ARIC Manuscript Proposal #4080

PC Reviewed: 7/12/22 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Association Between Mid-Life Social Factors and Estimated Late-Life Amyloid Burden: the Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group:

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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 July 12th ARIC Publications committee meeting. Analysis and manuscript to be written in 4-6 months pending approval.

4. Rationale:

Cognitive reserve remains a key concept in Alzheimer's disease (AD) research as we strive to elucidate how certain compensatory mechanisms allow some aging individuals to maintain normal cognitive function despite pathological disease burden.[1,2] Factors such as level and quality of education, intelligence, engagement in complex occupations, physical exercise, and cognitively stimulating activities, have been identified as significant features that underlie cognitive reserve.[3,4] In individuals with "high" cognitive reserve, it has been shown that the onset and diagnosis of dementia are often delayed due to enduring cognitive function.[3]

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 in older adults can have on cognition, mortality rates, and general well-being.[5-8] Two such studies were previously conducted in the Atherosclerosis Risk in Communities (ARIC) Study cohort. A recent study by Liu et al. (under review) examined the relationship between social factors and cognition and reported lower baseline cognitive function in individuals who were more socially isolated and/or had lower perceived social support.[8] What remains less clear is whether social engagement in mid-life impacts the neurobiological underpinnings of AD in later life. Understanding this relationship between mid-life social factors and later life outcomes is significant as it could provide promising targets for AD and dementia intervention.[6,8,9]

A few studies have provided initial evidence that factors pertaining to cognitive reserve may not impact the biological basis of AD and dementia. For instance, both the study by Liu et al. (under review) and another study conducted in the ARIC cohort by Gottesman and colleagues showed that social support and education, respectively, did not alter the rate of cognitive decline.[8,10] An ARIC study by Rawlings et al. showed years of education was strongly associated with late-life cognition, but not with amyloid-beta (Aβ) accumulation as measured on amyloid positron emission tomography (PET).[11]

In addition to studies using the ARIC cohort, studies using the Harvard Aging Brain Study (HAB) cohort have also examined the relationship between social factors and Aβ accumulation. However, the HAB cohort does not assess mid-life factors as it consists exclusively of cognitively normal older adults (majority age > 65 years, 81.3% White) and the results have been mixed.[12] One such study examining social engagement and subsequent cognitive decline in 217 participants in the HAB cohort found the relationship between social engagement and cognitive decline was not modified by Aβ burden.[5] Interestingly, another study looking at a smaller subset of this cohort (n = 79) found a significant association between self-perceived loneliness and Aβ burden as measured via Pittsburgh Compound B (PiB) PET.[13]

Paired together, these previous ARIC studies examining mid-life measures of cognitive reserve in conjunction with HAB studies measuring social factors and Aβ burden in late-life have formed the basis of the present study. Of further interest to us and the premise of the present study is previous ARIC studies that have examined the relationship of mid-life vascular risk factors with the prevalence of dementia in late-life and shown strong associations.[14,15] The goal of this study will be to examine how mid-life measures of social isolation and social support are related to Aβ burden in later life.

We will further examine how this relationship may vary based upon both race and sex. Previous ARIC studies looking at race and sex differences in amyloid burden have shown higher amyloid retention in Black participants (when compared to White participants) and in women (when compared to men).[16,17] Likewise, the recent study by Liu et al. (under review) also examined race and sex differences in social factors and reported higher levels of social isolation and lower levels of social support in Black participants (when compared to White participants) and men (when compared to women).[8] Altogether, the interaction between these different factors (social factors and amyloid burden in relation to race and sex) remains unclear and is something to be addressed in the present study.

Finally, our primary outcome measure for the above analyses will be amyloid burden in the global cortical region. However, we will also examine amyloid burden in specified cortical regions. We expect to see regional differences in amyloid uptake (as measured by standard uptake value ratio (SUVR)), specifically in the anterior cingulate, which previous studies have shown is strongly involved in evaluations and feelings surrounding social interactions.[18,19] Meanwhile, the relationship between social factors and amyloid accumulation has not been explicitly examined.

