Social networks, social support, and association with Age Acceleration of Proteomic Aging Clocks :The Atherosclerosis Risk in Communities

Eri Eguchi[1,2], Anna Prizment[3,4], Shuo Wang[5], Sanaz Sedaghat[1], Mako Nagayoshi[6], Susan Everson-Rose[7], Kevin Sullivan[8], Ganga Bay[8], Anna Kucharska-Newton[9], Weihua Guan[10], Pamela L Lutsey[1]

1. Division of Epidemiology & Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA
2. Department of Epidemiology, Fukushima Medical University School of Medicine, Fukushima, Japan
3. Division of Hematology, Oncology and Transplantation, Medical School, University of Minnesota, Minneapolis, MN, USA.
4. Masonic Cancer Center, University of Minnesota, Minneapolis, Minnesota, USA.
5. Department of Laboratory Medicine and Pathology, Medical School, University of Minnesota, Minneapolis, MN, USA.
6. Department of Preventive Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan
7. Department of Medicine, University of Minnesota Medical School, Minneapolis, MN, USA.
8. Department of Surgery, University of Washington, Seattle, Washington, USA.
9. Department of Epidemiology College of Public Health, University of Kentucky, Lexington, KY, United States.
10. Division of Biostatistics and Health Data Science, School of Public Health, University of Minnesota, Minneapolis, MN.

background

- Aging clocks have been developed
- The epigenetic clock (Hannum G et al, *Mol Cell.* 2013, Horvath S et al, *Genome Biol. 2013*), is the most recognized, based on a set of biomarkers of DNA methylation in blood and/or tissue.
- Mechanisms of age-related changes in DNA methylation sites are unclear.
- 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 (Argentieri MA et al, Europe PMC, 2023)

background

- Social network and social support is associated with positive health outcomes(Freak-Poli R et al, *BMC Geriatr, 2021,* Golaszewski NM et al, *JAMA Netw Open,* 2021, Freak-Poli R et al, Health Promot J Austr, 2022, Teshale AB et al, *Arch Gerontol Geriatr, 2023)*
- ARIC (The Atherosclerosis Risk in Communities) have reported associations of social isolation and low social support with increased risk of heart disease (Cené CW et al, *Eur J Heart Fail.*2012) and stroke (Nagayoshi M et al, *Stroke J Cereb Circ* 2014).
- Greater social contacts may be associated with reduced biological age via psychophysical factors, which in turn may prevent cardiovascular disease.

Purpose

To examine the association between social network and support and age acceleration.

ARIC Overview and Timeline of Study Components

Four Study Communities

Forsyth County, NC | Jackson, MS | Minneapolis, MN | Washington County, MD

Community-Based Surveillance, 1987 - 2014

Community Data, 1987 - 2014
CHD Incidence
CHD Mortality
CHD Case Fatality

Hospital Data, 1987 - 2014
Hospitalized Heart Failure

Expanded Hospital Data, 2005-14
Decompensated HF Incidence
Chronic Stable HF Incidence
HF Medical Care
Outpatient HD (Medicare data)

