ARIC Manuscript Proposal #4229

PC Reviewed: 4/11/23 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Social Engagement, MRI Markers of Cerebrovascular Disease Burden, and Dementia: the ARIC-NCS Study

b. Abbreviated Title (Length 26 characters): Social & CVD Health

2. Writing Group [please provide a middle name if available; EX: Adam Lee Williams]:
Writing group members:

Renee C. Groechel, PhD (first); Rebecca F. Gottesman, MD, PhD (last); Thomas H. Mosley Jr., PhD; A. Richey Sharrett, MD DrPH; Priya Palta, PhD; Anna M. Kucharska-Newton, PhD; Silvia Koton, PhD; Keenan A. Walker, PhD; Pamela L. Lutsey, PhD; MPH; David S. Knopman, MD; Chelsea Liu, PhD; Albert C. Liu, MD; Kevin J. Sullivan, PhD

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

First author [please provide a middle name if available; EX: Adam Lee Williams]:
Address: Renee Constance Groechel, PhD
Address: 10 Center Drive. Building 10 Room: 4D37
Bethesda, MD 20814

Phone: (248) 417 - 9644 Fax:
E-mail: renee.groechel@nih.gov

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: Rebecca F. Gottesman, MD; PhD
Address: 10 Center Drive. Building 10 Room: 4D37
Bethesda, MD 20814

Phone: (301) 435 – 9321 Fax:
E-mail: Rebecca.gottesman@nih.gov

3. Timeline:
Proposal submitted for April 5th ARIC Publications committee meeting. Abstract submission planned for International Stroke Conference (August 2023 deadline); Analysis and manuscript written in 4-6 months pending approval.

4. Rationale:

Attention to cognitively stimulating activities, such as psychosocial factors, has increased in recent years due to studies which have shown the positive impact being socially engaged can have on cognition, mortality, and general well-being in older adults.[1-4] Since psychosocial factors are modifiable, many believe this risk factor may be a promising target for Alzheimer's disease (AD) and dementia intervention.[2,5-6]

To better understand the mechanism underlying how psychosocial factors relate to dementia, studies are actively investigating the relationship between psychosocial factors and cardiovascular health. Such studies have shown psychosocial factors are a strong predictor of cardiovascular disease (CVD), CVD mortality, and CVD progression over a short follow-up period.[7-10] A recent study using data from the National Health and Nutrition Examination Survey further showed that being socially isolated was associated with poorer fasting blood glucose, smoking, and (less) physical activity.[11] Other investigators using data from the Atherosclerosis Risk in Communities (ARIC) cohort have shown that social isolation is a risk factor for incident heart failure,[12] and a recent proposal using ARIC data (MP#4131) has plans to examine how psychosocial factors relate to measures of cardiovascular health, as indicated by the American Heart Association's Life's Essential 8.

Previously, the writing group for this proposal has assessed the relationship between mid-life psychosocial factors, such as social support and social isolation, in ARIC participants with late life amyloid burden and incident dementia. Following our initial study (MP#4080) which assessed the independent associations of mid-life social support and social isolation with late life amyloid burden, we further explored whether the association between amyloid burden and incident dementia could be modified by a composite measure, termed social engagement (further elaboration on this measure follows in subsequent sections of this proposal). Specifically, we investigated whether contributions of mid-life social engagement and amyloid burden on incident dementia were synergistic or independent (MP#4156). We found no interaction but that both mid-life social engagement and late-life amyloid burden were independently related to incident dementia, leaving us curious to see what other factors might be influencing this relationship.

Unrelated to psychosocial factors, studies using the ARIC cohort and other aged cohorts have consistently shown strong associations between vascular pathologies detectable by magnetic resonance imaging (MRI) with cognitive decline and dementia incidence.[13-15] Many of the most prevalent vascular pathologies on MRI are markers of cerebral small vessel disease and include white matter hyperintensities (WMH), infarcts (primarily lacunes), and microbleeds.[16-17] Additionally, measures of white matter (WM) integrity, such as fractional anisotropy (FA) and mean diffusivity (MD) have shown cross-sectional and longitudinal associations with incident dementia in the ARIC cohort and elsewhere.[18]

While the relationship of various vascular MRI markers with dementia is well established, it remains less explored how modifiable risk factors, like psychosocial measures, could potentially impact the relationship between these markers and incident dementia. In the present study, we aim to further explore the contributions of both mid-life social engagement and markers of cerebrovascular health, imaged with MRI, in participants of the ARIC cohort to see whether these contributions are independent or if they interact.