5. Main Hypothesis/Study Questions:

The aim of this study will be to determine whether mid-life measures of social isolation and social support are independently associated with amyloid burden roughly 20-years later (ARIC visit 2 to ARIC visit 5). We will also explore how these relationships are modified by demographic factors such as race (Black, White) and sex.

Hypothesis #1: The amount and quality of social isolation and support in midlife will not be associated with global cortical amyloid burden in later life.

The reason we do not expect to see a direct association is because we do not think these social factors will directly impact the process of amyloid accumulation and late-life amyloid burden. If we were to see an association between social factors and global cortical amyloid burden, we would further explore whether this relationship is mediated by other lifestyle and vascular factors.

Hypothesis #2: High social isolation and low social support will be associated with greater amyloid burden in Black participants and in women.

Hypothesis #3 (Exploratory): High social isolation and low social support will be associated with greater amyloid burden in the anterior cingulate in late-life.

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. At visit 2, the age of participants was 47 - 67 years old. Florbetapir PET data will come from ARIC visit 5 (2011 – 2013).

Participant inclusion/exclusion: All ARIC-PET participants without dementia will be eligible for inclusion. Participants who are nonwhite or nonblack or who have missing social isolation/social support data will be excluded.

Independent variables:

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 categories for interpretation: ≤20= isolated; 21-25= high risk for isolation; 26-30=moderate risk for isolation; ≥31= low risk for isolation.[20,21]

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.[22,23] Scores will be distributed into the following categories for interpretation: ≤16 = lack of support; 17 – 23 = low social support; 24-31 = moderate social support; ≥ 32 high social support.

Outcome: Standardized uptake volume ratio (SUVR) as measured by ARIC-PET in the global cortical 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 primary outcome measure for analysis of amyloid PET. For exploratory purposes (see Hypothesis #3), we will examine the SUVR of each cortical region. Due to skewedness, the SUVR for the global cortical region and individual cortical regions will be evaluated as binary variables based on a hypothetical cut-point (SUVR = 1.2) that has been established in prior literature. Other commonly used cut-points (1.11 and 1.10) will be explored in sensitivity analyses.[16]

Other variables: We will include demographic variables such as race, sex, education, age, and APOE 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, diabetes, body mass index (BMI), hypertension, and history of coronary heart disease and/or stroke. Additional covariates that will be taken into consideration are work/employment status and occupational complexity as measured by the Nam-Powers-Boyd composite score.[24]

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. Given that ARIC-PET participants only represent a small portion of all participants that had social measures assessed at visit 2, we will also examine if any differences in social factors exist between the subset of participants used in this study in comparison to the larger sample used at visit 2. Next, we will use logistic regression to examine the independent association of both social isolation and social support (as categorical measures) with elevated SUVR of the global cortical region. We will also conduct logistic regression models examining the independent association of social isolation and social support with elevated SUVR of the anterior cingulate.

Model 1 will be adjusted for age, sex, race, education, and APOE status.

Model 2 will include adjustment for the above covariates in addition to work/employment status and occupational complexity.

Model 3 will include adjustment for the mentioned variables in addition to smoking status, hypertension, diabetes, and history of coronary heart disease and/or stroke.

Model 4 will be adjusted for the mentioned variables in addition to BMI to see if obesity (BMI > 30) further impacts the relationship between social factors and amyloid burden.

Lastly, analyses will be stratified by race and sex.

Sensitivity analysis: We will also restrict analyses to those with normal cognition (excluding MCI) and no APOE e4 alleles.

Challenges and/or Limitations:

- Selection bias of who has PET taken at visit 5 may limit generalizability of findings (additional comparison of social factors in ARIC-PET participants and everyone with social factors measured at visit 2 will be conducted to best understand if/what selection bias exists)
- Limited power in race/sex analyses
- Residual confounding factors will be hard to discern
- Social factors only measured at visit 2 – unclear how these factors may change over time

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/aricproposals/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 (#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 (#3042) (Rawlings): Association of midlife cognition, cognitive decline and education with late-life cerebral amyloid deposition

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.
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 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.
Understood.

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