EHR Events 2015

EHR Pilot 2017-2019

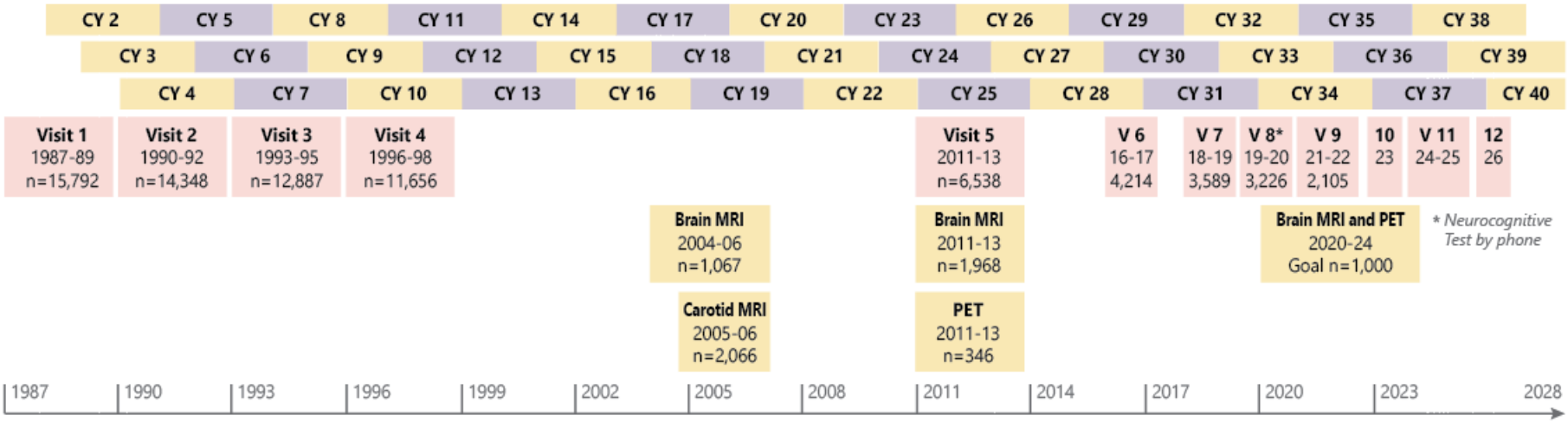
CHD = Coronary Heart Disease
HF = Heart Failure
EHR = Electronic Health Records
MI = Myocardial Infarction
CY = Contact Years

Cohort Study, 1987 - Present, with 15,792 original enrolled Participants, Annual Follow-Up Contact Years (CY), and Visits on a rotating cycle

Cohort Surveillance, 1987 - Present
Incident MI
Incident Stroke
Sudden Death

Hospital Data, 1987 - 2005
Incident Hospitalized Heart Failure

Expanded Hospital Data, 2005 - Present
Incident Decompensated HF
Incident Chronic Stable HF
Outpatient HF



Methods

Participants:

ARIC Data Visit 2 (1990-1992): 14,348 attendance

2,550 were excluded	Insufficient information about social participation and support
37 were excluded	Not white or black
42 were excluded	black participants from the MD and MN study communities

Final analytic sample of 11,719

Methods

Study design：

cross-sectional study

Methods

Measurement :

- **Social network**
  - 10-item Lubben Social Network Scale
  - (Lubben J et al, The Gerontologist, 2006).
  - It assesses the size of the participant's active social network of family, friends, and neighbors.
  - Each ranges 0-5, and total of 50.
  - Three categories were created:

    ≤25 : small social network

    26-30 : moderate social network

    ≥31 : large social network

Methods

Measurement :

- **Perceived social support**
  - 16-item Modified version of the Interpersonal Support Evaluation List-Short Form (ISEL-SF)(Payne TJ et al, *SAGE Open*. 2012).
  - This scale assesses appraisal, tangible assets, belonging, and self-esteem support.
  - Each ranges 0-3. Total of 48.
  - Three categories were created:

    ≤23 : low social support

    24-31 : moderate social support

    ≥32 : high social support

Methods

Outcome：

Age acceleration:

- Using the SomaLogic platform, there was measurement of over 5000 plasma proteins in frozen plasma samples collected during Visit 2
- “ARICPAC” and Sathyan’s PAC were created with the healthy individuals and tested in Visit 2 (Wang AS et al, *MedRxiv Prepr Serv Health Sci*. 2023).
- Age acceleration for each PAC was calculated as residuals after regressing PAC on age.
- We defined age acceleration of 2.0 years or greater as indicative of older biological age.

Methods

Analysis

1. Characteristics of participants was described using means and proportions stratified by the strata of social networks and social support.
2. Linear regression was conducted to obtain marginal mean age acceleration calculated by the midlife ARIC PAC and Sathyan's PAC according to the size of the social network and social support.
3. Logistic analysis was conducted to calculate odds ratios and 95% confidence intervals of older for age of those who have larger social network or support compared to smaller.

