ARIC Manuscript Proposal Form

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Publication Committee Review Date: **09/17/24**
ARIC Manuscript Proposal Number: **# 4534**

1.a. Full Title: The Association between Cerebral Microbleed Patterns and Incident Dementia

b. Abbreviated Title (Length 26 characters): **Microbleed and dementia**

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
Writing group members: Richard Q. Vuong (first/lead); Valerie N. Morrill; Jonathan Graff-Radford; David Knopman; Thomas Mosley; Michelle Johansen; Keenan Walker; Cliff Jack; James Pike; Andrea L.C. Schneider; Rebecca Gottesman (senior) others welcome.

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

Abstract to be submitted late September 2024 for International Stroke Conference; manuscript prepared and submitted in ~6 months.

4. Rationale:

Cerebral amyloid angiopathy (CAA) is a condition where amyloid-beta (A-beta) peptides, a central pathological marker of dementia secondary to Alzheimer's disease, deposit in the cerebral vasculature and lead to intracerebral macro- and microbleeds, with a predilection for lobar/cortical locations.[1] Lobar microbleeds, in combined analysis with another imaging marker often associated with CAA called superficial siderosis (SS), have been associated with elevated global cortical A-beta levels in populations with no clinical history of dementia or intracerebral hemorrhages[2] according to prior published work using data from ARIC-NCS and ARIC-PET. These findings suggested that a CAA-like pattern in the general community shares pathologic changes similar to those seen in clinical CAA populations and suggests one mechanism that might link these microbleed patterns to dementia and other adverse cognitive outcomes. In this same prior analysis, however, other subclinical bleeding patterns such as subcortical and mixed subcortical and lobar hemorrhages did not share these associations with elevated A-beta, suggesting that the underlying etiology of these patterns is likely different (e.g., hypertension).[2] With increased A-beta burden seen in only one microbleed category, the relevance of each of these specific bleeding patterns on the development of clinically detectable dementia from dementia-free populations is less clear.

The presence of microbleeds in nonclinical (community-based) populations, in the absence of formal diagnoses of CAA, is independently associated with incident dementia. The META-MICROBLEEDS Initiative published a meta-analysis of 31 cohorts, each with at least 100 participants, which evaluated microbleeds on MRI. In three community-based cohorts (contributing a total of 6,535 participants), which included dementia-free participants at baseline, the presence of microbleeds in any part of the brain was associated with an increased risk of all-cause incident dementia.[3] However, the exact distribution of these microbleeds is not specified nor was SS considered in the analysis. The ability to separate out the location of microbleeds (lobar vs. subcortical) allows consideration of distinct mechanisms. In ARIC, lobar microbleeds were more frequently associated with APOE e4, as well as smaller Alzheimer's Disease signature regions, both of which are more likely to be markers of CAA. SS is another imaging marker commonly found in CAA and has emerged as one of the strongest predictors of lobar intracerebral hemorrhage recurrence, thus adding to its importance for stroke risk stratification and potential role in dementia risk.[4] Subcortical microbleeds often co-occur with lacunar infarcts and white matter hyperintensities, both markers of (frequently hypertensive) small vessel disease.[5] In this study, we propose to test the association between multiple microbleed patterns and incident dementia in participants without prior history of intracerebral hemorrhage or dementia to further explore the potential clinical relevance of these imaging findings and understand a potential mechanism of their link to dementia in a community-based population.

