ARIC Publication Admin Use Only: ARIC Manuscript Proposal # 4357

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1.a. Full Title: Social networks, social support, and association with Proteomic Aging Clocks: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Social support and Aging Clock

2. Writing Group [please provide a middle name if available; EX: Adam Lee Williams]:
Writing group members: Pamela L. Lutsey, Anna Prizment, Shuo Wang, Susan Everson-Rose, Sanaz Sedaghat, Kevin Sullivan, Ganga Bey, Anna Kucharska-Newton and other interested investigators

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

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3. Timeline: Data analysis to being immediately, anticipated draft completion Winter 2023

4. Rationale: Average life expectancy of the population is increasing worldwide, especially in developed countries, and burden of death due to aging-related diseases is increasing. Healthy aging, which is a continuous process of optimizing opportunities to maintain and improve physical and mental health, independence, and quality of life throughout the life course[1], is an area of priority for individuals and the broader society. Chronological age relates to the length of time a person has lived. People, however, age differently, and the construct of biological age has been developed as an indicator of how old an individual's body and cells are based on various factors, such as genetics, lifestyle, and environment. Biological age is correlated with chronological age[2], but accruing research reports that in the absence of disease biological age "better predicts functional capacity at later ages than chronological age."[3] In recent years, aging clocks have been developed to define an individual's biological age from a set of molecules, such as DNA methylation and proteomics biomarkers.

Aging clocks make it possible to provide specific information about how old an individual is biologically, independent of chronological age[4]. Several aging clocks have been created. The most recognized is the epigenetic clock[5,6], based on a set of biomarkers based on DNA methylation in blood and/or tissue, that has been reported to predict health outcomes such as cardiovascular disease, cancer, and mortality. However, the underlying mechanisms of age-related changes in DNA methylation sites are unclear. Recently, there is increasing interest in developing aging clocks from proteomic biomarkers. Proteomic biomarkers are promising because they, as intermediate phenotypes, may be a more accurate indicator of aging-related pathologies[7].

Social support is associated with positive health outcomes, while social isolation has been linked to adverse health.[8–11]Studies using ARIC data have reported associations of social isolation and low social support with increased risk of heart disease[12] and stroke[13]. Although it is not entirely clear how social networks and social support are associated with cardiovascular disease and mortality, it has been speculated that psychological stress related to social isolation may affect the cardiovascular system through mental and physical changes[14], and that people with greater social networks and support may be more likely to engage in behaviors that promote health[15]. Greater social contacts may be associated with reduced biological age via psychophysical factors, which in turn may prevent cardiovascular disease, dementia, etc. Very few studies have explored associations between social support and biological aging. In one of the few studies that exists, conducted among U.S. children, childhood police encounters (and loneliness and community isolation resulted from the encounter) was associated with epigenetic age acceleration adulthood[16]. Association of social participation and isolation after midlife with biological age has not yet been reported, and whether social isolation in midlife negatively affects epigenetic aging acceleration, or whether midlife adversity may also enhance resilience to biological aging, is not known. Thus, the relationship between social support in midlife and biological aging needs to be examined in more detail. Therefore, using ARIC data we will test the hypotheses that larger social networks and greater social support are associated with lower biological age (estimated using proteomic aging clocks (PACs)) in midlife. We also hypothesize that the association will be stronger for women compared to men, since the association between social isolation and all-cause mortality in the US is stronger for women compared to men[17] and

for older compared to younger age groups. We also check interaction of other characteristics such as race or SES. In exploratory analyses we will also evaluate social networks and support and change in PACs from midlife to later life..

5. Main Hypothesis/Study Questions

: *Primary Hypothesis*

- People who are less socially isolated (10-item Lubben Social Network Scale, 4 levels) and have more social support (a modified version of the Interpersonal Support Evaluation List-Short Form, 4 levels) will have a younger biological age (estimated using PACs) than those who are more socially isolated and have lesser social support, respectively.

Secondary Hypotheses

- The associations between social networks and support with PACs will be stronger in older compared to younger adults (we will use median age for cutoff point), and in men compared to women.

Exploratory Hypothesis

-People with larger social networks and more social support will experience less biological aging from midlife to late life than those with lesser social networks and support, respectively.