Secondary analyses in the present study will further explore how associations between social engagement and cerebrovascular markers with dementia may vary by sex and race. A recent study in an aged Australian cohort showed more prominent associations between poor social health and estimated CVD risk in men but this was not explored in relation to dementia.[10] A study conducted using data from the Washington Heights/Hamilton Heights-Inwood Columbia Aging Project further assessed how modifiable lifestyle factors, such as physical and cognitive activities, influenced cognitive performance in older adults and if this association was modified by sex or race.[19] This study found an association between physical activity and processing speed in women, but not in men. Sensitivity analyses also examined whether race/ethnicity moderated any of the associations found, but results were not significant.[19] Other studies have suggested that the relationship between poor cardiovascular health and CVD with dementia is particularly prevalent in Black participants,[20-21] but how race may modify the relationship between constructs, such as social engagement and MRI markers of cerebrovascular health, with dementia remains less clear.

5. Main Hypothesis/Study Questions:

We aim to assess whether strong mid-life **social engagement** will modify the association between MRI markers of cerebrovascular health (measured in late life) and incident dementia.

The social engagement variable to be used was created following previous examinations of psychosocial measures in the ARIC-PET cohort which revealed that the relationship between continuous Interpersonal Support Evaluation List Short Form (ISEL-SF) and Lubben Social Network Scale (LSNS) scores is weak and that a small proportion of participants fall into the categorization of “high risk of socially isolated” or “isolated.” For these reasons, we will use a composite measure termed “social engagement” which categorizes a participant’s social health and environment based on both social support and social isolation categorizations (Figure 1).[22]

Figure 1. Categorization of Social Engagement

		Lubben Social Network Scale (Quartiles)			
Social Support Tertiles (ISEF-SF)		Low risk	Moderate risk	High risk	Isolated
	High				
	Intermediate				
	Low				

High Social Engagement

Intermediate Social Engagement

Low Social Engagement

H1a: The relationship between *WMH volume* and incident dementia will be modified by social engagement in mid-life. Specifically, we expect that high social engagement in mid-life will attenuate the association between WMH volume and incident dementia.

H1b: The relationship between *cerebral microbleeds* and incident dementia will be modified by social engagement in mid-life. Specifically, we expect that high social engagement in mid-life will attenuate the association between cerebral microbleeds and incident dementia.

H1c: The relationship between *infarcts* and incident dementia will be modified by social engagement in mid-life. Specifically, we expect that high social engagement in mid-life will attenuate the association between infarcts and incident dementia.

H1d: The relationship between *white matter (WM) integrity measured using DTI* and incident dementia will be modified by social engagement in mid-life. Specifically, we expect that high social engagement in mid-life will attenuate the association between global WM integrity and incident dementia.

H2: The degree to which the relationship between MRI markers of cerebrovascular health and likelihood of dementia will be modified by social engagement in *men* will be weaker than that observed in women. We expect this association to be weaker in men because of previous studies which have shown factors associated with cognitive reserve are less likely to modify long term health outcomes in men versus women.[19]

H3: The degree to which the relationship between MRI markers of cerebrovascular health and likelihood of dementia will be modified by social engagement in *Black* participants will be weaker than that observed in White participants. We expect this association to be weaker in Black participants because of previous studies that have shown a stronger association between markers of CVD and dementia,[20-21] in addition to other studies that have shown associations between socioeconomic factors and cognitive decline are less likely to be mediated by biological measures in Black participants.[23]

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).

Study Design: We will utilize a longitudinal study design examining participants who had both psychosocial factors (social support and isolation) measured at ARIC Visit 2 (1990 – 1992) and a

brain MRI scan at ARIC Visit 5 (2011-2013). Previously defined adjudicated ARIC diagnoses between visit 5 and visit 8 will be evaluated as the primary dependent outcome.

Participant inclusion/exclusion: Of the 1,864 dementia free participants who underwent ARIC-NCS Visit 5 imaging, we will include those with psychosocial factors (support and isolation) measured at ARIC Visit 2. From inclusion of both these measures and subsequent categorizations, we can compose the composite social engagement variable for all participants.

ARIC participants with prevalent stroke prior to visit 5 or those who develop incident stroke between visits 5 and 8, with race other than White and Black, and/or missing key covariates will be excluded. Due to the small sample, non-white participants from either the MN or MD sites will be excluded.

Independent variables: Social engagement will be evaluated in models with indicated MRI markers of cerebrovascular health as the other independent variable of interest. The interaction between the two will be further assessed.

Social Engagement
Previous examinations of psychosocial factors in the ARIC-PET cohort have revealed that the relationship between continuous ISEL-SF and LSNS scores is weak and that a small proportion of participants fall into categorization as "high risk of socially isolated" or "isolated." For these reasons, we have begun using a composite measure, "social engagement," which categorizes a participant's social health and environment based on both social support and social isolation categorizations.[22] Following the categorization of social support and isolation, participants fall into 12 social engagement groups ("high social support – low risk social isolation," "high social support – moderate risk of isolation," etc.). We then classified these groupings as high, intermediate, or low social engagement (Figure 1).

