ARIC Manuscript Proposal #3574 (Amended)

PC Reviewed: 11/16/20 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:
The association of motoric cognitive risk with neuroimaging and incident dementia: The ARIC Study

b. Abbreviated Title (Length 26 characters):
Motoric cognitive risk and dementia

2. Writing Group:
Writing group members:
Gabriela Gomez (first author), Rebecca Gottesman, Kelley Gabriel, Priya Palta, Alden Gross, Kevin Sullivan, Cliff Jack, David Knopman, Anja Soldan, Marilyn Albert, B. Gwen Windham, Keenan Walker (senior author), others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.

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3. Timeline:
1-3 months: analysis of data
1-3 months: writing of manuscript

4. Rationale:

Gait changes and gait dysfunction are common among older adults and have been associated with cognitive decline[1,2], mild cognitive impairment (MCI)[3], and increased dementia risk[4], and thus may represent an easily assessed and inexpensive clinical marker of incipient dementia. Associations between gait and dementia are especially strong for vascular dementia and other non-Alzheimer's dementia subtypes[4]. Current theories posit that higher order cognitive processes, namely executive functioning, may contribute to control of gait. Thus, the frontal lobe may represent one of many brain structures central to the control of gait and cognitive functions[5,6].

A syndrome defined by slow gait speed and subjective cognitive complaints known as "motoric cognitive risk" (MCR) has recently been described and validated[7]. Multiple large-scale community-based studies have shown that, like MCI, MCR is associated with increased dementia incidence[8,9]. While MCI and MCR overlap to an extent, these syndromes can and often do occur independently of one another. For example, one study found that only 39% of participants who met criteria for MCR also met criteria for MCI[8]. Although multiple reports have highlighted the predictive power of MCR as a pre-dementia syndrome, the neural correlates of MCR, and whether or not they differ from MCI, remain poorly understood. To our knowledge, only one previous study has examined the pattern of reduced brain volume associated with MCR[10]. However, this study relied on a relatively small sample, used a 1.5T MRI, and used an ROI approach which is unable to assess the neuroanatomical correlates of the MCR syndrome in an unbiased fashion. While one study has found an association between frontal lacunar infarcts and MCR[11], the degree to which MCR is associated with white matter macrostructural and microstructural changes also remains unclear.

The goal of the current study is to examine whether MCR syndrome is associated with a specific pattern of neurodegenerative brain changes and cognitive impairment. Using a large community-based sample form the Atherosclerosis Risk in Communities (ARIC) Study, we will test the hypothesis that MCR, when compared to those classified as cognitively normal, is associated with lower brain volume/cortical thickness in superior frontal brain regions, poorer white matter integrity, and poorer executive functions. We will compare the structural brain abnormalities associated with MCR to those associated with MCI to determine whether these two pre-dementia syndromes have a distinct neurodegenerative signature. Lastly, we will examine the association of MCR (with and without MCI) with incident dementia in an attempt to replicate recently published findings. Together, these results could help to establish the neurobiological underpinnings and the clinical utility of the MCR syndrome.

5. Main Hypothesis/Study Questions:

1. Persons who meet criteria for MCR will have reduced brain volume/cortical thickness in the superior frontal brain regions, reduced white matter integrity, greater cortical

amyloid, and greater impairment on measures of executive function, compared to cognitively normal individuals.

2. Compared to the MCR group, those with MCI will demonstrate more diffuse reductions in brain volume/cortical thickness and greater cortical amyloid when compared to cognitively normal participants. Compared to the MCI group, those with MCR will show more evidence of reduced white matter integrity when compared to cognitively normal participants. A secondary analysis will compare MCR+/MCI- and MCR-/MCI+ groups to a cognitively normal reference group. (**Table 1**).

