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ORIGINAL RESEARCH

OUTCOMES AND QUALITY

Association Between Social Isolation With Age-Gap Determined by Artificial Intelligence-Enabled Electrocardiography

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ABSTRACT

BACKGROUND Loneliness and social isolation are associated with poor health outcomes such as an increased risk of cardiovascular diseases.

OBJECTIVES The authors aimed to explore the association between social isolation with biological aging which was determined by artificial intelligence-enabled electrocardiography (AI-ECG) as well as the risk of all-cause mortality.

METHODS The study included adults aged ≥18 years seen at Mayo Clinic from 2019 to 2022 who respond to a survey for social isolation assessment and had a 12-lead ECG within 1 year of completing the questionnaire. Biological age was determined from ECGs using a previously developed and validated convolutional neural network (AI-ECG age). Age-Gap was defined as AI-ECG age minus chronological age, where positive values reflect an older-than-expected age. The status of social isolation was measured by the previously validated multiple-choice questions based on Social Network Index (SNI) with score ranges between 0 (most isolated) and 4 (least isolated).

RESULTS A total of 280,324 subjects were included (chronological age 59.8 ± 16.4 years, 50.9% female). The mean Age-Gap was −0.2 ± 9.16 years. A higher SNI was associated with a lower Age-Gap (β of SNI = 4 was −0.11; 95% CI: −0.22 to −0.01; $P < 0.001$, adjusted to covariates). Cox proportional hazard analysis revealed the association between social connection and all-cause mortality (HR for SNI = 4, 0.47; 95% CI: 0.43-0.5; $P < 0.001$).

CONCLUSIONS Social isolation is associated with accelerating biological aging and all-cause mortality independent of conventional cardiovascular risk factors. This observation underscores the need to address social connection as a health care determinant. (JACC Adv. 2024;3:100890) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

SDoH = social determinants of health

SNI = Social Network Index

Social isolation, a key component of psychosocial determinants of health, is associated with poor health outcomes, higher medical expenditure, and more hospitalization rates.[1-3] Despite the substantial evidence of the impact of social isolation on health, the importance of screening for isolation and loneliness of patients is often overlooked in clinical settings. Beyond the deleterious effects of social isolation on emotional well-being and mental health,[4] it is also recognized as a risk factor for cardiovascular disease,[5] high blood pressure,[6] poor control diabetes mellitus,[7] and higher mortality rate.[8,9] The earlier studies on the role of social isolation on cardiac health are mostly focused on cardiovascular events as an outcome, and the majority are limited to older adults, while the research addressing the ultimate consequence of social isolation on biological aging across age groups is limited.

Biological age provides a better estimation of overall physiological function and well-being compared to chronological age.[10,11] It is been shown that a higher deviation of estimated biological age from chronological age correlates with a higher risk of adverse health outcomes such as the increased risk of cerebrovascular accident,[12] cardiovascular diseases,[13] cancer,[13] and all-cause mortality.[14] Various models were developed in attempting to better determine the biological age, mostly involving epigenetic studies (pattern of DNA methylation, telomere length, etc) and measuring biochemical parameters.[12] We previously developed a model of artificial intelligence-enabled 12-lead electrocardiography (AI-ECG) to estimate a person's biological age with high accuracy.[15] We further demonstrated that a positive difference between AI-ECG age estimation and chronological age (Age-Gap) is correlated with increased risk of cardiovascular and all-cause mortality even after adjusting for cardiovascular risk factors.[16]

While there is extensive evidence of the substantial role of social determinants on health, our understanding of the impact of social isolation on biological age is limited. The current study aimed to investigate the role of social isolation on biological aging, through the lens of the novel method of the AI-enabled algorithm of ECG age estimation.

METHOD

STUDY DESIGN. This is an observational cross-sectional study approved by the Institutional Review Board of the Mayo Clinic. All investigators conformed to the principles outlined in the Declaration of Helsinki.

The study's primary aim was to investigate the association between social isolation and accelerated biological aging, as determined by the AI model from ECGs. The secondary aim was to evaluate the association of social isolation with all-cause mortality.

