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Research Article

Social relationships and epigenetic markers of aging in middle-aged and older adults: cross-sectional and prospective analyses

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Abstract

Objectives: Social relationships play an important role in maintaining physical and psychological health. Epigenetic age is a potential mechanism underlying health-related aspects of social relationships. We aimed to assess the cross-sectional and prospective associations of social relationships and epigenetic age in middle-aged and older adults.

Methods: Blood DNA methylation data were collected from 6,208 participants in the Melbourne Collaborative Cohort Study at baseline (1990–1994, mean age = 59) and 1,110 at follow-up (2003–2007, mean age = 69). Four epigenetic aging measures were considered: *PCPhenoAge*, *PCGrimAge*, *bAge*, and *DunedinPACE*. Social relationship variables were collected via self-reported questionnaires at baseline, including social activities, living arrangements, marital status, and numbers of close relatives and friends. A social isolation index was calculated. Linear regression was used to assess the associations of social relationships with baseline and follow-up epigenetic age.

Results: Cross-sectionally, living alone and overall social isolation were associated with older epigenetic age in men only (e.g., living alone, *DunedinPACE*, per *SD* $\beta = 0.20$, 95% CI: 0.10–0.29), with strong evidence of effect modification by sex ($p = .002$ to 4×10^{-5}). Moderate amounts of social activities and a greater number of relatives and friends were also associated with a younger epigenetic age. Generally weaker associations were observed in prospective analyses.

Discussion: In middle-aged and older Australians, positive components of social relationships showed weak associations with lower epigenetic age. Social isolation and living alone were associated with older epigenetic age only in men. Our study suggests that the benefits of social relationships to health are partially captured by epigenetic markers of aging.

Keywords: Biological aging, DNA methylation, Living arrangement, Social connectedness, Social isolation

Social relationships influence psychological and physiological health and well-being (Cyranowski et al., 2013; Xu et al., 2023). The NIH Toolbox identifies three domains in social relationships: social support (defined as the perception of the extent of the support individuals could receive from their social relationships), companionship (including friendship, intimacy, and loneliness), and distress (defined as distress experienced during social relationships and interactions, mainly from perceived rejection and hostility) (Cyranowski et al., 2013). Social relationships have been investigated both quantitatively by assessing their frequency, density, or diversity, and qualitatively by describing individuals' perceptions and feelings toward their own relationships (Due et al., 1999). The health impacts of social relationships have been widely studied, with multiple and varied potential mechanisms being proposed, including better management of stress levels, provision of emotional, material, and practical supports, improved health consciousness, and reduction of health hazards, as well as strengthening of resilience to adversity (Cohen, 2004; House et al., 1988). Social relationships of both high quantity and high quality contribute to successful aging (Depp & Jeste, 2006; Rowe & Kahn, 1997). As the most fundamental characteristics of social relationships (Cacioppo & Cacioppo, 2014), social isolation and loneliness have been widely reported to be associated with increased risks of depression (Wickramaratne et al., 2022), all-cause mortality (Demographic Change and Healthy Ageing, 2021), adverse health conditions such as type 2 diabetes (Demographic Change and Healthy Ageing, 2021), total cancer incidence (Kraav et al., 2021), and poor quality of life (Demographic Change and Healthy Ageing, 2021). Although various age-related variables have been studied (Hodge et al., 2013; Shankar et al., 2011; Steptoe et al., 2013, 2024), the biological

mechanisms linking social relationships to disease risk and their overall contribution to health are not fully understood (Ghiara & Russo, 2019). Epigenetic markers of aging were constructed using variables that reflect many health-related aspects, including lifestyle (e.g., smoking and body size), inflammation (e.g., C-reactive proteins [CRPs] and numerous cytokines) and other clinical variables (e.g., glucose concentration) and as such are likely to provide a promising indicator of biological aging (Belsky et al., 2022; Bernabeu et al., 2023; Horvath & Raj, 2018; Levine et al., 2018; Lu et al., 2019), and have been reported to be associated with adverse mental and physiological health events, as well as mortality and cancer risk (Beydoun et al., 2022; Dugué et al., 2018, 2021, 2022; Faul et al., 2023; Li, Hodge, et al., 2025; Li, Xu, et al., 2025). In this context, epigenetic age may help provide biological grounds for the contribution of social isolation and lack of social activity to physiological health and the associated risk of diseases and death.

