ARIC Manuscript Proposal Form

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 # 4419 (Revised)

1.a. Full Title: Sensorimotor Function Score and Mild Cognitive Impairment

b. Abbreviated Title (Length 26 characters): Sensorimotor Function and Mild Cognitive Impairment

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _AAW____ **[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 (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

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3. Timeline: We expect that data cleaning and analyses will take 3 to 6 months, and manuscript writing and submission another 9-12 months.

4. Rationale: Early detection of persons at risk for, or living with, mild cognitive impairment (MCI) is an important public health priority. MCI is an emerging state of cognitive impairment, beyond normal aging, that commonly precedes a dementia diagnosis. Diagnosing MCI relies on clinical judgement using data from neuropsychological testing[1] and at times neuroimaging[2]. Sensory and motor functioning are often measured clinically, but not formally used in helping to diagnose MCI. Yet, a growing number of studies are demonstrating a link between sensorimotor function and cognitive impairment.

Substantial evidence suggests that slowed gait speed and impaired motor function precedes declines in memory, executive function, processing speed, and global cognition, and also precedes the onset of MCI, by as many as 10-15 years[3–7]. Yet, a limitation of slowed physical functioning is that it is common with aging and not highly specific to progression of dementia[3,8,9]. Sensory impairments, specifically in hearing[10–12], vision[13,14], and olfaction[15,16] have also been linked to incident cognitive decline, MCI, and dementia. Further, most studies investigating the link between sensory and cognitive functioning have only considered the independent effects of each type of sensorimotor impairment or dual effects[17], as opposed to their cumulative effect.

Sensorimotor functioning—the integration of sensory information with motor function signaling to perform tasks and interact with the environment—is a novel domain intertwined with complex thinking and mental ability. One recent study showed that the addition of separate mid-life sensory and motor functioning variables to traditional parameters improved prediction of cognitive decline and impairment[18]. These results are consistent with the notion that impairment across multiple sensory and motor systems might augment (and differ) from established associations between single sensory impairment or motor impairment and cognitive decline, yet gaps remain about how to best clinically operationalize sensorimotor function.

5. Main Hypothesis/Study Aims: This study will set the stage to operationalize sensorimotor functioning using common clinical measures. We propose to use two datasets: the Atherosclerosis Risk and Communities Study (ARIC) and Baltimore Longitudinal Study of Aging (BLSA).

With ARIC data, we will develop a sensorimotor function construct using a variety of sensory and motor variables and confirmatory factor analysis (called "sensorimotor factor score"). Then, we will cross-sectionally examine whether a higher sensorimotor factor score is related to lower MCI odds. We hypothesize that higher sensorimotor functioning is related to lower odds of MCI. We also hypothesize that, due to nonlinear combinations of individual sensory and motor features, sensorimotor functioning algorithmically derived from confirmatory factor analysis is uniquely associated with MCI, above and beyond a summary (count) of sensory and motor functioning.

We will repeat/validate this analysis using similar variables found in the BLSA dataset to test robustness of findings and increase generalizability.

6. Design and analysis - please address the following aspects:

a) inclusion/exclusion

a. All participants aged 65 years and older who: 1) have MCI measured, 2) do not have dementia, 3) have data for all three sensory measures (Jackson and Washington County sites only) and 3) have at least one motor function assessment

b) study design

a. Cross-sectional at visit 6 (v6, 2016-17). The EyeDOC ancillary study where vision was measured occurred over visits 6/7 (2017-19).

c) outcome and other variables of interest with specific reference to the time of their collection

a. The primary exposure is a sensorimotor factor score generated from CFA models. This will initially be constructed with sensory information including hearing, vision, olfaction and motor information including time to complete 5 chair stands, standing balance tests, usual gait speed, and grip strength; all measured at v6 except vision, which was measured over v6/7. Each sensory or motor function variable will be categorized as 0 (impaired) and 1 (unimpaired) using published thresholds[19,20].
b. An alternative method to create a sensorimotor variable is to simply add the number of unimpaired sensory and motor function variables where a higher score represents higher sensorimotor functioning. We will derive this variable and call a sensorimotor summary score. The sensorimotor summary score will be treated as an exposure variable.
c. The primary outcome of logistic regression models is mild cognitive impairment measured at v6.
d. Covariates include (but are not limited to) baseline age (continuous in years), sex (male/female), race-center, body mass index (kg/m^2), smoking (ever vs. never), depressive symptoms (CES-D 11), multimorbidity including hypertension

(diastolic blood pressure ≥ 90 mmHg, systolic blood pressure ≥ 140 mmHg, or self-reported antihypertensive medication use in the past 2 weeks), cardiovascular disease, stroke, pulmonary disease, diabetes (fasting blood glucose level ≥ 126 mg/dL, participant self-reported physician diagnosis of diabetes, or the self-reported use of medications for diabetes in the past 2 weeks), cancer and ≥1 *APOE* ε4 alleles.