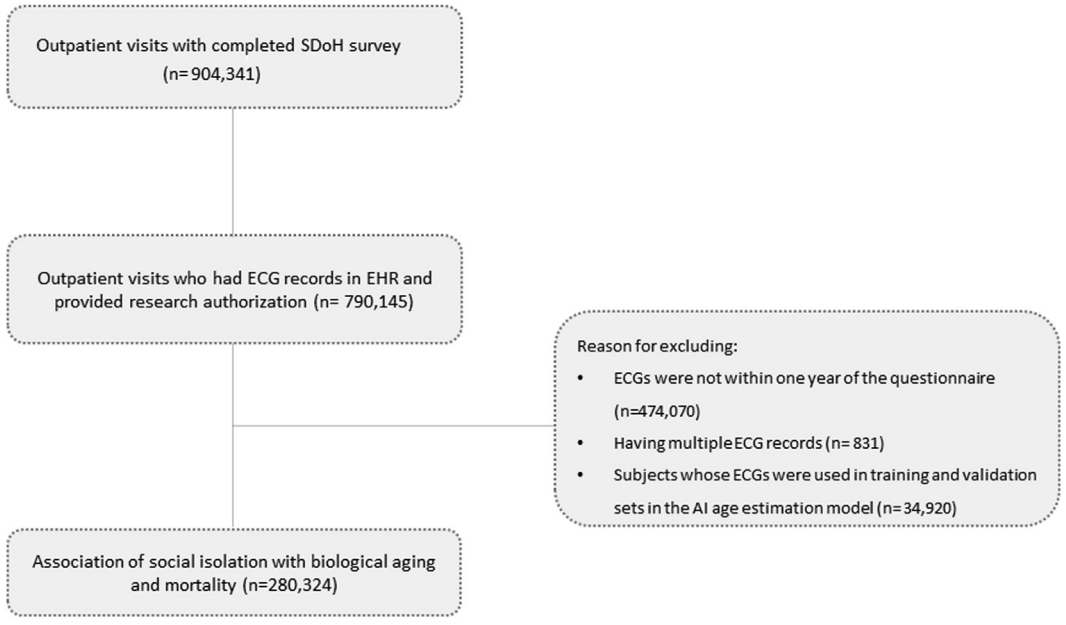
STUDY POPULATION. The study included all patients who came to Mayo Clinic between June 2019 and March 2022 for outpatient visits. The inclusion criteria consisted of all patients aged 18 years and older who visited Mayo Clinic (outpatient) and completed the questionnaire regarding the status of social determinants of health (SDoH) via the patient's online portal and had 12-lead ECG records as part of their routine clinically indicated medical care within 1 year of completing the questionnaire (**Figure 1**). For participants with multiple ECG records, the 1 closest to the date of the questionnaire was chosen.

The exclusion criteria consisted of subjects who did not provide research authorization and those whose ECGs were used previously to train or validate the AI model.

SOCIAL ISOLATION ASSESSMENT. A standard questionnaire for screening SDoH, including social isolation status, has been implemented at Mayo Clinic since 2019 for all outpatient visits through the patients' portal within 1 week prior to their appointment. Patients could also complete the questionnaire via a tablet at the time of check-in.[17] The status of social isolation was assessed through 6 distinct multiple-choice questions based on Social Network Index (SNI) developed by Berkman and Syme[18] and has been validated in previous research.[19] A score of 0 or 1 was assigned to each response for each SNI domain (belonging to any social club or organization, the frequency of participating in social activity per year, frequency of interacting with family and friends per week, being married or living with partnership) and the total score was calculated (**Table 1**). The total score ranged from 0 to 4, representing the most to the least social isolation. The methodology to measure the level of social connection was consistent with previous studies.[19,20]

AI-ECG METHOD. The biological age was estimated using the previously developed and validated convolutional neural network of ECG records. The methodology of the AI model was described in detail in a previously published paper.[15] In brief, a 10-second rested, standard 12-lead ECG from a total of 7,747,830 unique adult subjects (chronological age ≥18 years) was used to develop the neural network. The network was built using stacked blocks of convolutional, max pooling, and batch normalization.[15] The output of the network was the AI-enabled

FIGURE 1 Flow Diagram of the Recruiting Study Population



EHR = electronic health record; SDoH = social determinants of health.

ECG age prediction as a continuous variable. The labels used for training the model were the patient's chronological age. The algorithm was then tested for internal validation. As neural networks can memorize huge amounts of data, to avoid any data leakage, none of the patients used for this analysis were also used to train the AI-ECG age model, providing more generalizable results.

The Age-Gap was then calculated by subtracting the chronological age from AI-ECG's estimated age. Subsequent studies have validated the hypothesis that the Age-Gap represented biological cardiac age as it was associated with a higher rate of total and CVD mortality. Accordingly, the positive Age-Gap indicated accelerated biological aging, and the negative value indicates slower biological aging.[15]

CARDIOVASCULAR DISEASES AND RISK FACTORS. Demographic and clinical variables were extracted from the electronic medical record including chronological age, sex, ethnicity, hypertension, hyperlipidemia, history of myocardial infarction (diagnosed based on ECG and/or enzyme changes), heart failure, atrial arrhythmia (atrial fibrillation, atrial flutter), diabetes, chronic obstructive pulmonary diseases, chronic kidney disease (those with creatinine >2 mg/dL, or undergoing dialysis, or those who received renal transplant), cerebrovascular accident (ischemic stroke, hemorrhagic stroke, transient ischemic attack), and cancer (solid tumor with or without metastasis). All-cause mortality data were obtained until August 19, 2022, using the electronic health records and the social security death index.