There is limited evidence for the association between social relationships and epigenetic age: many studies only assessed cross-sectional associations; a few prospective studies mainly investigated the qualitative aspects of social relationships. A study based on 1,315 Canadian adults found no association between the number of people in the household and epigenetic age (Joshi et al., 2024). Another study of 1,479 participants from the same cohort reported a negative association between social participation and *HannumAge* (Liang & Gomaa, 2024). Rentscher et al. (2023) assessed both quantitative (presence of relationships) and qualitative (perceived support and stress) aspects of social relationships in 3,647 participants from the Health and Retirement Study (HRS), and reported that the presence of relationships with friends and families and greater support from them were associated with lower epigenetic age. A prospective study of 1,912 adults (mean age: 63 years) from the HRS found that those with higher baseline levels of support and more frequent social contacts had slower *DunedinPACE* and lower *GrimAge* over a 10-year follow-up (Hillmann et al., 2023). Additionally, two American studies reported relatively strong positive prospective and longitudinal associations between loneliness and epigenetic age in middle-aged and older Americans (Freilich, Markon, Cole, et al., 2024; Freilich, Markon, Mann, et al., 2024).

As highlighted by several authors (Fuhrer & Stansfeld, 2002; House et al., 1988; Umberson & Montez, 2010), the strains and benefits from social relationships may be gender-specific, which would explain their differential impact on health. Such differences are likely due to long-existing stereotypes of "gendered division" of social participation, where women are considered to play a more important role in the family than at work, and vice versa (Calasanti, 2009). This may involve, for men, positive health behaviors associated with socialization and partnership, and for women, greater responsibility and work associated with looking after a family (Umberson & Montez, 2010). For example, a study reported that males had poorer mental well-being when engaging in activities alone but better mental and physical well-being when participating in outdoor socializing activities, whereas the opposite was observed for women (Dury et al., 2021). It is likely that under such stereotypes, women and men may perceive their social relationships, particularly being alone, differently, and therefore benefit differently from social participation and social relationships. The hypothesis of gender differences in the impact of social relationships on health is also grounded in empirical findings, generally showing stronger associations of social isolation and living alone with mortality and other health-related traits were observed in men (compared to those in women) (Gove, 1973; Qi et al., 2023; Sbarra, 2009; Umberson & Montez, 2010; Waite, 1995; Wang et al., 2023; Zhao et al., 2022). Therefore, we hypothesized that the associations of social isolation and living alone with epigenetic age might differ between men and women.

Additionally, there have been recent improvements in epigenetic markers of aging that have not been widely explored, including (1) principal-component (PC-) based improved versions of *PhenoAge* and *GrimAge*, which showed better reliability than non-PC-based versions (Cribb et al., 2025; Higgins-Chen et al., 2022); and (2) the combination of additional epigenetic surrogate markers of plasma proteins with *GrimAge* components to improve the prediction of mortality (Bernabeu et al., 2023). These epigenetic aging measures have been found to be more strongly associated with lifestyle factors (Andrasfay & Crimmins, 2023; Zheng et al., 2025) and age-related traits (Faul et al., 2023; Li, Hodge, et al., 2025; Miao et al., 2024) than previous measures, and were therefore considered to provide a more reliable and comprehensive assessment of aging-related health.

In this study, we aimed to assess in a large sample of middle-aged and older Australians: (i) the cross-sectional and prospective associations between social relationship components and epigenetic aging and (ii) whether the associations of living alone and social isolation with epigenetic age vary by sex.

Method

Study population

The Melbourne Collaborative Cohort Study (MCCS) is a prospective cohort study that recruited 41,513 middle-aged to older Australians (99% aged between 40 and 69 years, 59% female) of White European origin in 1990–1994 (baseline) (Milne et al., 2017). During 2003–2007, a face-to-face follow-up (wave 2) was carried out. Sociodemographic, lifestyle, and health data, as well as physical measurements and blood samples, were collected at both waves.

Among these participants, 6,374 were selected for inclusion in at least one of eight nested cancer case-control studies, including a total of 7,688 peripheral blood samples, collected as dried blood spots on Guthrie cards (70%), peripheral blood mononuclear cells (28%), or buffy coats (2%). Genome-wide blood DNA methylation data were extracted from all participants at baseline, and 1,251 of the controls from 7/8 case-control studies at follow-up, and processed using the Illumina HumanMethylation450 BeadChip array (Milne et al., 2017). The detailed methods used for normalization and quality control have been described previously (Dugué et al., 2016; Joo et al., 2013). A small number of missing methylation data points (0.2%) were imputed using the k-nearest neighbors algorithm. After excluding duplicates, participants who failed in the DNAm quality control, and participants who had missing data for social factors and other covariates, the study included 6,208 participants for cross-sectional analyses and 1,110 for prospective analyses (Supplementary Figure 1 [see online supplementary material]). Details on cancer case-control studies have been described in several previous publications (Dugué et al., 2018, 2021, 2022; Milne et al., 2017). The incident cancer cases were

identified through annual linkage to the Victoria Cancer Registry and were matched to controls on age, sex, and country of birth (and smoking history for the lung cancer study) using incidence density sampling (Milne et al., 2017).