3. MCR+ status at ARIC Visit 5 will be associated with incident dementia at ARIC Visit 6; dementia risk associated with MCR will be comparable to the dementia risk associated with MCI. Primary analyses will examine dementia risk associated with MCR (regardless of MCI status) and dementia risk associated with MCI status (regardless of MCR status). A secondary analysis will compare MCR+/MCI+, MCR-/MCI+, MCR+/MCI- groups to a cognitively normal reference group.

Table 1. Hypothesized association of MCR and MCI status with neuroimaging and cognitive variables

	Reduced Executive Functioning	**Poor White Matter Integrity**	**Diffuse Reduction Brain Volume/ Cortical Thickness**
MCR+	++	++	+
MCI+	+	+	++
MCR-/MCI-	-	-	-

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).

Participants

Inclusion/Exclusion Criteria:

Inclusion Criteria:

1) Attended ARIC visit 5
2) Visit 5 4m walk and Subjective Memory Form data available

Exclusion Criteria:

1) Missing post-visit 5 follow-up information
2) Dementia diagnosis at visit 5
3) Non-white or non-black race
4) Hemiplegia

Exposure Variables

Motoric Cognitive Risk (MCR). MCR diagnosis is defined as the presence of cognitive complaints and slow gait among non-demented individuals without mobility disabilities[7].

1. *Walking speed* was measured at visit 5 as the time needed to walk 4 m at a usual pace. Slow walking speed will be defined as a time one standard deviation (within lowest 16th percentile) below the means, adjusted for gender and height, in the total V5 sample. We will conduct a sensitivity analysis using the cutoff defined in the Cardiovascular Health Study (CHS).
2. *Subjective Memory Complaints* were assessed at Visit 5 using the Subjective Memory Form (SMF). Participants will be categorized as having a subjective memory complaint if they respond "often" or "very often" to either of the following questions: 1) "In the past month, how often did you misplace or lose things around the house?" 2) In the past month, how often did you have trouble remembering conversations that occurred just a few days earlier?" A continuous subjective memory rating score will also be derived.

Mild Cognitive Impairment (MCI). MCI was defined as at least one domain score worse than -1.5 Z, a CDR sum of boxes between >0.5 and ≤3, an FAQ ≤5, and a decline on the serial ARIC cognitive battery below the 10th percentile on one test or below the 20th percentile on two tests[12].

Cognitively Normal. Non-demented participants who do not meet criteria for MCI or MCR at ARIC visit 5, as defined above.

Outcome Variables

Incident Dementia after Visit 5. The analysis will relate MCR status to incident dementia occurring between Visit 5 and Visit 6. This analysis will include participants who were classified as either cognitively normal or MCI at Visit 5. Dementia will be defined using both the information from the full Visit 6 examination (and Visit 7 when data available) with expert committee diagnosis and information captured in annual follow-up (AFU) interviews using the Six Item Screener (SIS) and the Ascertain Dementia 8-item Informant Questionnaire (AD8). Date of dementia onset will be captured using the SIS and AD8; dementia diagnosis will be confirmed at Visit 6 for those who attend Visit 6. Participants who attended Visit 5, but not Visit 6, and have SIS and AD8 information available from the AFU will also be included. For participants who did not attend Visit 6, the SIS, AD8, hospital discharge codes, and death certificates will be used to define dementia diagnosis and date of onset. As a sensitivity analysis, only adjudicated diagnoses will be included, i.e. only participants who completed Visit 6.

NCS Comprehensive Cognitive Battery. We will examine cognitive functioning in areas of memory, language, processing speed and executive function using previously defined factor scores[13].

MRI Variables. 3T MRIs were conducted in approximately 2,000 participants at Visit 5 as part of the ARIC Neurocognitive Study (NCS). The acquisition sequence for the ARIC Visit 5 MRI has been described previously[14]. At each ARIC site, a common set of sequences were performed for all participants: MP-RAGE, Axial T2*GRE, Axial T2 FLAIR, and Axial DTI.