STATISTICAL ANALYSIS. Analysis of continuous variables was reported as mean ± SD if symmetrically distributed and median (IQR) if skewed. Categorical data were reported with frequencies or percentages as appropriate. The SNI was treated as an ordinal variable, with lowest score of 0,1 indicating the highest social isolation and highest score of 4 indicating the least social isolation.

Between-group differences were analyzed using chi-squared for categorical variables, and the *U* test, *t*-test, or analysis of variance for continuous variables as appropriate.

The association between SNI and Age-Gap was evaluated by univariable regression analysis. Then, the multivariable generalized linear model was fitted to data to investigate the association between Age-Gap and demographic (age, sex, race, living partnership), comorbidities, and social isolation (SNI) as independent predictors.

A secondary analysis was conducted to determine the association between social isolation and Age-Gap in each age and sex group. For age-specific analysis,

TABLE 1 Questions of the Survey for Evaluating the Status of Social Connection

Social Connections	Response (Score)
Do you belong to any clubs or organizations such as church groups, unions, fraternal or athletic groups, or school groups?	Yes (1) No (0) Decline (N/A)
How often do you attend meetings of the clubs or organizations you belong to?	Never (0) 1 to 4 times per year (0) More than 4 times per year (1) Decline (N/A)
In a typical week, how many times do you talk on the telephone with family, friends, or neighbors?	Never (0) Once a week (0) Twice a week (0) 3 times a week (1) More than 3 times a week (1) Decline (N/A)
How often do you attend church or religious services?	Never (0) 1 to 4 times per year (0) More than 4 times per year (1) Decline (N/A)
How often do you get together with friends or relatives?	Never (0) Once a week (0) Twice a week (0) 3 times a week (1) More than 3 times a week (1) Decline (N/A)
Are you now married, widowed, divorced, separated, never married, or living with a partner?	Never married (0) Separated (0) Divorced (0) Widowed (0) Living with a partner (1) Married (1) Decline (N/A)

the chronological age was categorized into 4 groups based on the quartile of the distribution (<50, 50-59, 60-69, and ≥70 years of age). The sex- and age-specific analysis was performed by measuring the interactions between sex and SNI for sex-specific analysis, and age groups and SNI for age-specific analysis, respectively.

For mortality data, Cox proportional hazard analysis was performed to investigate the association between SNI and all-cause mortality. Survival time was calculated from the date of survey completion, and it was censored at the end of the follow-up time on August 19, 2022. In the adjusted model, the association between social isolation and mortality was controlled for comorbidities. The results were reported as a hazard ratio (HR) with a 95% CI.

For all analyses, the 2-sided P value <0.05 was considered statistically significant. Analyses were performed using the IBM SPSS statistics software version: 28.0.0.0 (190) (IBM Corp) and R programming version 4.2.2 (R Foundation for Statistical Computing, https://www.R-project.org/).

RESULTS

DESCRIPTIVE BASELINE CHARACTERISTICS. During the study period from 2019 to 2022, there were a total number of 904,341 completed surveys. After removing the duplication and applying the inclusion and exclusion criteria, 280,324 unique individuals were included in the study for further analysis (Figure 1 shows the flow diagram of patients' selection). The average chronological age was 59.8 ± 16.4 years, 50.9% were females, and 86.3% were non-Hispanic White. The average Age-Gap was −0.2 ± 9.16 years.

Previous medical history was remarkable for hypertension in 33%, hyperlipidemia in 18.8%, and diabetes in 11.8% of participants. Overall, a low SNI score was associated with a higher prevalence of comorbidities. Details of baseline characteristics and their distribution across different social isolation statuses are presented in Table 2.

ASSOCIATION BETWEEN SOCIAL ISOLATION WITH AGE-GAP. The overall response rate to the survey was 70.3%, and for questions assessing social isolation was 93.7%, 84%, 93%, 90.9%, 87.7%, and 92.6%, respectively. There was no significant difference in baseline characteristics between responder and nonresponder groups. To analyze the data for the current study, we only included full cases with 100% response rate to social isolation questions.

In total, 44.9% of participants were members of the club or organizations such as religious or athletic groups, and 44% were attending group meetings more than 4 times a year. About 69.2% had frequent (3 times or more per week) interactions with their family and friends, and 69.5% were married or had a living partner.

The median SNI in the total population was 2 (1,3) with no significant changes between men and women. Higher SNI (better social network) was associated with an increasing Age-Gap in all sex and age groups (Central Illustration). There was a significant difference in the mean Age-Gap between SNI = 0 (0.64 ± 9.9) compared to SNI = 4 (−1.2 ± 8.4) ($P < 0.001$).

In a secondary analysis comparing ethnicity groups (White vs non-White), the average Age-Gap in all SNI subgroups was higher in non-White compared to White participants and the difference was more prominent in lower SNIs (Table 3).