The MCCS was approved by the Human Research Ethics Committee of the Cancer Council Victoria, Melbourne, Victoria, Australia, and informed consent was provided by all participants according to the Declaration of Helsinki.

Social relationships

Information on social connectedness was collected through a self-administered questionnaire at baseline, which included five items that assessed several aspects of social relationships: (i) the total number of hours per week involved in social activities ("How many hours a week, if any, do you spend involved in social activities outside your home or work? [e.g., ethnic clubs, work clubs, church groups or sporting groups and other community groups or regular social meetings with friends]". Answers: none, 1–2, 3–4, 5–9, ≥10), (ii) the number of relatives who visited at least once per month ("Apart from those who live with you, how many relatives do you usually see at least once a month?". Answers: none, 1–2, 3–4, 5–9, and ≥10), (iii) the number of friends who could visit without invite ("Excluding your relatives, how many friends do you have who you could visit at any time without an invitation?". Answers: none, 1–2, 3–4, 5–9, and ≥10), (iv) living arrangement ("Including yourself, how many people live in your household?". Answers: 1, 2, 3–4, ≥5), and (v) marital status (married/de facto, single, divorced/separated/widowed) (Milne et al., 2017). Living arrangements were re-categorized into a binary variable, living alone, or with more than one person. In addition to being used as categorical variables, the numbers of relatives and friends, as well as the amount of social activity (hours/week) were considered as pseudo-continuous variables by assigning to each category its midpoint: none: 0, 1–2: 1.5, 3–4: 3.5, 5–9: 7, and ≥10: 10.

We created a social isolation index (range 0–5) where higher values indicated greater isolation, using the same approach as previous publications (Shankar et al., 2011), with one point given for each of (i) being not married, (ii) living alone, (iii) having less than monthly contact with relatives, (iv) or friends, and (v) and not being part of any social organizations (Shankar et al., 2011). This index has proved to be representative of the overall social isolation in previous studies (Shankar et al., 2011; Steptoe et al., 2013, 2024).

Epigenetic age

We considered four recent and powerful epigenetic aging measures: *PCPhenoAge*, *PCGrimAge*, *bAge*, and *DunedinPACE*. *PhenoAge* was developed to predict phenotypic age using 10 clinical markers (Levine et al., 2018). *GrimAge* consists of methylation-based markers of smoking pack-years and seven plasma proteins and predicts mortality (Lu et al., 2019). These measures were trained on principal components (PCs) to improve their reliability, resulting in *PCPhenoAge* and *PCGrimAge* (Higgins-Chen et al., 2022). *bAge* improved mortality prediction by incorporating 6/8 methylation *GrimAge* components and 28/109 protein *EpiScores* (including CRP and a range of cytokines) (Bernabeu et al., 2023). *DunedinPACE* was developed based on methylation markers of the trajectory of 19 clinical markers over 20 years to estimate the rate of aging (Belsky et al., 2022). The epigenetic markers of aging were calculated using the *methscore* function in R (Xu et al., 2024); *bAge* was calculated based on *PCGrimAge*. The residuals from the regression of these measures on chronological age were used to obtain age-adjusted measures and were further standardized to a mean of zero and a standard deviation of one for all analyses.

Covariates

The confounders we considered were collected via questionnaires during interviews at baseline, including age (years), sex (male, female), country of birth (Australia/New Zealand, Northern Europe, Southern Europe), socioeconomic status (decile of socioeconomic indexes for areas (Australian Bureau of Statistics, 2023) based on postcode of residence at baseline), education level (1–8), smoking status (current, former, never smokers), smoking pack-years (log-transformed), alcohol consumption (grams/day), physical activity (frequency score, 0–16; Ainsworth et al., 1993), and diet quality (Alternative Healthy Eating Index 2010; Chiuve et al., 2012, calculated from the food frequency questionnaire). The physical activity frequency score summarized weekly frequencies of walking, non-vigorous activity, and vigorous activity (Ainsworth et al., 1993) with a score assigned to each type of activity: 1 = none, 1.5 = 1–2 times per week, and 4 = over 3 times per week. The overall frequency score was calculated as the sum of each individual score for the three types of activity, with vigorous activity being assigned twice the weight of the other categories (Ainsworth et al., 1993). Body mass index (BMI, kg/m^2) was calculated from weight and height physically measured by trained personnel at baseline.

