

ARIC Manuscript Proposal #3513

PC Reviewed: 11/12/19
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Social Isolation, Social Support, and the Risk of Incident Dementia and MCI: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Social Isolation and Dementia

2. Writing Group:

Writing group members: Albert C. Liu, MD, MPH (first author); Rebecca F. Gottesman, MD, PhD (senior author); Alden L. Gross, PhD; ; Pamela L. Lutsey, PhD MPH; Keenan A. Walker, PhD; Renee C. Groechel, PHD; others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _ACL_ **[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 (this must be an ARIC investigator).

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3. Timeline:

Preliminary analysis to be completed by: Dec 31, 2019

Final analysis to be completed by: Jan 31, 2020

Initial draft of manuscript to be completed by: Feb 28, 2019

Manuscript to be submitted for publication by: Apr 30, 2019

4. Rationale:

Dementia is one of the major concerns in our increasing aging population. The Atherosclerosis Risk in Communities Study (ARIC) previously demonstrated that the prevalence of dementia and

mild cognitive impairment (MCI) was 9% and 21%, respectively, at ARIC visit 5, which was similar to the prevalence found in other populations.¹

The social environment has both psychological and physiological effects on human health. The effect of “enriched environment” on cognitive function in experimental animals was reported as early as the late 1940s.² In the 1990s, the MacArthur Studies of Successful Aging³, among other studies on cognitive aging showed that “emotional support” and “social ties” are associated with longitudinal maintenance of cognitive function.

Recent epidemiological studies had also shown associations between social environment and cognitive impairment and dementia incidence. Grande et al showed that living alone was associated with higher risk of incident dementia for MCI patients.⁴ Rawtaer et al also showed that living alone was associated with higher risk of incident dementia, and that being married could be protective of incident dementia.⁵ Saito et al showed that being married, exchanging support with family members, having contact with friends, participating community groups, and engaging in paid work were associated with lower risk of incident dementia.⁶ Riccardo et al showed that increased social engagement was associated with lower risk of incident dementia, higher baseline cognitive function, but no significant effect on the rate of cognitive decline.⁷

The underlying mechanism of the effect of social environment on dementia is largely unknown; it was proposed by some to be mediated through emotional stress or systematic inflammatory burden.⁸⁻¹⁰

5. Main Hypothesis/Study Questions:

The aim of this study is to determine whether midlife social isolation and perceived social support are associated with long-term incident dementia and MCI independent of other major risk factors for dementia and MCI. We will also explore whether the magnitude of these relations differs by sex and race.

Hypothesis: More socially isolated individuals and individuals with lower perceived social support at midlife will be at higher risk of developing dementia or MCI at older ages.

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: Prospective cohort study. The baseline of our analyses will be ARIC visit 2 (1990-1992), when social isolation was measured. The end of follow-up will be ARIC visit 6 (2016-2017).

Inclusion/Exclusion: We will exclude those with prevalent dementia at visit 2.

Outcome variables: Incident dementia and MCI. ¹¹⁻¹³

Incident Dementia between Visit 2 and Visit 5: Dementia occurring before Visit 5 was ascertained at three levels. Consistent with the dementia classification after Visit 5, the current analysis will use dementia classified in person (level 1), using Telephone Interview for Cognitive Status–Modified (TICSm, level 2), and using ICD-9 hospital discharge codes (290.0, 290.1, 290.2, 290.3, 290.4, 290.9, 294.1, 294.2, 294.8, 294.9, 331.0, 331.1, 331.2, 331.8, 331.9) and

death certificates (level 3).

Incident Dementia between Visit 5 and Visit 6: Dementia will be defined using both the information from the full Visit 6 examination with expert committee diagnosis and information captured in annual follow-up (AFU) interviews using the Six Item Screener (SIS) and the Ascertain Dementia 8-item Informant Questionnaire (AD8). Date of dementia onset will be captured using the SIS and AD8, and dementia diagnosis will be confirmed at Visit 6 for those who attend Visit 6. Participants who attended Visit 5, but not Visit 6, and have SIS and AD8 information available from the AFU will also be included. For participants who did not attend Visit 6, the SIS, AD8, hospital discharge codes, and death certificates will be used to define dementia diagnosis and date of onset.

MCI between Visit 5 and Visit 6: MCI was adjudicated at visits 5 and 6 with similar methods, but cannot be adjudicated for non-attendees, and our ability to identify time of onset of MCI is limited.

Exposure 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. The score is frequently interpreted as follows: <20= isolated; 21-25= high risk for isolation; 26-30=moderate risk for isolation; ≥ 31 = low risk for isolation.^{14,15}

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 in the scale; (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.^{16,17}

Mediator variables: Vital exhaustion and inflammatory biomarkers.

Vital exhaustion will be calculated by using the 21-item Maastricht Questionnaire (visit 2). The total score is an equally weighted sum, with scores ranging from 0-42; the higher the score, the more exhausted. A score of ≥ 14 will be used for present vital exhaustion, which is the suggested cut-off point for a clinical diagnosis; its Cronbach alpha has been reported as 0.89.^{18,19}

Inflammation will be evaluated by serum CRP level. The average of visit 2 and visit 4 will be used as an indicator of midlife inflammation.

Covariates:

Demographic factors: age, sex, race/geographic center

Socioeconomic and lifestyle factors: education, smoking, alcohol consumption, physical activity, body mass index (BMI)

Genetic factors: APOE4 genotype

Statistical analysis: Descriptive statistics will be generated for demographic variables and for select covariates. We will use multivariable adjusted Cox proportional hazard regression to estimate the hazard ratios (HR) and 95% confidence interval (95% CI) between different levels of social isolation and social support and incident dementia (since visit 4). We will also use multivariable adjusted logistic regression to estimate the odds ratios (OR) and 95% confidence interval (95%

CI) between different levels of social isolation and social support and incident dementia (by visit 6) and multivariable adjusted multinomial logistic regression to estimate the ORs and 95% CIs between different levels of social isolation and social support and incident of MCI and dementia, in the same model.

Model 1: will adjust for age and center, stratified by sex and race

Model 2: will additionally adjust for APOE 4, education, BMI, smoking status, current alcohol use, and physical activity

Model 3: will additionally adjust for marital status

Model 4: will additionally adjust for vital exhaustion or serum CRP level (to assess the mediation effects)

Sensitivity analysis:

We will exclude participants whose global cognitive function falls in the lowest 5th percentile at baseline (visit 2).

We will utilize inverse probability weighting (IPW) method to address the potential differential loss of dementia/MCI cases due to loss of follow-up.

7.a. Will the data be used for non-CVD analysis in this manuscript? _V_ Yes ____ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? _V_ Yes ____ No

(This 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? _V_ Yes ____ No

We will include APOE4 genotype status on our Model 4 for the participants included.

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”? _V_ 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.csc.unc.edu/aric/mantrack/maintain/search/dtSearch.html>

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

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ☒ Yes ☐ No

11.b. If yes, is the proposal

- ☐ **A. primarily the result of an ancillary study (list number* _____)**
☐ **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 at <https://www2.csc.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.csc.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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