The univariable linear regression model showed a significant association between social isolation and Age-Gap (β of SNI = 4 [SNI = 0 as the reference] = −1.9; 95% CI: −20. to −1.7; $P < 0.001$).

TABLE 2 Baseline Characteristics of All Included Study Participants

	Total (N = 280,324)	SNI = 0 (n = 21,202)	SNI = 1 (n = 62,003)	SNI = 2 (n = 77,575)	SNI = 3 (n = 60,855)	SNI = 4 (n = 58,689)	*P* Value
Age, y	59.8 ± 16.4	57.6 ± 18.9	57.2 ± 18.0	59.1 ± 16.1	61.3 ± 16.3	62.6 ± 13.4	<0.001
Age-Gap	−0.2 ± 9.16	0.645 ± 9.91	0.772 ± 9.49	0.125 ± 9.17	−0.892 ± 9.06	−1.24 ± 8.43	<0.001
Sex (female)	137,619 (50.9%)	10,172 (49.4%)	30,108 (50.2%)	37,841 (50.7%)	30,651 (52.3%)	28,847 (51.0%)	
Ethnicity							
Asian	5,590 (2.0%)	458 (2.2%)	1,409 (2.3%)	1,748 (2.3%)	1,152 (1.9%)	823 (1.4%)	<0.001
Black/African American	11,797 (4.2%)	1,276 (6.0%)	2,820 (4.5%)	3,026 (3.9%)	2,689 (4.4%)	1,986 (3.4%)	<0.001
Hispanic White	9,419 (3.4%)	703 (3.3%)	2,240 (3.6%)	3,027 (3.9%)	1,878 (3.1%)	1,571 (2.7%)	<0.001
Non-Hispanic White	241,969 (86.3%)	17,603 (83.0%)	52,761 (85.1%)	66,361 (85.5%)	52,952 (87.0%)	52,292 (89.1%)	<0.001
Other	11,549 (4.1%)	1,162 (5.5%)	2,773 (4.5%)	3,413 (4.4%)	2,184 (3.6%)	2,017 (3.4%)	<0.001
BMI, kg/m^2	29.0 ± 5.94	28.9 ± 5.68	28.9 ± 5.34	28.8 ± 5.09	28.6 ± 4.70	28.8 ± 5.29	<0.001
Smoking (ever smoker)	53,207 (19.7%)	5,058 (24.6%)	13,778 (23%)	15,365 (20%)	10,427 (17.8%)	8,579 (15.2%)	<0.001
Diabetes	33,061 (11.8%)	3,170 (15.0%)	7,989 (12.9%)	9,253 (11.9%)	6,823 (11.2%)	5,826 (9.9%)	<0.001
Hypertension	92,620 (33.0%)	7,820 (36.9%)	20,873 (33.7%)	25,042 (32.3%)	20,384 (33.5%)	18,501 (31.5%)	<0.001
Hyperlipidemia	52,710 (18.8%)	4,660 (22.0%)	11,835 (19.1%)	14,174 (18.3%)	11,745 (19.3%)	10,296 (17.5%)	<0.001
Myocardial infarction	7,564 (2.7%)	731 (3.4%)	1,847 (3.0%)	2,076 (2.7%)	1,596 (2.6%)	1,314 (2.2%)	<0.001
Congestive heart failure	18,498 (6.6%)	1,865 (8.8%)	4,460 (7.2%)	5,120 (6.6%)	3,918 (6.4%)	3,135 (5.3%)	<0.001
Peripheral vascular disease	21,579 (7.7%)	2,041 (9.6%)	5,109 (8.2%)	5,978 (7.7%)	4,580 (7.5%)	3,871 (6.6%)	<0.001
Atrial fibrillation	23,492 (8.4%)	1,898 (9.0%)	4,968 (8.0%)	6,239 (8.0%)	5,419 (8.9%)	4,968 (8.5%)	<0.001
Cerebrovascular disease	12,314 (4.4%)	1,149 (5.4%)	2,893 (4.7%)	3,441 (4.4%)	2,631 (4.3%)	2,200 (3.7%)	<0.001
Chronic pulmonary disease	29,338 (10.5%)	3,047 (14.4%)	7,485 (12.1%)	7,969 (10.3%)	5,956 (9.8%)	4,881 (8.3%)	<0.001
Renal disease	28,052 (10.0%)	2,660 (12.5%)	6,781 (10.9%)	7,733 (10.0%)	6,041 (9.9%)	4,837 (8.2%)	<0.001
Death	13,764 (4.9%)	1,636 (7.7%)	3,550 (5.7%)	3,902 (5.0%)	2,606 (4.3%)	2,070 (3.5%)	<0.001

Values are mean ± SD or n (%).
BMI = body mass index; SNI = Social Network Index.