Statistical analysis

We used linear regression models to assess the cross-sectional and prospective associations of baseline social factors and social isolation index with epigenetic age at baseline and follow-up. To assess the cross-sectional associations at baseline, two models were considered: Model 1 adjusted for age, sex, and country of birth; Model 2 additionally adjusted for socioeconomic status, education level, smoking status, smoking pack-years (log-transformed), alcohol consumption, physical activity, BMI, and diet quality. We further assessed the prospective associations of baseline social relationships and social isolation index with epigenetic age at follow-up, using the same models described above with additional adjustment for baseline epigenetic age. A restricted cubic spline term (3 knots at the 10th, 50th, and 90th percentiles) was applied to alcohol consumption to account for its nonlinear association with various health outcomes (Visontay et al., 2022).

Subgroup analysis

We used Model 2 in cross-sectional analyses for the social isolation index and living arrangement to assess potential effect modification by sex using the likelihood ratio test (LRT), and performed subgroup analyses for male and female, respectively.

A p-value threshold was calculated for cross-sectional and prospective analyses separately using the Bonferroni correction to control for type I error. The number of tests carried out using Model 1 was $N = 64$, which corresponds to a corrected p value of $0.05/64 = 8 \times 10^{-4}$.

Analyses were conducted with R 4.4.1.

Results

Sample characteristics

Of 6,208 participants at baseline, 2,504 (40.3%) were female. The average age was 58.8 years at baseline and 68.9 years at follow-up. The majority of participants were married (72%) and did not live alone (85.1%). Approximately half of the participants had more than five relatives who visited at least once a month, 30.6% of participants had more than 10 friends who could visit them without invitation, and 29.6% participated in social activities for more than 10 hours/week. Table 1 presents the full sample characteristics.

Cross-sectional associations

Higher levels of social isolation were associated with older epigenetic age (e.g., Model 1, per *SD*, *bAge*, β = 0.08, 95% CI: 0.05, 0.10, Table 2). Living alone was associated with older epigenetic age (e.g., *DunedinPACE*, β = 0.12, 95% CI: 0.05, 0.19). Participants who were divorced/separated/widowed had an older epigenetic age than those who were married/de facto (e.g., *bAge*, β = 0.21, 95% CI: 0.15, 0.28), whereas participants who were single had a similar epigenetic age to those who were married (e.g., *bAge*, β = 0.06, 95% CI: −0.03, 0.15; Supplementary Table 1 [see online supplementary material]). Compared with participants who did not participate in social activities, those with a social activity of 1–2 and 3–4 hours/week had slightly lower epigenetic age (e.g., *bAge*, 1–2 hours/week: β = −0.12, 95% CI: −0.21, −0.03; 3–4 hours/week: β = −0.15, 95% CI: −0.23, −0.07), whereas the benefits appeared lower in those with more than 5 hours/week (e.g., 5–9 hours/week, bAge: β = −0.08, 95% CI: −0.16, −0.01). Associations were all attenuated greatly after adjusting for sociodemographic and lifestyle factors (e.g., social isolation/*bAge*, β = 0.02, 95% CI: 0, 0.05; living alone/*DunedinPACE*, β = 0.06, 95% CI: −0.01, 0.12; divorced/*bAge*, β = 0.05, 95% CI: −0.01, 0.11).

Both the number of relatives and the number of friends visited had a weak negative association with epigenetic age (e.g., Model 2, relatives/*PCGrimAge*: β = −0.01, 95% CI: −0.02, 0.00; Supplementary Table 1 [see online supplementary material]).