Analyses models are as follows:

Model 1: adjusted for age, sex and race-center

Model 1a: additionally adjusted for education and marital status

Model 2: further adjusted for smoking status, alcohol use, exercise, sleep quality, and Body Mass Index

Model 2a: additionally adjusted for eGFR

Results

Social network

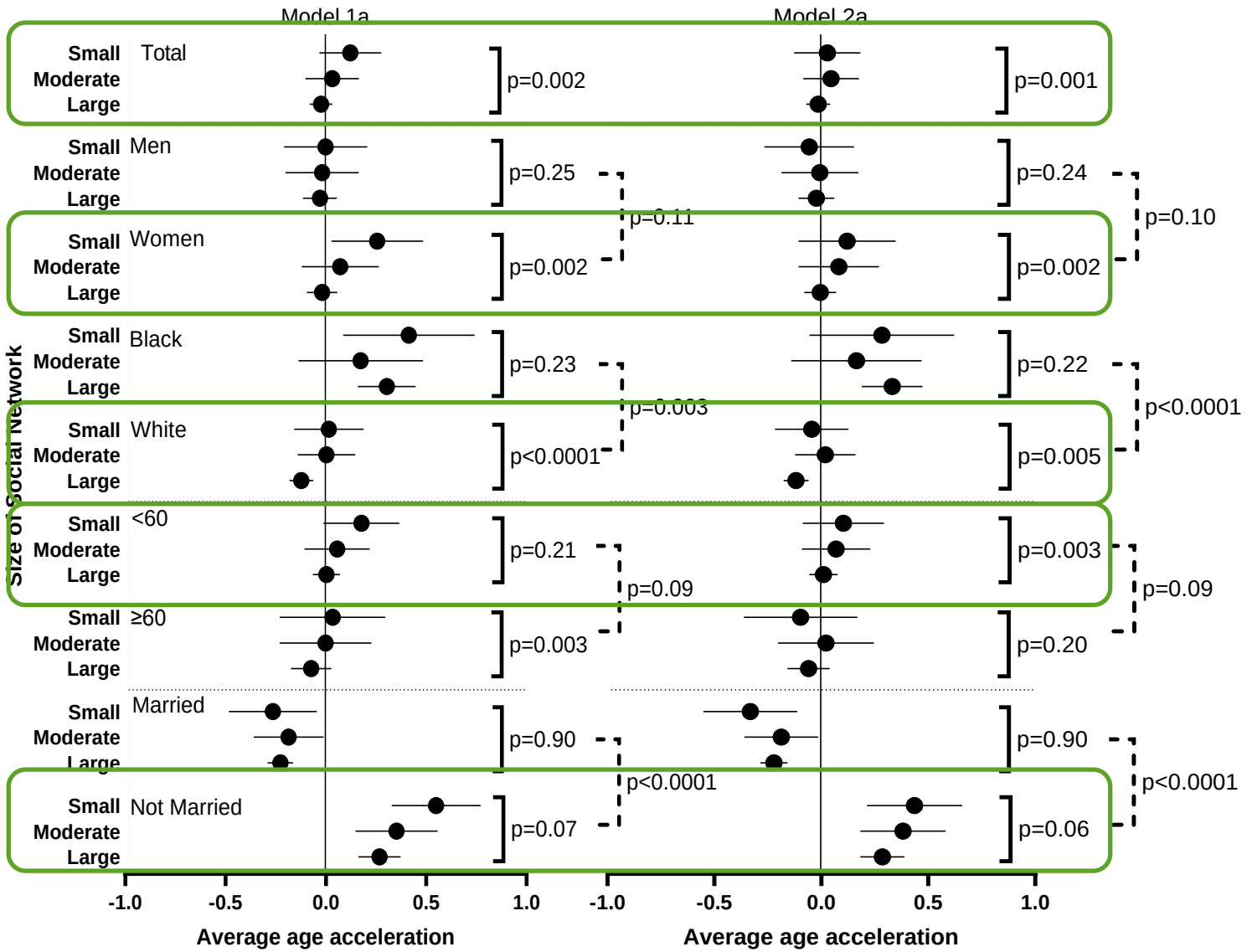
Characteristics of participants

Size of social network	Small	Moderate	Large
Social network score	≤25	26-30	≥31
N total	1216	1607	8896
Age, mean years ± SD	57.3±5.81	57.2±5.89	57.0±5.69
Male, %	52.4	49.8	42.3
Black, %	31.3	25.9	21.8
Income, %			
<$25,000	50.2	39.2	30.5
$25,000-$49,999	29.2	35.8	37.4
≥$50,000	14.8	20.2	26.6
Education, %			
Less than high school	30.6	23	20.2
High school graduate	38.5	42.1	42.5
Beyond high school	30.6	34.6	37.2
Employed, %	66	71.6	69.7
Married, %	56.3	64	80.5
Physical activity*	2.28±0.79	2.40±0.79	2.48±0.80
Current drinker, %	54.6	57.4	56.9
Current smoker, %	30.1	27.3	20.4
Trouble falling asleep, %	25.6	24.4	21.1
Wake up repeatedly during the night, %	43.3	39.8	37.8
BMI, kg/m2 ± SD	27.9±5.44	27.7±5.30	28.0±5.33
eGFR, ml/min/1.73m2 ± SD	95.6±15.8	96.4±14.3	96.8±13.7