In sensitivity analyses, we will further evaluate models using social support as measured with the ISEL-SF at visit 2 and we will also evaluate social isolation by means of the LSNS (also administered at visit 2).

MRI Markers of Cerebrovascular Disease

- WMH (adjusted for total intracranial volume then log transformed) – continuous variable
- Microbleeds (binary variable – present or not).
    - We will also specifically assess microbleeds that are "deep" due to this form of microbleeds being a form of cerebral small vessel disease
- Infarcts (binary variable – present or not)
- Mean MD/FA of global WM integrity- continuous variable

Outcome: Dementia diagnosis/date of diagnosis (per adjudicated research diagnoses) after visit 5 through visit 8 will be our outcome variable. Participants will be categorized as dementia/not having dementia depending on whether they develop dementia through the time of visit 8.

Other variables: We will include demographic variables such as race, sex, education, age, and *APOE* ε4 genotype measured at baseline. Other vascular risk factors defined at visit 2 (when

psychosocial factors were measured) will include: smoking status (current, former, or never), drinking status (current, former, or never), diabetes, body mass index (BMI), hypertension, and total cholesterol. The Maastricht Vital Exhaustion Questionnaire was also administered at visit 2 to measure symptoms of depression and fatigue.[24-26] Questionnaire scores were dichotomized at ≥ 14 to indicate depressive symptomology.[25] This measure will be adjusted for due to previous ARIC studies which have shown depression could be a possible confounder when examining the proposed association.[12,15]

Data Analysis: Descriptive statistics (means and standard deviations for continuous variables, frequencies and percentages for categorical variables) will be generated for demographic variables and covariates. To address our hypotheses, we will use Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident dementia between visit 5 and visit 8 (with visit 5 considered to be time 0). Social engagement will be treated as a categorical measure. Social engagement and each MRI marker of cerebrovascular disease will be treated as the primary independent variables of interest. Within models, the contributions of each social engagement tertile in addition to indicated MRI markers of cerebrovascular health (WMH, microbleeds, infarcts, mean MD/FA of global WM integrity) will be evaluated independently. To evaluate for a synergistic association between social engagement and cerebrovascular burden on dementia, we will test for multiplicative interaction by assessing an interaction term between social engagement tertiles and each MRI marker of cerebrovascular health. We will test the proportional hazards assumption by log-rank tests with Kaplan-Meier curves. For H2 and H3, we will formally test for interactions by sex and race, respectively, and explore stratified results if deemed appropriate.

The following models will be conducted for each MRI marker of cerebrovascular health.

- Model 1a: adjusted for age, sex, race, education, and *APOE* ε4 status
- Model 1b: above covariates and evaluate the interaction between social engagement tertiles and respective MRI marker of cerebrovascular health

- Model 2a: adjustment for the variables in Models 1a in addition to other risk factors measured at visit 2 such as:
    - (having) depressive symptoms
    - smoking status (former, current or never)
    - drinking status (former, current, never)
    - diabetes
    - BMI
    - hypertension
    - total cholesterol
- Model 2b: adjustment for above covariates and evaluate interaction between social engagement tertiles and respective MRI marker of cerebrovascular health

Sensitivity analyses: All analyses will include ARIC-NCS sampling weights to account for selection for an MRI scan at visit 5. We will also restrict analyses to those with normal cognition (excluding MCI) and no *APOE* ε4 alleles. Further sensitivity analyses will be conducted using vascular risk factors measured at visit 5 (instead of visit 2) as covariates within the outlined models. Lastly, we will also assess models using measures of social support (ISEL-SF) and

social isolation (Lubben Social Network Scale) instead of the composite social engagement measure to see whether results are congruent across different measures of social health.

Limitations

- Social factors measured only in mid-life, not time of imaging
- Relatively few dementia cases within the sample which may result in limited power
- Survival bias – those who with poorest social or vascular health are unlikely in current analytic sample due to attrition

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __x_ 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 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 current derived consent file ICTDER05 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/mantrack/maintain/search/dtSearch.html

___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)?

- 4080 (Groechel): Association Between Mid-Life Social Factors and Estimated Late-Life Amyloid Burden: the Atherosclerosis Risk in Communities (ARIC) Study.
- 4156 (Groechel): Social Factors, Amyloid Burden, and Dementia: the ARIC-PET Study
- 3119 (Gottesman): Vascular risk factors, brain amyloid deposition, and cognitive decline: The ARIC-PET Study
- 3054 (Wu): Brain Structural MRI Abnormalities Predict Dementia, MCI and Cognitive Decline in an Older Population
- 3686 (Liu): Mid-life Social Engagement and Risk of Post-Stroke Dementia

- 4131 (Peter): Associations of psychosocial factors and cardiovascular health measured by Life's Essential 8: the Atherosclerosis Risk in Communities (ARIC) 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)* _____ _____ _____)

*ancillary studies are listed by number https://sites.cscc.unc.edu/aric/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 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.

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