A recent analysis of the ARIC-NCS cohort does show an association between microbleed patterns and incident dementia in specific demographics and in the context of other effect modifiers (in this case, social relationships).[6] An in-press study accepted at Stroke (Eswaran et

al.) found a statistically significant association of dementia risk with subcortical microbleeds in those with poor social relationships [HR(95% CI): 2.02 (1.33-3.06)] but not in those with strong social relationships [HR(95% CI): 1.35 (0.90-2.04)].[6] Lobar microbleeds showed an association with dementia in women [HR(95% CI): 2.69 (1.69-4.38) but not in men [HR(95% CI): 1.36 (0.73-2.51)], and both microbleed patterns (lobar and subcortical) had stronger associations with dementia risk in Black participants than White participants (lobar: [HR(95% CI): 2.89 (1.70 – 4.90) vs. 1.85 (1.12 – 3.04)]; subcortical: [HR(95% CI): 2.16 (1.33 – 3.52)] vs. 1.35 (0.93 – 1.96)]). This prior study highlights significant heterogeneity among associations of microbleed subtypes with dementia risk and provides evidence that certain covariates modify associations of microbleed subtypes with dementia risk. For this proposed study, we will expand upon these microbleed patterns to include a total of 4 distinct microbleed pattern categories for analysis that parallel those we previously evaluated in association with A-beta: no microbleeds, lobar and/or SS only, subcortical only and mixed (lobar and/or SS + subcortical). Further, we plan to control for several covariates such as demographics, cardiovascular risk factors, and other brain imaging markers of small vessel disease.

5. Main Hypothesis/Study Aims:

1. Cerebral microbleeds are associated with increased risk of incident dementia in ARIC-NCS participants without prior history of intracerebral hemorrhage or dementia.
2. Lobar microbleeds (presence and frequency, +/- SS) are associated with increased risk of incident dementia in the same population as #1, and a pattern with subcortical-only microbleeds will have a present but weaker association. Individuals with a mixed (lobar and/or SS + subcortical) pattern of microbleeds will have an association less than lobar only distribution microbleeds but greater than subcortical-only microbleeds. We believe lobar and/or SS will have a higher risk of incident dementia than the mixed pattern of microbleeds because prior work shows a stronger global cortical A-beta burden in lobar and/or SS compared to a mixed microbleed pattern.[2]
3. (Exploratory) A pattern of lobar microbleeds with or without SS is associated with an increased risk of incident dementia compared to other patterns, and dementia risk is greater compared to lobar microbleeds alone. SS alone will be associated with elevated risk of dementia (exploratory due to likely small sample size).
4. (Exploratory) The associations described above are stronger in participants with MCI than those with normal cognition. We will also evaluate effect modification by sex, race, and APOE status.

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

a) inclusion/exclusion
b) study design
c) outcome and other variables of interest with specific reference to the time of their collection
d) summary of data analysis
e) Any anticipated methodologic limitations or challenges if present

Design: longitudinal from V5 baseline through most recent dementia adjudication

Participant inclusion: All ARIC-NCS participants with an MRI at visit 5 (2011-13) will be eligible for inclusion. *Exclusion:* Intracerebral hemorrhage or dementia prior to visit 5

Outcome: New-onset dementia as defined by adjudicated research diagnoses which include in-person assessments in clinic, telephone cognitive assessments, and family member or caretaker interviews, hospital discharge codes, or death certificates.[7]

Exposure: The primary independent variable will be microbleeds from the visit 5 MRI. These are rated by presence (in any part of the brain), location (lobar y/n; subcortical or deep y/n), and frequency (in any part of the brain and within each location; we will likely categorize these as 0; 1; 2; 3+ or similarly, depending on the distribution). As such, lobar hemorrhages will be defined as the presence of hemorrhages within the cortical regions of the brain and the frequency of the lobar hemorrhages in their respective areas. Subcortical hemorrhages will be defined as the presence of hemorrhages in any part of the noncortical (subcortical) parts of the brain and the frequency of the subcortical hemorrhages in their respective areas. Since SS is a highly predictive finding for recurrent lobar hemorrhages, its presence will be added together with the analysis for lobar microbleeds. Thereby, we will define a "mixed" pattern of microbleeds as the concurrent presence of either lobar and/or SS (defined by its presence on any part of the brain), in combination with subcortical microbleeds within the brain. In our exploratory analysis, lobar with SS will be defined by the presence of lobar microbleeds and the concurrent presence of SS. Lastly, SS alone will be defined by its presence in the absence of other discretely defined microbleeds.