The general linear model was then fitted to the SNI and covariates. After controlling for demographic and comorbidities, the total SNI was independently associated with Age-Gap (β of SNI = 4 was −0.11; 95% CI: −0.22 to −0.01; $P < 0.001$) (**Table 4**). The calculated variance inflation factor for all the included variables in the multivariable model was close to 1, indicating no collinearity between predictors. Secondary analysis in each age group revealed that the association between SNI and Age-Gap was significant across age groups with a more prominent effect found in younger adults (detailed results can be found in Supplemental Table 1 and the **Central Illustration**).

ASSOCIATION BETWEEN SOCIAL ISOLATION AND ALL-CAUSE MORTALITY. During the study period, there were 4,858 patients lost for further follow-up on mortality incidents (average age of 59.7 ± 16.4 years, with 49.55% female and 82.55% identified as non-Hispanic White). The number accounts for 1.7% of the total study population. The missing population did not differ remarkably from the follow-up participants regarding the baseline characteristics and the status of social isolation. To conduct survival analysis, we excluded patients who were lost to follow-up.

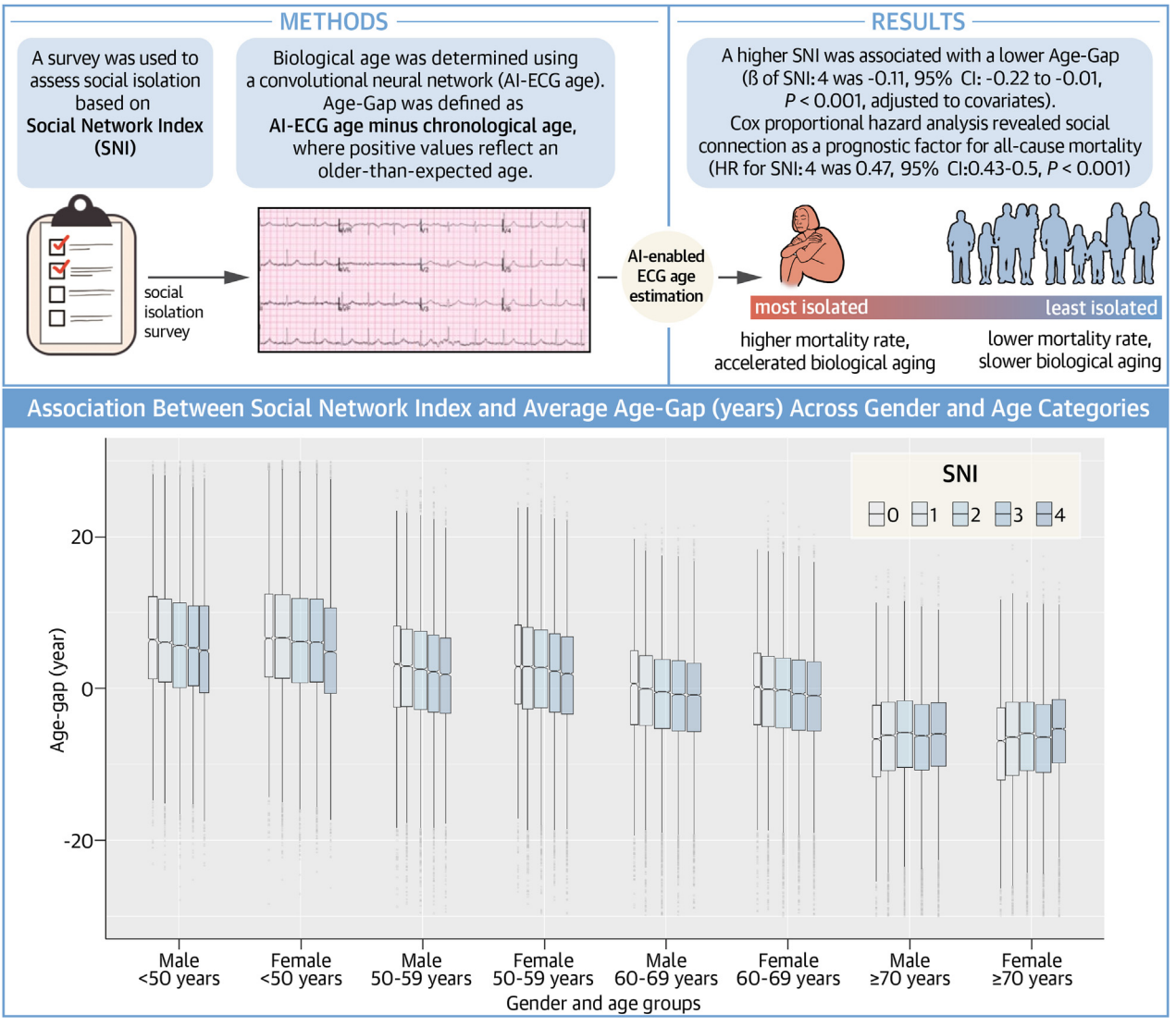
During the median follow-up time of 24 (IQR: 14-33) months, the total incidence of mortality was 13,764 (4.9%), of which 42% were women. Deceased patients were significantly older (70 ± 14.2 years vs 59.3 ± 16.3 years). The most frequent comorbid conditions in deceased patients included hypertension (48.6%), hyperlipidemia (33.9%), and chronic kidney disease (24.8%). The mortality incidence differed significantly across social network status with higher SNI associated with lower mortality risk (between groups log-ranked $P < 0.001$). The highest mortality risk was observed in SNI = 0 and 1 compared to other groups (**Figure 2**).