d) summary of data analysis

a. CFA will be used to determine the most parsimonious model of sensorimotor function by removing single sensory or motor function variables, one at a time until model fit criteria are reached. This includes CFI of ≥0.95, TLI of ≥0.95, RMSEA of ≤0.05, and SRMR of ≤0.08[21].
b. Structural equation modeling (SEM) will be used to evaluate the association between CFA-derived sensorimotor function and mild cognitive impairment.
c. If an association is detected, the sensorimotor factor score will be extracted from the CFA-derived sensorimotor model for each participant to compare against their sensorimotor summary score.
d. The sensorimotor summary score will be derived via CFA and will be plotted against the sensorimotor sum score to examine differences between the two constructs.
e. Separate logistic regression models will be conducted to assess the association between either the sensorimotor factor score or sensorimotor summary score with mild cognitive impairment. Likelihood ratio tests can be used to compare the goodness of fit between logistic regression models to detect a non-shared association between the sensorimotor factor score with mild cognitive impairment.
f. All analyses will be repeated using BLSA data under the same study design and inclusion/exclusion criteria.

e) any anticipated methodologic limitations or challenges if present

This is a cross-sectional analysis. Therefore, temporality of the results is undetermined. However, this study design provides a first step in determining the value of defining sensorimotor function as a consolidated clinical variable and risk of mild cognitive impairment.

There will be missing sensory and motor information for some participants. We will examine the pattern(s) of missingness to understand whether our construction of sensorimotor function is biased toward one or a set of exposure variables or missing at random.

Generalizability will be increased by repeating the cross-sectional analyses in the BLSA. The same exclusion criteria applied to ARIC data will be applied to BLSA data. Because BLSA is ongoing, the most recently available BLSA data will be used. There is a possibility that the creation of the sensorimotor construct slightly differs in the BLSA based on how each sensory or motor function variable is measured. However, these differences can be theorized to increase external validity of the sensorimotor construct if we detect similar model fit statistics and associations with mild cognitive impairment. Table 1 highlights differences of sensory or motor variables between ARIC and BLSA.

While we plan to use thresholds for function (inverse of sensor or motor loss), we will run sensitivity analyses on different published thresholds to determine function versus impairment.

A possible limitation is that some measures (e.g., vision) are not measured identically in ARIC and BLSA which may bias results and affect interpretation of the findings. However, if findings are robust across ARIC and BLSA, despite measurement differences either within test or between tests, the generalizability of the findings is greatly enhanced.

Table. Differences in sensory and motor variables collected between ARIC and BLSA

Variable	ARIC (V6 only)	BLSA (most recent visit)	Difference
Hearing	Pure tone audiometry (PTA). Air conduction thresholds in each ear were obtained at standard octaves from 0.5 kHz to 8 kHz.[22]	PTA. Air-conduction thresholds at 0.5, 1, 2, and 4 kHz was calculated for each ear.[22]	ARIC upper bound threshold is +4 kHz higher but only 0.5, 1, 2 and 4 are used for speech frequency PTA.
Vision	Presenting and best-corrected visual acuity, near vision and contrast sensitivity measured at Jackson and Washington county sites only[22]	Visual acuity, visual field, contrast sensitivity, and stereo acuity.[22]	ARIC does not collect visual field and stereo acuity.
Olfaction	Smelling sticks to assess 12 smell types[23]	Smelling sticks to assess 16 smell types.[22]	ARIC collects 4 fewer order types.
Gait speed	4m usual-paced from the Short Physical Performance Battery[24]	6m usual-paced from the Short Physical Performance Battery[25,26]	While ARIC uses the more commonly used 4m walking course, gait speed differences due to measurement are not anticipated.
Grip strength	Hand grip strength via dynamometer[27,28]	Hand grip strength via dynamometer[25]	None
Leg strength + motor control	5 repeated chair stands from the Short Physical Performance Battery[24]	5 repeated chair stands from the Short Physical Performance Battery[25]	None
Balance	Full tandem stance from the Short Physical Performance Battery[24]	Full tandem stance from the Short Physical Performance Battery[25]	None

f) Will the author need Limited data to complete the proposed manuscript? ☒ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) . ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded,

Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ **Yes** ☒ **No**

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ☐ **Yes** ☐ **No**
(The file ICTDER is distributed to ARIC PIs annually, 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 current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ☒ **Yes** ☐ **No**

9. The lead author or the "sponsoring" ARIC 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website□Publications□Proposal Search]

☒ 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)?
Davoudi et al. Predicting Cognitive Impairment Using Machine Learning, Sensorimotor Function, and Biomarkers of ADRD (MS Proposal #: 4060)

Smith et al. Multisensory impairment and cognitive decline and progression to mild cognitive impairment and dementia among older adults in ARIC-NCS (MS Proposal #: 3963)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☒ **Yes** ☐ **No → Skip to question 12**

11.b. If yes to 11.a., is the proposal

☒ **A. primarily the result of an ancillary study**

☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

11.c. If yes to 11.a., list number* 2018.07__

*ancillary studies are listed by number https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website□Ancillary Studies□Approved Ancillary Studies]

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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website□Publications□Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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