Covariates: Demographic covariates include visit 5 age, sex, race, and education. Vascular risk factor covariates include V5 hypertension (measured blood pressure and antihypertensive use also to be considered), diabetes, body mass index, smoking status, and APOE genotype. Imaging covariates include white matter hyperintensity volume and total intracranial volume, also from visit 5.V5 traumatic brain injury (TBI) will also be included as microbleeds can be evidence of axonal injury if sample size allows for adequate analysis.

Data analysis: In the primary analysis, we will use Cox proportional-hazards regression models to assess the association between patterns of microbleeds (patterns described above) and incident dementia. The reference group for all analyses will be participants who did not have a measured microbleed of any type at visit 5. All models will be adjusted minimally with demographic covariates and then fully adjusted with vascular risk factors and imaging covariates described above. Cox-proportional hazards model assumptions will be evaluated using Schoenfeld residuals. Kaplan-Meier curves will be generated to show percentage of dementia-free survival for each microbleed category. We will use multiple imputation by chained equations (MICE) when appropriate to impute missing covariate information. Analyses will consider the use of sampling weights to account for weighting into the MRI sample.

For hypothesis 1, we will estimate the association between presence of any microbleed in the brain and frequency of any microbleed in the brain with dementia in two separate Cox proportional-hazards models. Fine-Gray subdistribution hazard models in conjunction with

Inverse Probability of Censoring Weights (IPCW) will be used to examine the competing risk of death in all eligible participants.

For hypothesis 2, relative to a comparison group of no microbleeds, in our first set of models we will estimate the associations between presence of a lobar microbleed and/or SS-only pattern, presence of subcortical-only microbleeds, and presence of a mixed microbleed pattern, with dementia. If feasible, we will also repeat this analysis evaluating frequency of microbleeds to capture severity of each of these patterns and will introduce interaction terms for pattern type X frequency (for instance, to evaluate if having 3+ microbleeds is associated with greater risk of dementia if there is a lobar/ SS-only pattern, vs if these 3+ are subcortical only microbleeds).

For hypothesis 3, we will estimate the association between presence of SS (vs no SS, which will include any other microbleed patterns) with dementia in Cox proportional-hazards models, as well as the association between lobar with SS (by creating a new fifth category as in the hypothesis 2 analysis plan, for the combination).

For hypothesis 4, we will stratify all models described above across MCI status and formally test for interaction terms by cognitive status. We will also evaluate effect modification using interaction terms by sex, race, and APOE status.

Limitations: The sample size for superficial siderosis may be small as only 3 participants in ARIC-PET had evidence of SS. The expanded sample pool of ARIC-NCS visit 5 through 2021 is expected to provide additional samples, but power may still be limited for hypotheses #3 and #4.

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)?
MP #3691. Gottesman et al. Cerebral microhemorrhages and cortical amyloid: The ARIC-PET study
MP #2288. Knopman et al., Associations of brain imaging with cognitive change over 20 years
MP #2266. Graff-Radford/ Knopman et al., Associations between brain vascular imaging features and regional volumetrics
MP # 2822. Gottesman et al., Subclinical cerebrovascular disease and brain amyloid deposition: The ARIC-PET study

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* _2008.06_

*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.

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 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.

CITED REFERENCES

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6. Eswaran S., Knopman DS, Koton S, Kucharska-Newton AM, Liu AC, Liu C, Lutsey PL, Mosley TH, Palta P, et al. The Association between Psychosocial Health and Cerebral Small Vessel Disease Markers with Dementia: The ARIC study. Stroke (in-press).
7. Knopman DS, Gottesman RF, Sharrett AR, Wruck LM, Windham BG, Coker L, Schneider AL, Hengrui S, Alonso A, Coresh J, Albert MS, Mosley TH Jr. Mild Cognitive Impairment and Dementia Prevalence: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). Alzheimers Dement (Amst). 2016;2:1-11. doi: 10.1016/j.dadm.2015.12.002. PMID: 26949733; PMCID: PMC4772876.

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