Cox proportional hazard analysis revealed a significant association between social isolation and mortality. The output of the analysis is presented in **Table 5**. In the unadjusted model, the HR of mortality for SNI = 4 (SNI = 0 as the reference) was 0.47 (95% CI: 0.44-0.52; $P < 0.001$). After controlling for demographic and comorbid conditions in multivariable mode, the HR of mortality for SNI = 4 (SNI = 0 as the reference) was 0.47 (95% CI: 0.43-0.5; $P < 0.001$).

DISCUSSION

This study demonstrated that social isolation was associated with a higher deviation of AI-ECG age

CENTRAL ILLUSTRATION **Association Between Social Isolation With Age-Gap Determined by Artificial Intelligence-Enabled Electrocardiography**



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Investigation of the association between social network index (SNI) and average AI-ECG Age-Gap (year) in a cohort of 280,324 patients revealed that in all age and sex categories, social isolation is associated with accelerated aging compared to more socially connected participants.

TABLE 3 **Comparative Analysis of the Impact of Social Isolation on Age-Gap Between White and Non-White Groups**

	Age-Gap				
Ethnicity	**SNI = 0**	**SNI = 1**	**SNI = 2**	**SNI = 3**	**SNI = 4**
White	0.4 ± 9.8	0.6 ± 9.4	0.001 ± 9	−1.05 ± 8.9	−1.3 ± 8.4
Non-White	2.1 ± 10.3	2.1 ± 9.8	1.3 ± 9.9	0.7 ± 9.8	−0.2 ± 9
P value	<0.001	<0.001	<0.001	<0.001	<0.001

Values are mean ± SD.
SNI = Social Network Index.

estimation than the actual age. According to the result of the present study, social isolation, in combination with demographic and medical conditions, is a significant risk factor for accelerated aging. However, the contribution of each component in Age-Gap prediction varied across different age groups. In addition, survival analysis indicated the association between social isolation and a higher mortality rate. Thus, the current study highlights the role of social

TABLE 4 Univariable and Multivariable Regression Analysis of the Association Between Social Isolation and Age-Gap

	Univariable			Multivariable		
	Beta	**95% CI**	***P* Value**	**Beta**	**95% CI**	***P* Value**
Chronological age	−0.32	−0.32 to −0.32	<0.001	−0.33	−0.33 to −0.33	<0.001
SNI[a] (SNI = 0)						
1	0.13	−0.02 to 0.27	0.081	0.09	−0.03 to 0.21	0.14
2	−0.52	−0.66 to −0.38	<0.001	0.13	−0.02 to 0.25	0.02
3	−1.5	−1.7 to −1.4	<0.001	−0.15	−0.27 to −0.03	0.01
4	−1.9	−2.0 to −1.7	<0.001	−0.11	−0.22 to −0.01	<0.001
Sex	0.98	0.91 to 1.0	<0.001	0.11	0.06 to 0.17	<0.001
BMI	0.12	0.11 to 0.12	<0.001	0.07	0.07 to 0.08	<0.001
Diabetes	−1.2	−1.3 to −1.1	<0.001	0.26	0.16 to 0.35	<0.001
Ever smoking	0.02	−0.06 to 0.11	0.6	0.11	0.04 to 0.19	0.002
Alcohol use disorder	2.6	2.4 to 2.7	<0.001	0.82	0.69 to 0.95	<0.001
Hypertension	−2.5	−2.6 to −2.4	<0.001	0.77	0.70 to 0.84	<0.001
Hyperlipidemia	−2.7	−2.8 to −2.6	<0.001	−0.28	−0.38 to −0.18	<0.001
Myocardial infarction	−2.2	−2.5 to −2.0	<0.001	−0.01	−0.19 to 0.17	>0.9
Congestive heart failure	−1.5	−1.6 to −1.4	<0.001	0.94	0.81 to 1.1	<0.001
Peripheral vascular disease	−2.5	−2.6 to −2.3	<0.001	0.28	0.16 to 0.39	<0.001
Atrial fibrillation	−2.6	−2.7 to −2.4	<0.001	1.3	1.2 to 1.4	<0.001
Cerebrovascular disease	−3.0	−3.2 to −2.9	<0.001	−0.21	−0.35 to −0.07	0.004
Chronic pulmonary disease	−0.27	−0.38 to −0.16	<0.001	0.49	0.20 to 0.78	<0.001
Chronic kidney disease	−1.6	−1.7 to −1.4	<0.001	0.94	0.81 to 1.1	<0.001
Cancer	−2.2	−2.4 to −2.0	<0.001	−0.54	−0.70 to −0.37	<0.001

[a]Social Network Index, the reference level for sex was female, for SNI was 0,1 and for comorbidities was not having the condition.
CI = confidence interval; BMI = body mass index.