6. Design and analysis

a) study design

Primary analysis: Cross sectional study using visit 2 (1990-1992) data, when social support and isolation was measured, and when the SomaScan assay was conducted.
Exploratory prospective analysis: longitudinal study of change using SomaScan data fromvisit 2 (1990-1992) and Visit 5 (2011-2013) data.

b) inclusion/exclusion

We include those who have the measurement of proteins at Visit 2 using the SomaScan assay and information on social networks and support. Per standard ARIC practice, due to small numbers we will exclude participants who self-reported a race/ethnicity other than white or Black, as well as Blacks participants from the MN and MD study centers.

c) outcome and other variables of interest with specific reference to the time of their collection

Exposures: Social networks will be calculated by using **the Lubben Social Network Scale** [18,19]. 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.

The Interpersonal Support Evaluation List-Short Form (ISEL-SF) will also be used to calculate perceived social support[20]. This 16-item scale was constructed by the original ARIC investigators from the original 40-item full scale[21], 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. The score is interpreted as follows: the score as follows: ≤16=lack of social

support; 17–23=low social support; 24–31=moderate social support; ≥32=high social support.

Outcome: For the biological age assessment, we will employ ARIC PACs, which were developed in a previous paper[22]. In brief, using the SomaLogic platform there was measurement of over 5000 plasma proteins in frozen plasma samples collected during Visit 2 (1990-1992, N=12,589) and Visit 5 (2011-2013, N=6538). The Bland-Altman coefficient of variation (CVBA) for split samples was 6% for Visit 2 and 7% for Visit 5. The proteins comprising the ARIC proteomic aging clock "ARICPAC"were created during Visit 2 (midlife) and updated during Visit 5 (late-life) [22]. Using ARICPAC from visit 2, Wang et al. calculated age acceleration, the deviation of PAC from chronological age, for each PAC. Age acceleration for each PAC will be calculated as residuals after regressing PAC on age. This variables will be used as a continuous variable and/or likely as a categorical variable as well (e.g., define the first quartile (greatest acceleration) versus upper 3quartiles, or an age acceleration of -2.0 or lower as indicative of younger biological age). Also, in exploratory analyses we will evaluate the change of age acceleration between the midlife and late-life ARICPACs. We will carefully evaluate the distributions of the PAC and their difference to guide decisions regarding how to model change.

***Potential effect modifiers and/or mediators*:** Race, sex, and age groups (median split of chronological age).

Covariates: chronological age, race, gender, marital status, lifestyle behaviors (smoking status, alcohol use, exercise, sleep, BMI), hypertension, diabetes, dyslipidemia, socioeconomic status (education, income, and occupation).

d) summary of data analysis

Characteristics of participants will be described using means and proportions stratified by the strata of social networks and social support. Logistic analysis (cross-sectional, Visit 2 PAC for outcome) Linear model will be used when PACs are modeled continuously. Analyses models are as follows.

Model 1 adjusted for sex and race-center,

Model 2a additionally adjusted for socioeconomic status, marital status, and

Model 2b additionally eGFR (to evaluate the influence of kidney function, which is known to influence proteomic markers, on our findings).

Model 3 (mediation model) further adjusted for lifestyle related factors (smoking status, alcohol use, sleep quality, and physical activity, and BMI).

We will conduct the same analysis stratified by Race, sex, and age groups (median age as a cut-point), and examine whether those factors modified the relationships of social networks and support with biological age, by including cross-product terms in the models.

As an exploratory analysis, we will also evaluate change of the midlife and late-life ARICPACs as an outcome.

In sensitivity analyses we will exclude participants with evidence of kidney disease.

e) Any anticipated methodologic limitations or challenges if present

f) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed. ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded,

and Proteomics/Somalogic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ☐ **Yes** ☒ **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 is distributed to ARIC PIs annually, 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? ☐ **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"? ☐ **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: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC WebsiteàPublicationsàProposal Search]

☒ 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)?

PUBLISHED

2827 Roetker NS, Pankow JS, Bressler J, Morrison AC, Boerwinkle E. Prospective Study of Epigenetic Age Acceleration and Incidence of Cardiovascular Disease Outcomes in the ARIC Study (Atherosclerosis Risk in Communities). *Circ Genomic Precis Med*. 2018;11(3):e001937. doi:10.1161/CIRCGEN.117.001937

2337 Bressler J, Marioni RE, Walker RM, et al. Epigenetic Age Acceleration and Cognitive Function in African American Adults in Midlife: The Atherosclerosis Risk in Communities Study. *J Gerontol A Biol Sci Med Sci*. 2020;75(3):473-480. doi:10.1093/gerona/glz245

3135 Garg PK, Claxton JS, Soliman EZ, et al. Associations of anger, vital exhaustion, anti-depressant use, and poor social ties with incident atrial fibrillation: The Atherosclerosis Risk in Communities Study. *Eur J Prev Cardiol*. 2021;28(6):633-640. doi:10.1177/2047487319897163

