVE13
- Age: calculated from birthdate and June 1, 2011 (start of Visit 5)

- Education level from DERIVE13 (3 levels: did not complete HS; HS grad or GED or vocational college training; at least one or more years of college)
- ApoE 4 (definition?)
- Exposures measured at baseline visit (V1):
 - Prevalent diabetes (DIABTS03)
 - Hypertension (definition from Rebecca’s paper: HT, pre-HT, Normal)
 - Elevated LDL). Ignore medication use as it was infrequent at that time.
 - Elevated Total Cholesterol Ignore medication use as it was infrequent at that time.
 - BMI (BMI21) grouped (underweight, normal, overweight, obese)
 - Cigarette smoking status (CIGT21 – current/former/never)

Methods:

Characterize analysis population with simple frequencies. Assess missingness of covariates.

All analyses will be conducted using complete cases and with IPAW to account for attrition.

- 1) Level 1 diagnosis is a multinomial random variable, taking on ordinal values (Normal, MCI, or Dementia); therefore multinomial logistic regression models will be used to model Level 1 diagnosis. To accommodate tests of hypotheses of the risk of MCI vs. Normal, baseline-category logit models will be used. No hypothesis tests will be conducted using the Dementia group.
- 2) Level 1 diagnosis with etiology will be modeled using multinomial models. Baseline-category logit models will be used to test hypotheses making the following comparisons:
 - MCI with AD primary vs. Normal
 - MCI with AD primary/CVD secondary vs. Normal
 - MCI with CVD primary vs. Normal

Secondary analyses:

Repeat analysis 1) and 2) with cognitive impairment as the outcome. Analysis 1) will be conducted using logistic regression. Analysis 2) will be conducted using multinomial regression.

For both primary and secondary analyses, a progressive modeling approach will be used, in which models are constructed with covariates added in groups:

Model 1: demographics (race, gender, age, education)

Model 2: demographics + APOE

Model 3: demographics + APOE + lifestyle (BMI, smoking)

Model 4a-4d: demographics + APOE + lifestyle + vascular exposures (one at a time of diabetes, hypertension, LDL, Total cholesterol)

Model 5: demographics + APOE + lifestyle + all vascular exposures together

Model 6: Model 5 with race interactions with vascular exposures

Model 7: Model 5 with age interactions with vascular exposures

Model 8: Model 5 with APOE interactions with vascular exposures

Sensitivity analyses:

- Exclude pts with stroke prior to Visit 5 to assess hypothesis that associations remain in participants with no stroke prior to Visit 5.
- Exclude pts with very low global Z-score at Visit 2 (lowest 5% of global Z-score)

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 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.csc.unc.edu/ARIC/search.php>

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)?

Manuscript #2120, as mentioned above. There has never been any ARIC studies of MCI until now.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes No

11.b. If yes, is the proposal

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)* _____)

*ancillary studies are listed by number at <http://www.csc.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.csc.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.