Abbreviations: PAC - proteomic aging clock; BMI - body mass index; eGFR - estimated glomerular filtration rate.

*Physical activity was assessed using a leisure-time sprots index that ranged from 1 to 5.

Marginal mean age accelerations according to the size of social network



Model 1a: age, sex, and race-center, education, and marital status.
Model 2a: Model 1a + smoking status, alcohol use, exercise, sleep quality, body mass index, and level of eGFR

Odds ratios and 95% confidence intervals of having older aging clock (age acceleration of >2) for those with larger social network compared to smaller

Size of Social	Small	Moderate	Large	
Social network	≤25	26-30	≥31	P for trend
N total	1216	1607	8896	
Total				
Numbers*	288	347	1692	
Model 1	Reference	0.88 (0.74-1.06)	0.75 (0.65-0.87)	<0.0001
Model 1a	Reference	0.93 (0.78-1.12)	0.83 (0.72-0.96)	0.006
Model 2	Reference	0.99 (0.82-1.19)	0.88 (0.76-1.03)	0.04
Model 2a	Reference	0.99 (0.82-1.19)	0.88 (0.75-1.02)	0.03

Model 1a: age, sex, and race-center, education, and marital status.
Model 2a: Model 1a + smoking status, alcohol use, exercise, sleep quality, body mass index, and level of eGFR

