ARIC Manuscript Proposal Form

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Publication Committee Review Date: 10/14/2025
ARIC Manuscript Proposal Number#: 4743

1.a. Full Title: Temporalis Muscle Characteristics and Risk of Dementia: Opportunistic Assessment of Brain MRIs

b. Abbreviated Title (Length 26 characters): Temporalis MRI & Dementia

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
Writing group numbers: Kamyar Moradi*, Roham Hadidchi*, Amyn Majbri, Timothy M. Hughes, Hanzhang Lu, Daisy Zhu, Soheil Mohammadi, Sara Momtazmanesh, Pratik Mukherjee, Eleanor Simonsick, Susan M. Resnick, Jennifer A. Schrack, Marcus D. Goncalves, Josef Coresh, Marilyn Albert, Shadpour Demehri; others welcome, * Co-first author

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

First author [please provide a middle initial; EX: Adam L Williams]:

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ARIC sponsor to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located. The ARIC sponsor is responsible for **carefully reviewing the proposal and ensuring its soundness prior to submission to the ARIC Publications Committee.** (The ARIC sponsor 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:

4. Rationale: Skeletal muscle size has been linked to cognitive decline, but the temporal direction of this association remains unclear (1). Since muscle loss is potentially modifiable, identifying an accessible imaging biomarker of skeletal muscle size could offer an opportunity for early intervention (2-6).

5. Main Hypothesis/Study Aims: To determine whether temporalis muscle cross-sectional area and tissue composition, measured from conventional brain MRI, are independently associated with incident dementia in participants with mild cognitive impairment.

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

a) **Inclusion/exclusion**

Participants with baseline dementia or normal cognition were excluded and those with mild cognitive impairment (MCI) and brain MRI at Visit 5 were included.

b) **Study design**

In each included ARIC participant, T1-weighted brain MRI was visually inspected and a standardized axial slice at the orbital roof landmark was selected for segmentation. A deep learning temporalis segmentation algorithm that was previously developed and trained on an independent dataset (ADNI) was applied to the axial slice of each included ARIC participant to obtain temporalis muscle mask. Segmentation accuracy was validated in ARIC via manual segmentation of the temporalis muscle on a randomly selected subset of participants. To measure temporalis muscle composition, 93 radiomic features that characterize tissue signal heterogeneity and structural complexity were extracted from the segmented temporalis muscle.

Baseline variables collected at Visit 5 (age, sex, race, BMI, *APOE*-ε4 status, Mini-the Mental State Examination [MMSE], and the Short Physical Performance Battery [SPPB]) were used as predictors in a Cox-proportional hazards model, with the outcome defined as incident dementia. In one model, the independent association between temporalis muscle volume and incident dementia was investigated. In another model, a Least Absolute Shrinkage and Selection Operator (LASSO) was used to condense all 93 radiomic features down to a single radiomic score. This LASSO, trained on an independent dataset (ADNI), was then applied to ARIC participants, deriving a single radiomic score for each participant, whose independent association with incident dementia was investigated.

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

The primary outcome is incident dementia, adjudicated during ARIC follow-up after Visit 5, with events ascertained through standardized surveillance and clinical adjudication procedures. Time-to-event will be calculated from Visit 5 until dementia diagnosis, death, loss to follow-up, or censoring at the end of follow-up.

Key exposure variables include temporalis muscle cross-sectional area and radiomic features, derived from brain MRI acquired at Visit 5. The radiomic

features will be summarized into a radiomic score previously trained in ADNI and applied to ARIC participants.

Baseline covariates collected at Visit 5 include age, sex, race, BMI, *APOE*-ε4 status, the MMSE, and the SPPB. These variables will be used as covariates in the regression models to adjust for demographic, genetic, cognitive, and physical function at baseline.

d) **Summary of data analysis**

We will use Cox proportional hazards regression to examine the association between temporalis muscle measures and incident dementia among ARIC Visit 5 participants with MCI and brain MRI. Time-to-event will be calculated from Visit 5 until dementia diagnosis, death, loss to follow-up, or end of study, whichever occurs first. Temporalis cross-sectional area will be modeled continuously and in standard deviation. A radiomic score, derived using a LASSO model trained in ADNI, will be applied to ARIC participants and analyzed similarly. Models will be adjusted for age, sex, race, BMI, *APOE*-ε4 status, and cognitive/physical performance measures such as the MMSE and SPPB at baseline. We will assess proportional hazards assumptions. Results will be reported as hazard ratios with 95% confidence intervals.

e) **Any anticipated methodologic limitations or challenges if present** No

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 PHF 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. Will the data be used by a for-profit organization in this manuscript? ☐ **Yes*** ☒ **No**

8. Will the DNA data be used in this manuscript? ☐ **Yes*** ☒ **No**

* Please carefully review the instructions and documentation on the ARIC website at: https://aric.cscc.unc.edu/aric9/researchers/Obtain_Submit_Data [ARIC website > Researchers > Obtain/Submit Data] for instructions on proper data use.

9. The lead author or the ARIC sponsor 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)?

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* 2025.18

*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. The NIH-NHLBI Public Access Brochure about the public access policy from http://publicaccess.nih.gov/ is 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.

References: 1. Peng TC, Chen WL, Wu LW, Chang YW, Kao TW. Sarcopenia and cognitive impairment: A systematic review and meta-analysis. Clinical nutrition (Edinburgh, Scotland). 2020;39(9):2695-701. Epub 2020/01/10. doi: 10.1016/j.clnu.2019.12.014. PubMed PMID: 31917049.
2. Hassan BH, Hewitt J, Keogh JW, Bermeo S, Duque G, Henwood TR. Impact of resistance training on sarcopenia in nursing care facilities: A pilot study. Geriatric nursing (New York, NY). 2016;37(2):116-21. Epub 2015/12/24. doi: 10.1016/j.gerinurse.2015.11.001. PubMed PMID: 26694694.

3. Geirsdottir OG, Arnarson A, Ramel A, Briem K, Jonsson PV, Thorsdottir I. Muscular strength and physical function in elderly adults 6-18 months after a 12-week resistance exercise program. Scandinavian journal of public health. 2015;43(1):76-82. Epub 2014/11/29. doi: 10.1177/1403494814560842. PubMed PMID: 25431460.
4. Chen HT, Chung YC, Chen YJ, Ho SY, Wu HJ. Effects of Different Types of Exercise on Body Composition, Muscle Strength, and IGF-1 in the Elderly with Sarcopenic Obesity. J Am Geriatr Soc. 2017;65(4):827-32. Epub 2017/02/17. doi: 10.1111/jgs.14722. PubMed PMID: 28205203.
5. Lau RW, Liao LR, Yu F, Teo T, Chung RC, Pang MY. The effects of whole body vibration therapy on bone mineral density and leg muscle strength in older adults: a systematic review and meta-analysis. Clinical rehabilitation. 2011;25(11):975-88. Epub 2011/08/19. doi: 10.1177/0269215511405078. PubMed PMID: 21849376.
6. Iuliano S, Fyfe J, Scott D, Kirk B, Thompson M, Dent E, et al. Screening, diagnosis and management of sarcopenia and frailty in hospitalized older adults: recommendations from the Australian and New Zealand Society for Sarcopenia and Frailty Research (ANZSSFR) Expert Working Group. The Journal of nutrition, health and aging. 2022;26(6):637-51.

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