1.a. Full Title: Social Isolation, Social Support, and Cognitive Decline: The Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group:
Writing group members: Albert C. Liu, MD, MPH (first author) Alden L. Gross, PhD (senior author); Rebecca F. Gottesman, MD, PhD; Silvia Koton, PhD; Pamela L. Lutsey, PhD MPH; Keenan A. Walker, 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]

First author: Albert C. Liu, MD, MPH
Address: 101 N Wolfe St., Unit 285
Baltimore, MD 21231

Phone: 657-272-3241 Fax:
E-mail: Albert.Liu@jhu.edu

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: Alden L. Gross, PhD
Address: 2024 E. Monument Street, Baltimore, Maryland 21205

Phone: 443-287-7196 Fax:
E-mail: agross14@jhu.edu

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:
Cognitive decline and dementia are major concerns in our increasing aging population. The Atherosclerosis Risk in Communities Study (ARIC), for example, 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 affects human health in both psychological and physiological aspects. 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.

It was proposed that dementia might be caused by age-related decline in cognitive reserve and the trajectories might be individual-specific⁴,⁵. Recent cross-sectional studies have shown associations between social environment and cognitive function or age-related cognitive decline. Kimura et al showed that people who engaged in activities with friends and went out frequently had lower risk of cognitive decline over 3 years of follow-up.⁶ Wilson et al showed that a higher frequency of negative social interactions is associated with higher risk of incident MCI in 529 older people followed up to 4.8 years in the Rush Memory and Aging Project.⁷ Marioni et al showed that increased social engagement was associated with lower risk of incident dementia, higher baseline cognitive function, but had no significant effect on the rate of cognitive decline over 20-years of follow-up.⁸ A social network study by Li et al also showed that higher network size, volume of contact, and more complex network make up were associated with higher cognitive function.⁹ Kats et al. has shown that in the ARIC cohort, higher mid-life social support was associated with greater cognitive function cross-sectionally, but was not associated with 20-year change in global cognition.¹⁰ However, the underlying mechanism of the effect of social environment on cognitive decline is largely unknown; it is proposed by some to be mediated through emotional stress or systematic inflammatory burden.¹¹-¹⁴

5. Main Hypothesis/Study Questions:
The aim of this study is to determine whether midlife social isolation and perceived social support are independently associated with cognitive change over a 25-year follow up (ARIC visit 2 to ARIC visit 6). We will also explore whether the magnitude of these relationships differs by sex and race. Hypothesis #1: More socially isolated individuals and individuals with lower perceived social support at midlife will have a greater decline in cognitive function at older ages. Hypothesis #2: The long-term impact of social isolation and lower social support on cognition will differ on the basis of sex and race.

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 and when the first cognitive assessment took place. The end of follow-up will be ARIC visit 6 (2016-2017).

Inclusion/Exclusion: We will exclude those with prevalent dementia, at visit 2 and participants missing relevant social isolation information.
Outcome variables:
Cognitive function will be analyzed using a global cognitive factor score of three cognitive function tests: Delayed Word Recall Test (DWR), Digit Symbol Substitution Test (DSS), and Word Fluency Test (WFT). We will use cognitive data measured at ARIC Visit 2 (the baseline for the present analysis) to Visit 6.

Exposure variables: (from visit 2; self-reported).
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. Continuous score as well as categorical score will be evaluated.
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.

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. 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: (from visit 2)
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. Our primary outcome will be a global cognitive factor score, calculated as the average of the Z-scores of aforementioned 3 cognitive function tests at each study visit and standardized using the visit 2 global Z-score mean and standard deviation (SD). We will use multivariable adjusted linear mixed effects models with random intercepts and random slopes to determine the cross-sectional and longitudinal (25-year change) association of social isolation and perceived social support with cognitive outcomes (the global Z-score, and the individual Z-scores for DWR, DSS, WFT).

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 perform both a complete case analysis, as well as use multiple imputations by chained equations (MICE) methods to account for missing data, imputing for both missing covariates and outcomes (for those who did not return for visit 5).

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

11.b. If yes, is the proposal

   ___ A. primarily the result of an ancillary study (list number* __________)
   _X__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* ____2008.06

*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.

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References