Voxel-based morphometry (VBM). VBM will be used to identify regional group differences in gray matter (GM) and white matter (WM) density using voxel-wise parametric statistical tests. The generation of VBM from MRI images involves multiple steps[15]. First, each T1 scan has a

geometric correction applied for gradient distortions and an intensity correction to remove inhomogeneity bias. Next the corrected scans are segmented and spatially normalized using the Unified Segmentation approach in spatial parametric mapping-5 (SPM5). The segmented, spatially normalized GM and WM images are then modulated to correct for stretching and compression induced by the spatial normalization. Finally, the modulated normalized WM and GM images are smoothed with a Gaussian smoothing filter. We will enter these pre-processed images into the general linear model framework of SPM to produce voxel-wise GM and WM tissue density comparisons between groups described above. We will correct for multiple comparisons. We will generate maps based on voxel-based associations. Generalizations will be drawn from these maps. These analyses will be used to compare MCR to cognitively normal participants (**H1**) and to compare MCI to cognitively normal participants (**H2**) for comparison.

White Matter Hyperintensity (WMH) Volume. WMH volume (mm^3) was be assessed quantitatively from FLAIR images using a computer-aided segmentation program (FLAIR-histoseg) to assess the total volumetric burden[18]. We will compare groups described above on measures of total WMH volume. All analyses of WMH volume and regional brain volume will be adjusted for total intracranial volume. These analyses will be used to compare MCR to cognitively normal participants (**H1**) and to compare MCI to cognitively normal participants (**H2**) for comparison.

Diffusion Tensor Imaging (DTI). Fractional anisotropy (FA) and mean diffusivity (MD) have been calculated from the DTI sequences, as has been described in detail elsewhere[19]. FA is a unitless measure of the directional constraint of water molecules imposed by cellular structure and other microstructural bodies. MD (mm^2/s) is a measure of the overall mobility of water molecules. Thus, reduced FA and higher MD are associated with poorer white matter microstructural integrity. Lobar and deep white matter regions were delineated using an in-house atlas based on the STAND400 template[20]. Tissue segmentation from T1-weighted and FLAIR images were intersected with white matter regions. Only voxels with a greater than 50% probability of being white matter (including WMH) were used to calculate FA and MD. Total brain FA and MD will be calculated for the current study by deriving the voxel weighted average of six brain regions (frontal, temporal, parietal, and occipital lobes, anterior and posterior corpus callosum). We may also examine FA and MD in four white matter networks: limbic, commissural, association, and projection tracts[21]. These analyses will be used to compare MCR to cognitively normal participants (**H1**) and to compare MCI to cognitively normal participants (**H2**) for comparison.
These networks will be derived by taking the weighted average FA and MD of multiple white matter tracts which make up each network, as listed below:

> *Limbic*: fornix/stria terminalis, body of fornix, cingulum bundle at cingulate gyrus, and cingulum bundle at hippocampus
>
> *Commissural*: genu of the corpus callosum, body of corpus callosum, splenium of corpus callosum
>
> *Association*: superior longitudinal fasciculus, superior fronto-occipital fasciculus, external capsule
>
> *Projection*: anterior corona radiata; posterior corona radiata, superior corona radiata, anterior limb of the internal capsule, posterior limb of the internal capsule.

PET Neuroimaging. Using data from participants enrolled in the ARIC-PET study, we will examine the association of MCR and MCI status cortical amyloid, as defined using florbetapir PET. Cortical amyloid status will be examined as a dichotomous variable (standardized uptake value ratio [SUVR] >1.2) and a continuous variable. We will examine the global cortex florbetapir uptake variable for primary analyses. We will use the calculated a global measure of florbetapir uptake using a volume-dependent weighted average of the following regions: orbitofrontal, prefrontal, and superior frontal cortices; the lateral temporal, parietal, and occipital lobes; and the precuneus, the anterior cingulate, and the posterior cingulate.