2139 Nagayoshi M, Everson-Rose SA, Iso H, Mosley TH, Rose KM, Lutsey PL. Social Network, Social Support, and Risk of Incident Stroke: The Atherosclerosis Risk in Communities Study. *Stroke J Cereb Circ*. 2014;45(10):2868-2873. doi:10.1161/STROKEAHA.114.005815

2211 Kats D, Patel MD, Palta P, et al. Social support and cognition in a community-based cohort: the Atherosclerosis Risk in Communities (ARIC) study. *Age Ageing*. 2016;45(4):475-480. doi:10.1093/ageing/afw060

1580 Cené CW, Loehr L, Lin FC, et al. Social isolation, vital exhaustion, and incident heart failure: findings from the Atherosclerosis Risk in Communities Study. *Eur J Heart Fail*. 2012;14(7):748-753. doi:10.1093/eurjhf/hfs064

920 Wattanakit K, Williams JE, Schreiner PJ, Hirsch AT, Folsom AR. Association of anger proneness, depression and low social support with peripheral arterial disease: the Atherosclerosis Risk in Communities Study. *Vasc Med Lond Engl*. 2005;10(3):199-206. doi:10.1191/1358863x05vm622oa

3434 Honda Y, Mok Y, Mathews L, et al. Psychosocial factors and subsequent risk of hospitalizations with peripheral artery disease: The Atherosclerosis Risk in Communities (ARIC) Study. *Atherosclerosis*. 2021;329:36-43. doi:10.1016/j.atherosclerosis.2021.04.020

#3739 Wang AS, Rao Z, Cao R, et al. Development and Characterization of Proteomic Aging Clocks in the Atherosclerosis Risk in Communities (ARIC) Study. *MedRxiv Prepr Serv Health Sci*. Published online September 2023:2023.09.06.23295174. doi:10.1101/2023.09.06.23295174

Not yet published

3513 Liu, AC. Social Isolation, Social Support, and the Risk of Incident Dementia and MCI: The Atherosclerosis Risk in Communities (ARIC) Study

3512 Liu, AC. Social Isolation, Social Support, and Cognitive Decline: The Atherosclerosis Risk in Communities (ARIC) Studyb.

192 Withdrawn. Social ties-age CHS and ARIC (M) McGovern, PG

692 Mosley, TH. Dimensions of social support and risk of CHD events, carotid arterial wall thickness, and mortality

691 Mosley, TH. The moderating effects of social support on the association between negative emotions and CHD events, carotid arterial wall thickness, and mortality

4101 Prizment, AE. Proteomic aging clock and brain structure, cognitive decline and the risk of dementia: Atherosclerosis Risk in Community Study

4094 Casanova, R. Investigating relationships between an MRI measure of brain aging with proteomics and cognition

4058 Jewett, P. Proteomic aging clock and quality of life

4227 Karra, P. Metabolic obesity phenotypes, age acceleration and cancer risk

4153 Peter, KM. Associations of social relationships and heart failure progression in the Atherosclerosis Risk in Communities (ARIC) Study and Jackson Heart Study (JHS) shared cohort

4152 Peter, KM. Social relationships and self-rated health in the Atherosclerosis Risk in Communities (ARIC) Study and Jackson Heart Study (JHS) shared cohort

4131 Peter, KM. Associations of psychosocial factors and cardiovascular health measured by Life's Essential 8: the Atherosclerosis Risk in Communities (ARIC) Study

#4148 Chen, H. Poor Olfaction and Epigenetic Markers of Age Acceleration

4081 Wang, S. Proteomic age acceleration and dementia and frailty in cancer survivors: The Atherosclerosis Risk in Communities Study

3848 Wang, S. Proteomic age acceleration and mortality in cancer survivors: The Atherosclerosis Risk in Communities Study

3739 Wang, S. Proteomic age acceleration and cancer incidence: The Atherosclerosis Risk in Communities Study

3658 Roberts, JD. Evaluation of Epigenetic Age Acceleration as a Risk Factor for Incident Atrial Fibrillation

2965 Hibler, E. Physical activity and Epigenetic Age Acceleration

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* _2021.06_)**

☐ **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://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC WebsiteàAncillary StudiesàApproved 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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC WebsiteàPublicationsàPublication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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22. Wang AS, Rao Z, Cao R, et al. Development and Characterization of Proteomic Aging Clocks in the Atherosclerosis Risk in Communities (ARIC) Study. *MedRxiv Prepr Serv Health Sci*. Published online September 2023:2023.09.06.23295174. doi:10.1101/2023.09.06.23295174

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