Prospective associations

Little evidence was found for an association between baseline social isolation index and follow-up epigenetic age (e.g., Model 2, *PCGrimAge*, β = 0.02, 95% CI: −0.01, 0.06, Table 3). We found a weak association for living alone at baseline with follow-up epigenetic age, with the highest point estimate observed for *bAge*: Model 2, β = 0.10, 95% CI: 0.00, 0.21. The prospective association between social activity and epigenetic age was similar to the cross-sectional association with those participating in social activities for 1–2 and 3–4 hours/week having the lowest epigenetic age (e.g., *PCGrimAge*, 3–4 hours/week: β = −0.15, 95% CI: −0.27, −0.03), those participating in social activities for over 5 hours/week showed less reduction in epigenetic age (e.g., *PCGrimAge*, β = −0.06, 95% CI: −0.17, 0.05). Compared to the cross-sectional results, similar but weaker associations were observed for baseline marital status (Supplementary Table 2 [see online supplementary material]). Weak positive to null associations were found for the number of friends and the number of relatives visited, with follow-up markers of epigenetic age.

Effect modification by sex

We found strong evidence of effect modification by sex for the associations of social isolation and living alone with epigenetic age (LRTs: p ranging between .009 and 4×10^{-5}, Figure 1). Higher social isolation index was associated with older epigenetic age in men (e.g., Model 2, bAge: β = 0.06, 95% CI: 0.03, 0.09), but not in women (e.g., bAge: β = 0, 95% CI: −0.04, 0.04). Men who lived alone had 0.10 – *SD* (*PCGrimAge*, 95% CI: 0.01, 0.19) to 0.20 – *SD* (*DunedinPACE*, 95% CI: 0.10, 0.29) older epigenetic age, whereas the association was weakly negative in women (e.g., *DunedinPACE*, β = −0.03, 95% CI: −0.12, 0.07).

Discussion

This study assessed the cross-sectional and prospective associations between social relationships and epigenetic age in a large sample of middle-aged and older Australian adults followed over a decade. The associations of living alone and being socially isolated with epigenetic age were only observed in men, with strong evidence of effect modification by sex. The social isolation index showed a weak association with older epigenetic age cross-sectionally and no association prospectively. Positive social relationships, such as moderate amounts of social activities and a greater number of close relatives and friends, were also associated with younger epigenetic age, with stronger associations cross-sectionally. Although the construction of each epigenetic aging measure involved varying statistical approaches and variables to derive an aging phenotype, all aimed to maximize quantification of biological age, and their associations with social relationships were not substantially different from each other.

Our study adds to the limited evidence for an association between social relationships and epigenetic age. Rentscher et al. (2023) investigated perceived social support and stress, and the presence of social relationships in a large cohort of older Americans (HRS, N = 3,647), and reported negative associations of social support and social relationships with epigenetic age, where the associations for marital status were generally weaker than in our study. Joshi et al. reported a null cross-sectional association for the number of people living in the household with *GrimAge* and *PhenoAge* in 1,315 Canadian adults (Joshi et al., 2024). Another study using the same cohort (N = 1,479) found that higher levels of social participation were associated with younger *HannumAge* (Liang & Gomaa, 2024). Hillmann et al. (2023) used longitudinal data of 1,912 HRS participants and found weak negative associations of similar strengths as in our study for contacts with friends and lower *GrimAge* and *DunedinPACE* after 10-year follow-up. Freilich et al. analyzed longitudinal and prospective associations between loneliness and epigenetic age using 4,018 (across three waves of follow-up, each 4 years apart) older Americans from HRS and 1,310 middle-aged Americans (follow-up ~2.6 years), respectively (Freilich, Markon, Cole, et al., 2024; Freilich, Markon, Mann, et al., 2024). Interestingly, the associations they observed with qualitative measures of social isolation were stronger than our findings assessing objective social relationship variables, such as living alone and social isolation.

Several of the social relationships we investigated, including living alone, social activity, and marital status, showed prospective associations, suggesting their long-term benefits. The

Table 1. Characteristics of the study sample from the Melbourne Collaborative Cohort Study.

