ARIC Manuscript Proposal #4156

PC Reviewed: 11/8/22 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Social Factors, Amyloid Burden, and Dementia: the ARIC-PET Study

b. Abbreviated Title (Length 26 characters): Social Factors and Amyloid

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 Lutsey, PhD; MPH; David S. Knopman, MD; Dean F. Wong, MD, PhD; Chelsea Liu, 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]**

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3. Timeline:
Proposal submitted for November 8th ARIC Publications committee meeting. Analysis and manuscript written in 4-6 months pending approval.

4. Rationale:

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

Participants in the Atherosclerosis Risks in Community (ARIC) study were surveyed for measures pertaining to social support and social isolation at ARIC visit 2 when participants were between 46 and 67 years old. Given the important relationships observed between mid-life vascular risk factors and later life outcomes previously described in this cohort,[7-8] many studies examining the relationship between these mid-life social factors with outcome measures such as global cognition, cognitive decline and risk of stroke using this cohort have also been characterized.[2-3,9]

The writing group for this proposal is finishing work on a study that assesses the independent association of mid-life social support and social isolation with late life amyloid burden, measured using florbetapir positron emission tomography (PET). Like other ARIC-PET studies, imaging was conducted at visit 5 and high amyloid burden was defined as elevated standard uptake value ratio (SUVR) > 1.2 of florbetapir in the global cortex. Results from this initial study unexpectedly showed that intermediate/low social support and a moderate risk of social isolation, compared to high social support and low risk of isolation, were each associated with *lower* odds of elevated SUVR. Interestingly, we further observed that many participants categorized in mid-life as having high social support, or at a low risk of social isolation, still had high amyloid burden in late life. Altogether these findings seem to reflect selection bias and survivorship and have motivated us to further explore whether the association between amyloid burden and incident dementia may be modified by these same mid-life factors.

Understanding what effects modifiable risk factors, such as social support and social isolation, may have on the relationship between amyloid burden and dementia could be instrumental to identifying potential targets for dementia intervention and prevention. To investigate this relationship, we propose to use a similar design as a recent ARIC-PET study that assessed how vascular risk factors might modify the association between amyloid and dementia and whether this interaction would be synergistic.[10]

Secondary analyses will explore how these associations may differ by sex. This interest stems from previous studies which continue to investigate sex differences in amyloid retention on PET, social factors, and dementia prevalence.[3,11-12] Some of these studies have indicated that women are more frequently categorized as having high social support and a lower risk of social isolation,[3] although the interaction between these complex factors remains unclear.

5. Main Hypothesis/Study Questions:

Hypothesis 1a: The relationship between amyloid burden and dementia will be modified by the amount of social support in mid-life. We expect a weaker association between amyloid burden and likelihood of dementia in participants with high social support.

Hypothesis 1b: The relationship between amyloid burden and dementia will be modified by the amount of social isolation in mid-life. We expect a weaker association between amyloid burden and likelihood of dementia in participants at a low risk for social isolation.

Hypothesis 2 (Exploratory – likely underpowered due to sample size): The degree to which the relationship between amyloid burden and likelihood of dementia will be modified by social factors in women will be weaker than that observed in the entire sample. We expect this association to be weaker when solely examining women because of previous work which has shown lower social support and increased risk of social isolation is particularly protective of amyloid burden in women.[13]

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: Participants who completed the ARIC-PET study (n = 346) will be included in this study. The baseline of our analysis will be ARIC Visit 2 (1990 – 1992) when social isolation and social support were measured and participants were between 46 - 67 years old. Florbetapir PET data will come from ARIC Visit 5 (2011 – 2013) when participants were 67 – 89 years old. Previously defined ARIC diagnoses will be monitored between visit 5 and visit 8 to assess which participants are diagnosed with dementia based upon adjudicated diagnoses.

Participant inclusion/exclusion: Participants who are nonwhite or nonblack or do not have an adjudicated dementia diagnosis and/or social measures will be excluded. The one ARIC-PET individual who was ultimately given an adjudicated dementia diagnosis at visit 5 will also be excluded.

Independent variables:

Social support and social isolation will be evaluated independently from one another. Both will be evaluated in models with standardized uptake value ratio (SUVR) of the global cortex as the other independent variable of interest. The interaction between the two will be further assessed.