Social support

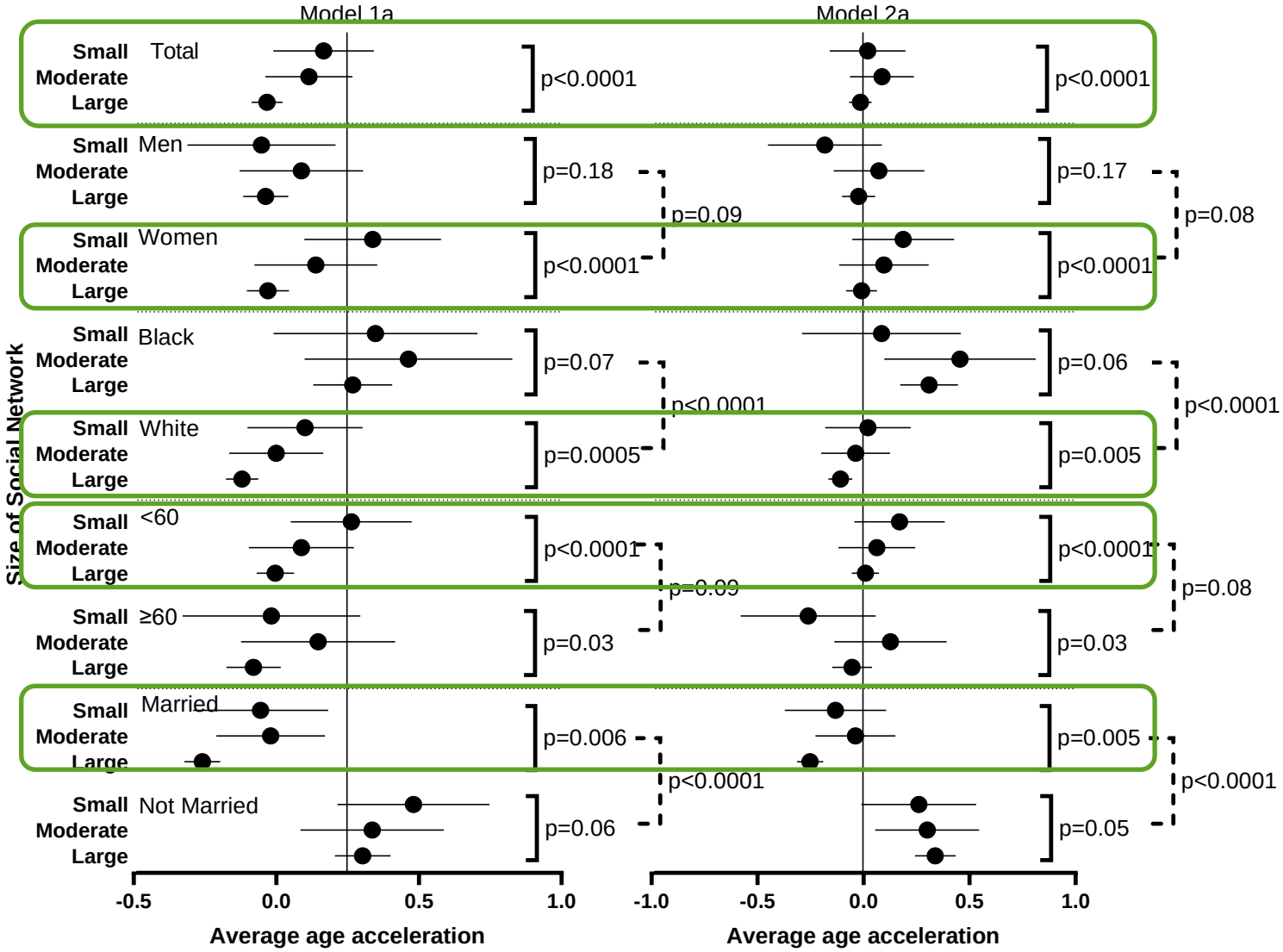
Characteristics of participants

Levels of social support	Low	Moderate	High
Social support score	≤23	24-31	≥32
N total	923	1203	9593
Age, mean years ± SD	57.1±5.90	57.1±5.69	57.1±5.72
Male, %	43.3	47.1	44.1
Black, %	34.7	25.4	22
Income, %			
<$25,000	51.8	39.5	31.3
$25,000-$49,999	28.8	34.6	37.3
≥$50,000	13.7	20.1	26.1
Education, %			
Less than high school	39	27.3	19.3
High school graduate	39.1	45.2	41.9
Beyond high school	21.6	27.4	38.7
Employed, %	61.6	68.4	70.5
Married, %	66.1	72.4	77.3
Physical activity*	2.22±0.73	2.33±0.78	2.49±0.80
Current drinker, %	48.8	54.9	57.7
Current smoker, %	31.3	28.2	20.7
Trouble falling asleep, %	37.5	29.7	19.8
Wake up repeatedly during	52.2	48	36.5
BMI, kg/m2 ± SD	28.4±0.18	28.3±5.72	27.8±5.23
eGFR, ml/min/1.73m2 ± SD	95.5±0.46	96.1±15.2	96.8±13.7

Abbreviations: PAC - proteomic aging clock; BMI - body mass index; eGFR - estimated glomerular filtration rate.

*Physical activity was assessed using a leisure-time sprots index that ranged from 1

Marginal mean age accelerations according to the size of social support



Model 1a: age, sex, and race-center, education, and marital status.
Model 2a: Model 1a + smoking status, alcohol use, exercise, sleep quality, body mass index, and level of eGFR

Odds ratios and 95% confidence intervals of having older aging clock (age acceleration of >2) for those with larger perceived social support compared to smaller

Social support levels	Low	Moderate	High	
Social support score	≤23	24-31	≥32	P for trend
N total	923	1203	9593	
Total				
Numbers*	218	258	1851	
Model 1	Reference	0.88 (0.72-1.09)	0.77 (0.66-0.91)	0.0005
Model 1a	Reference	0.96 (0.78-1.18)	0.90 (0.77-1.06)	0.18
Model 2	Reference	1.03 (0.83-1.28)	0.99 (0.83-1.18)	0.78
Model 2a	Reference	1.03 (0.83-1.28)	1.01 (0.84-1.20)	0.97