Other Variables

Visit 1 demographic variables, including race, sex, education, *APOE* ε4 status, and center will be extracted. Additionally, participant age and laboratory and physiologic data, including systolic and diastolic blood pressures, total/high density lipoprotein cholesterol, and body mass index (BMI, kg/m^2) will be extracted from study Visit 5. Cardiovascular risk factors and disease information (i.e., diabetes, hypertension, coronary heart disease, and cigarette use) will also be extracted from Visit 5. Additionally, non-neurologic factors potentially affecting gait (i.e. arthritis/joint deformities, peripheral vascular disease, cardiac disease, chronic lung disease) will be extracted and used as exclusionary criteria in sensitivity analyses.

Data Analysis

We will use multivariable linear regression to compare MCR, MCI, and cognitively normal groups on measures of cognition, cortical thickness and white matter integrity in the manner described above (**H1, H2**). Similarly, we will use logistic and linear regression analyses to compare MCR, MCI, and cognitively normal participants on measures of amyloid (florbetapir uptake SUVR; **H1, H2**).

Cox proportional hazards models will be used to evaluate the risk of dementia using the level 3 dementia variable (dementia onset measured after visit 5, utilizing Ascertain Dementia-8 informant questionnaires, Six-Item Screener telephone assessments, hospital discharge and death certificate codes, and visit 6 neurocognitive evaluation) in MCR+ and MCI+ groups, using a cognitively normal reference group (**H3**).

We will first examine results in an unadjusted model (Model 1). We will also analyze a second regression model (Model 2) which incorporates covariates to account for group differences in demographic characteristics: age, sex, race-center (Maryland white; Minnesota white; North Carolina white; North Carolina African American; Mississippi African American), education (less than high school; high school/GED/vocational school; or any college), and *APOE* ε4 status (0, 1, or 2 ε4 alleles).

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 ____ 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)?

#2791: Association of Life's simple 7 at mid-life with frailty in older adults

#2215: Development of longitudinal measures of general and domain-specific latent factors for cognitive performance

#2586: Neural correlates of prior domain-specific cognitive decline: a voxel-based morphometry study

#2288: Associations of brain imaging with cognitive change over 20 years

#2671: Cardiovascular characterization of frailty in the elderly: The ARIC study

#2465: Operationalizing frailty in the ARIC cohort

#2303: Diabetes, hyperglycemia, and the burden of frailty syndrome in the Atherosclerosis Risk in Communities 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)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s) * 2013.10)

*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.
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.
Understood

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 pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

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disease with full diffusion tensor characterization. *Neurobiol. Aging* **33**, 2029–45 (2012).

Appendix

SMF Coding

Dichotomous measure
If SMF1 is Often or Very Often (3 or 4) (losing items question)
Or
If SMF3 is Often or Very Often (3 or 4) (problems remembering conversations)
Then MemProb_SR = 1
Otherwise MemProb_SR = 0.
MemProb_SR is missing only if both SMF1 and SMF3 are missing

Continuous Measure
7.4 MEMORY, Memory problems in past month (0-20)
= missing if 2 or more memory questions are missing
= sum(SMMA1, SMMA2, SMMA3, SMMA4) with recoding as follows
Recode SMMA1-SMMA3 from (1, 2, 3, 4, 5, 6) to (0, 1, 2, 3, 4, 5) where responses are 0=Almost Never, 1=Seldom, 2=Sometimes, 3=Often, 4=Very Often, 5=Constantly
Recode SMM04 from (0, 1, 9) to (0, 5, missing).
SMMA1: In past month, how often have you misplaced or lost things around the house?
SMMA2: In past month, how often have you written reminder notes to yourself?
SMMA3: In past month, how often have you had trouble remembering conversations that occurred just a few days earlier?
SMMA4: Has anyone in your family ever expressed concern or worry about your memory? (0=No, 5=Yes, 9=Don’t Know)