FIGURE 2 Comparison of Cumulative Hazard Ratios of Social Network Index in Predicting Mortality

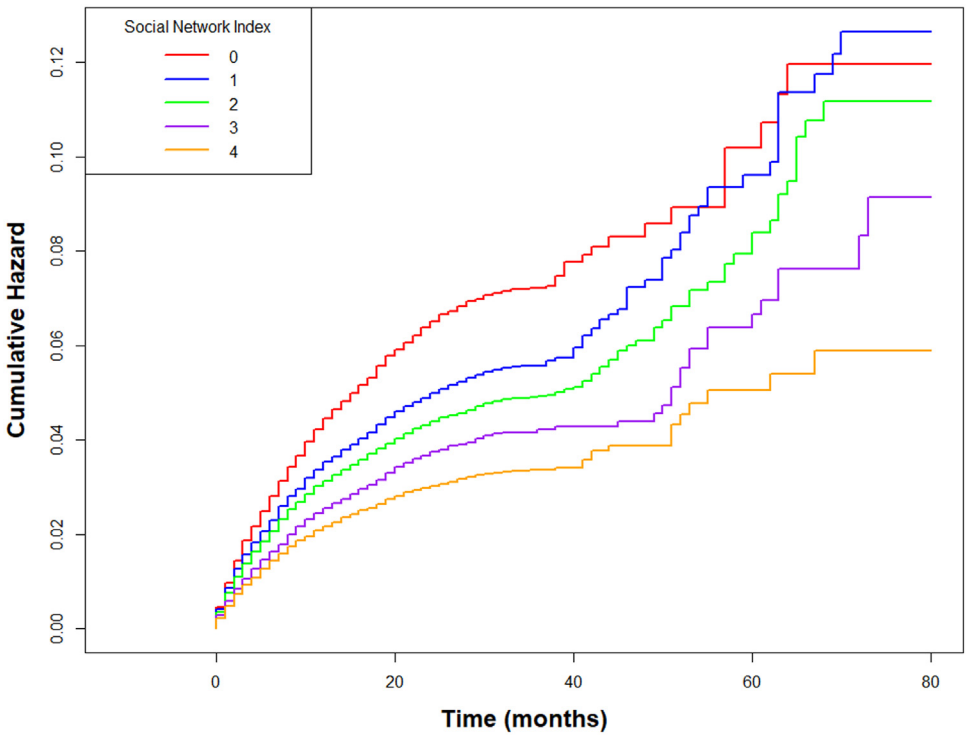

TABLE 5 The Result of Cox Proportional Hazard Analysis for the Association Between Social Connection and All-Cause Mortality

	Cox Proportional Hazard					
	Unadjusted Model			Adjusted Model[a]		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
SNI = 0 (reference)						
SNI = 1	0.78	0.73-0.84	<0.001	0.82	0.76-0.87	<0.001
SNI = 2	0.69	0.64-0.73	<0.001	0.71	0.66-0.76	<0.001
SNI = 3	0.58	0.54-0.62	<0.001	0.56	0.52-0.59	<0.001
SNI = 4	0.47	0.44-0.51	<0.001	0.47	0.43-0.50	<0.001

[a]Controlled for demographic (age, sex), and comorbidities including hypertension, hyperlipidemia, diabetes, myocardial infarction, congestive heart failure, peripheral vascular disease, atrial fibrillation, chronic kidney disease, cerebrovascular diseases, chronic pulmonary disease, cancer.

HR = hazard ratio; SNI = Social Network Index.

isolation as the potential target in decreasing aging and mortality.

The etiology of cardiovascular diseases is multifactorial, resulting from the interplay between genetic, and psychosocial determinants, and physiological and environmental factors. The relationship between social isolation and cardiovascular outcomes has been extensively recognized in the literature. There is a bidirectional relationship between social isolation and chronic illnesses.[21,22] As mentioned above, social isolation increases the risks of cardiovascular events through both direct and indirect pathways. Likewise, patients with chronic medical conditions are more susceptible to experiencing social isolation and loneliness.[21,23] In our study, the multivariable regression model showed that both social isolation and medical conditions were independently associated with accelerated aging and mortality. This was in line with previous studies. As such, The English Longitudinal Study of Ageing indicated the independent predicting role of social isolation in all-causes mortality after controlling for the demographic and long-standing illnesses such as cancer, chronic obstructive pulmonary disease, and stroke.[24] According to the INTERHEART study in 52 countries, psychological stress ranked as the third most important risk factor of myocardial infarction after dyslipidemia and smoking and had an even higher risk than diabetes and obesity.[25] A meta-analysis of observational longitudinal studies showed that social isolation was associated with an increased risk of coronary heart disease and stroke.[26] Moreover, the Atherosclerosis Risk in Communities study showed an increase in the likelihood of heart failure incidents in high compared to low social isolation risk group.[27] Our study is in line with and further extends previous findings to underscore the impact of social isolation on accelerated aging independent of established cardiovascular risk factors.