*Numbers of people who have age acceleration of >2
Model1: age, sex, and race-center
Model1a: Model1 + education and marital status
Model2: Model1a + smoking status, alcohol use, exercise, sleep quality, and BMI
Model2a: Model2 + level of eGFR

Marginal mean age accelerations calculated by Sathyan's PAC according to the size of social network

Size of Social network	Small	Moderate	Large	
Social network score	≤25	26-30	≥31	P for trend
Age acceleration				
Sathyan's PAC				
N total	1216	1607	8896	
Model 1	0.24	0.1	-0.05	0.007
Model 1a	0.19	0.09	-0.04	0.007
Model 2	0.08	0.07	-0.02	0.006
Model 2a	0.08	0.08	-0.02	0.005

Model : age, sex, and race-center
Model 1a: Model 1 + education, and marital status.
Model 2: Model 1a + smoking status, alcohol use, exercise, sleep quality, body mass index
Model 2a: Model 2 + level of eGFR

Marginal mean age accelerations calculated by Sathyan's PAC according to the levels of social support

Levels of Social support	Low	Moderate	High	
Social support score	≤23	24-31	≥32	P for trend
Age acceleration				
Sathyan's PAC				
N total	923	1203	9593	
Model 1	0.29	0.13	-0.04	0.0002
Model 1a	0.22	0.1	-0.03	0.0002
Model 2	0.09	0.1	-0.02	0.0002
Model 2a	0.07	0.09	-0.01	0.0001

Model : age, sex, and race-center
Model 1a: Model 1 + education, and marital status.
Model 2: Model 1a + smoking status, alcohol use, exercise, sleep quality, and body mass index
Model 2a: Model 2 + level of eGFR

Summary of the results

- Larger social networks and higher levels of social support were associated with smaller biological age
- The associations persisted after adjustment for social factors and lifestyle.
- The were stronger for women, White participants, adults <60 years and participants who were not married.

Discussion

- Resent study reported that social support were associated with biological age acceleration developed based on epigenetic aging clocks with 3,647 individuals

  (Rentscher KE, et al. *Brain Behav Immun*. 2023)

- It has also been reported that loneliness and isolation accelerate the age calculated by the epigenetic aging clock in adulthood

  (Das A, *Soc Sci Med*. 2022)

- The proteomic aging clock is considered to be a more accurate estimate of an individual's biological age, since the molecular phenotypes can be captured more directly compared to epigenetic aging clocks

  (Argentieri MA et al, Nat Med, 2023)

Strength

- Based on a large community-based sample of individuals while previous studies on PACs have either had small sample sizes or focused primarily on White individuals.
- The PAC we employed is also novel in that it was developed and validated using approximately 5,000 proteins evaluated through the SomaLogic platform.
- Also, we were able to adjust for a broader range of confounding factors, such as lifestyle and social factors, whereas previous studies on PAC have typically adjusted only for demographic factors.
- In addition to the ARIC PAC, we conducted a supplemental analysis using Sathyan's PAC and obtained similar results.

Furthermore, similar results were obtained in supplemental analyses excluding participants from the training set used to create the ARIC PAC. These sensitivity analyses support the robustness of our findings.

Limitation

- The social network and social support scales were self-reported and administered at a only a single point in time, which could have resulted in measurement error and misclassification.
- The possibility of protein degradation during long-term storage cannot be excluded. However, since the blood samples were frozen immediately after collection and never thawed, the possibility of degradation is low. Furthermore, no evidence of protein degradation was observed (CVBA = 6% at Visit 2).
- Although we adjusted for potential confounders, residual or unmeasured confounders may have influenced the relationship between social networks and support and biological age acceleration through other pathways.
- Aging clock was created in a relatively young population therefore the effect estimates are relatively small.
- Because this is a cross-sectional study and causality is unclear.

Conclusion

The size and level of social networks and support were inversely associated with biological age acceleration in a community-based individuals at midlife. Social engagement, in addition to risk factor control, may be beneficial to overall health.

Thank you very much