Perceived **social support** will be evaluated using the Interpersonal Support Evaluation List-Short Form (ISEL-SF). This 16-item scale was constructed by the original ARIC investigators from the original 40-item full scale and assesses perceived social support with four subscales including (a) appraisal support, (b) tangible assets support, (c) belonging support, and (d) self-esteem support. The total score is an equally weighted sum, with scores ranging from 0-48; the higher the score, the greater perceived social support.[14-15] Scores will be assessed using distribution based *tertiles*: high ≥42, intermediate 36 – 41, and low ≤ 35).[3,13]

Social isolation will be evaluated by the Lubben Social Network Scale. This 10-item scale assesses the size of the participant's active social network and the perceived social support received by family, friends, and neighbors. The total score is an equally weighted sum, with scores ranging from 0-50; the higher the score, the greater the level of social support. Scores will be distributed in the following *quartiles* to be used for interpretation: ≤20= isolated; 21-25= high risk for isolation; 26-30=moderate risk for isolation; ≥31= low risk for isolation.[16-17]

Standardized Uptake Volume Ratio (SUVR) as defined by ARIC-PET, in the global cortex region (weighted average of precuneus, orbitofrontal cortex, prefrontal cortex, superior frontal cortex, lateral temporal lobe, parietal lobe, occipital lobe, anterior cingulate, and posterior cingulate) will be our second primary independent variable. Due to skewedness, SUVR will be evaluated as a binary variable based on the hypothetical cut-point (SUVR = 1.2) established in prior literature.

Outcome: Dementia diagnosis (per adjudicated research diagnoses) after visit 5 through visit 8 will be our outcome variable. Participants will be categorized as dementia/not 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 social support and social isolation measures were taken) will include: smoking status (current or not), drinking status (current or not), diabetes, body mass index (BMI), hypertension, and total cholesterol.

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. We will evaluate such variables for the entire sample and for individuals who develop dementia over the follow-up period and those who did not. To address all three 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 factors will be treated as categorical measures. Each social factor and SUVR of global cortex will be treated as the primary independent variables of interest. Additionally, we will evaluate the formal interaction between the two and explore stratified models for all levels of both social factors. We will test the proportional hazards assumption by log-rank tests with Kaplan-Meier curves. We will formally test for interactions by sex and race. For hypothesis 2, we will explore stratified models by sex.

Models will be conducted for each respective social factor ("a" for social support, "b" for social isolation).

- Models 1a and 1b will be adjusted for age, sex, race, education, and APOE ε4 status and we will evaluate the interaction between each social engagement variable and SUVR.
- Models 2a and 2b will include adjustment for the variables in Models 1a and 1b in addition to smoking status (current or not), drinking status (current or not), diabetes,

BMI, hypertension, and total cholesterol. We will additionally evaluate the interaction between each social engagement variables and SUVR.

Sensitivity analysis: We will include exclude participants with prevalent stroke at visit 5.

Limitations

- Social factors measured only in mid-life, not time of imaging or dementia onset
- Short follow-up from time of amyloid imaging – may take longer to see amyloid burden exert an influence
- Relatively few number of dementia cases within the sample which may result in limited power
- Survival bias – many of those with highest amyloid burden or who were most isolated at visit 2 are unlikely in ARIC-PET study and 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)?

ARIC Manuscript Proposal (#4080) (Groechel): Association Between Mid-Life Social Factors and Estimated Late-Life Amyloid Burden: the Atherosclerosis Risk in Communities (ARIC) Study.

ARIC Manuscript Proposal (#3119) (Gottesman): Vascular risk factors, brain amyloid deposition, and cognitive decline: The ARIC-PET Study

ARIC Manuscript Proposal (#3512) (Liu): Social Isolation, Social Support, and Cognitive Decline: the Atherosclerosis Risk in Communities (ARIC)

ARIC Manuscript Proposal (#2139) (Nagayoshi): Social Isolation, Social Support, and the Risk of Incident Stroke: the Atherosclerosis Risk in Communities Study

ARIC Manuscript Proposal (#2211) (Kats): Midlife psychosocial factors and cognitive decline

ARIC Manuscript Proposal (#3686) (Liu): Mid-life Social Engagement and Risk of Post-Stroke Dementia

ARIC Manuscript Proposal (#2466) (Gottesman): The ARIC-PET Amyloid Imaging Study: Differences in Brain amyloid deposition by Age, Race, Sex and ApoE genotype

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* __2009.29, 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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