Several mechanisms have been proposed to underlie the association between social isolation and aging. The 2 most identified biological processes include systemic inflammation and the endocrine system.[28] Social isolation alters the activity of the hypothalamic-pituitary-adrenal axis, by flattening the diurnal cortisol decline and elevation of the overall cortisol level.[29] The overactivation of the hypothalamic-pituitary-adrenal axis due to social isolation further yields hypertension and accelerated atherosclerosis.[30,31] Moreover, social isolation and loneliness trigger the upregulation of pro-inflammatory genes and enhance myelopoiesis.[32,33] This subsequently leads to oxidative stress in vascular tissues, a proceeding mechanism of atherosclerosis.[34,35] Social isolation is also associated with dysregulation of the autonomic nervous system.[36] It is shown that poor social integration is associated with lower heart rate variability[36] which is regulated predominantly by the parasympathetic nervous system and is highly correlated with cardiovascular diseases and all-cause mortality.[37,38] On the other hand, social isolation is associated with a higher likelihood of health-risk behaviors such as smoking, alcohol consumption, unhealthy diet, and physical inactivity,[39-41] in addition to poor medication adherence which exacerbates the medical conditions[42]

One important finding of our study was the variation in the impact of social isolation across age groups. A socially isolated lifestyle had a greater impact on younger compared to older age groups. While in older age, the role of comorbidities was more prominent. The possible explanation for the observed effect might be that the accumulating negative effect of social isolation is more likely to manifest physiologically.[43] This finding is also consistent with the meta-analysis of 70 studies involving over 3 million participants, which revealed the higher odds ratio of social isolation in predicting mortality in adults with an average age of 65 years and younger compared to 65 to 75 and >75 years (OR: 1.57 vs 1.25 vs 1.14, respectively).[8]

The findings of our study can be applied in future health promotion planning and direct the way for further research on social isolation through early identification of its adverse effects by the mean of AI-enabled biological age estimation. Future longitudinal studies are warranted to examine whether the improvement in social connection delays biological aging or even reverses it. To date, there are only a limited number of interventions attempting to reduce

the negative health consequences of social isolation, and only a few shows promising results.[44,45] A meta-analysis of 87 randomized control trials revealed that incorporating psychosocial support (such as family support or group meetings) into medical care was associated with a 20% higher survival rate and a 29% higher likelihood of longer survival compared to standard care.[46]

STUDY LIMITATIONS. There are some limitations attributed to this study that are worth mentioning and considering in future works. First, we were not able to include all different racial groups equally. Although we included all patients that attended Mayo Clinic campuses located in Minnesota, Florida, and Arizona, our study population is not completely representative of the general population, thus any extrapolation of the results to a certain population needs to be applied with caution. The second 1 is the inherent limitation of AI-ECG-enabled age estimation. Despite its high accuracy in predicting age, the AI-ECG age model was trained to estimate the patient's chronological age, and the biological information was hidden in the model estimation error, thus, further investigation is warranted to improve the algorithm. Third, the decision not to adjust the reported *P* values for multiple comparisons was made to maintain clarity and avoid complexity in our analyses. However, we acknowledge that this choice may lead to an increased risk of type I errors and the results should be interpreted with caution. In addition, it should be noted that the AI model was developed and validated internally; therefore, any extrapolation of the result to the general population needs further external validation.

Finally, even though there was an inclusive list of covariates in our analysis, there is still the possibility of unmeasured confounders that might affect the results. Last, since our study population was selected based on medical services visits, there is the risk of selection bias, however, we tried to minimize the risk by including all patients who visited the hospital for any medical reasons instead of only those with cardiovascular conditions.

CONCLUSIONS

This large population cohort demonstrated the independent association of social isolation with accelerated aging and a higher risk of mortality, even after controlling for demographic and clinical comorbidities.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Drs Friedman, Lopez-Jimenez, and Attia are coinvestigators of the AI-ECG age algorithm, which has been licensed to Alumana, Mayo Clinic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: This study provides evidence of the continuity of the social isolation impact from young to older age groups in accelerated aging in both men and women independent of other traditional risk factors.

TRANSLATIONAL OUTLOOK: The results can be translated to medical practice to increase awareness of the impact of social isolation on health outcomes and to encourage initiatives to increase social network. Exploring other SDoH, particularly in marginalized population is still warranted.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.