Variables	Cross-sectional			Prospective[a] *n* = 1,110
	Total *N* = 6,208	Male *n* = 3,704	Female *n* = 2,504	
Age, mean (*SD*)	58.8 (7.7)	59.4 (7.5)	58.0 (7.8)	57.6 (7.9)
Age at follow-up, mean (*SD*)				68.9 (8.0)
Country of birth, *N* (%)				
Australia/New Zealand	4,229 (68.1%)	2,370 (64.0%)	1,859 (74.2%)	842 (75.9%)
Northern Europe	403 (6.5%)	253 (6.8%)	150 (6.0%)	100 (9.0%)
Southern Europe	1,576 (25.4%)	1,081 (29.2%)	495 (19.8%)	168 (15.1%)
SEIFA score, median (IQR)	6 (3, 8)	5 (3, 8)	6 (3, 8)	7 (3, 9)
Smoking status, *N* (%)				
Never smoked	2,979 (48.0%)	1,340 (36.2%)	1,639 (65.5%)	561 (50.5%)
Current smoker	862 (13.9%)	592 (16.0%)	270 (10.8%)	110 (9.9%)
Former smoker	2,367 (38.1%)	1,772 (47.8%)	595 (23.8%)	439 (39.5%)
Smoking pack-years, mean (*SD*)	3.0 (3.1)	3.81 (3.07)	1.90 (2.76)	2.8 (3.0)
Alcohol consumption, median (IQR)	4.3 (0, 17.1)	9.1 (0, 25.7)	0 (0, 8.57)	7.1 (0, 19.1)
Education level, median (IQR)	4 (4, 6)	4 (4, 6)	4 (4, 6)	5 (4, 8)
BMI (kg/m^2), mean (*SD*)	27.2 (4.1)	27.4 (3.6)	26.9 (4.8)	26.7 (3.8)
AHEI-2010, mean (*SD*)	65.4 (14.2)	61.5 (10.9)	71.1 (16.5)	63.9 (11.2)
Physical activity score[b], median (IQR)	4 (1.5, 5.5)	4 (1.5, 5.5)	4 (1.5, 5.5)	4 (1.5, 6)
Living alone, *N* (%)				
No	5,281 (85.1%)	3,294 (88.9%)	1,987 (79.4%)	949 (85.5%)
Yes	927 (14.9%)	410 (11.1%)	517 (20.6%)	161 (14.5%)
Social activity, *N* (%)				
None	1,045 (16.8%)	654 (17.7%)	391 (15.6%)	167 (15.0%)
1–2 hours/week	881 (14.2%)	529 (14.3%)	352 (14.1%)	135 (12.2%)
3–4 hours/week	1,077 (17.3%)	640 (17.3%)	437 (17.5%)	191 (17.2%)
5–9 hours/week	1,367 (22.0%)	802 (21.7%)	565 (22.6%)	261 (23.5%)
10+ hours/week	1,838 (29.6%)	1,079 (29.1%)	759 (30.3%)	356 (32.1%)
Number of relatives, *N* (%)				
None	585 (9.4%)	382 (10.3%)	203 (8.1%)	95 (8.6%)
1–2	1,201 (19.3%)	736 (19.9%)	465 (18.6%)	224 (20.2%)
3–4	1,275 (20.5%)	813 (21.9%)	462 (18.5%)	253 (22.8%)
5–9	1,563 (25.2%)	884 (23.9%)	679 (27.1%)	285 (25.7%)
10+	1,584 (25.5%)	889 (24.0%)	695 (27.8%)	253 (22.8%)
Number of friends, *N* (%)				
None	405 (6.5%)	263 (7.1%)	142 (5.7%)	74 (6.7%)
1–2	839 (13.5%)	507 (13.7%)	332 (13.3%)	157 (14.1%)
3–4	1,374 (22.1%)	770 (20.8%)	604 (24.1%)	227 (20.5%)
5–9	1,691 (27.2%)	960 (25.9%)	731 (29.2%)	309 (27.8%)
10+	1,899 (30.6%)	1,204 (32.5%)	695 (27.8%)	343 (30.9%)
Baseline epigenetic aging measures				
***PCPhenoAge*, mean (*SD*)**	−0.10 (6.57)	−0.31 (6.10)	0.21 (7.20)	−0.82 (5.08)
***PCGrimAge*, mean (*SD*)**	−0.15 (3.87)	0.78 (3.66)	−1.53 (3.77)	−0.22 (3.18)
***bAge*, mean (*SD*)**	−0.02 (0.46)	0.09 (0.43)	−0.18 (0.44)	−0.05 (0.39)
***DunedinPACE*, mean (*SD*)**	−0.003 (0.13)	0.008 (0.12)	−0.020 (0.13)	−0.02 (0.12)
Follow-up epigenetic aging measures				
***PCPhenoAge*, mean (*SD*)**	–	–	–	0.47 (5.62)
***PCGrimAge*, mean (*SD*)**	–	–	–	0.10 (3.32)
***bAge*, mean (*SD*)**	–	–	–	0.01 (0.43)
***DunedinPACE*, mean (*SD*)**	–	–	–	0.004 (0.12)
Sample size, *N*[c]	**5,920**	**3,521**	**2,399**	**1,087**
Marital status, *N* (%)				
Married/De facto	4,470 (72.0%)	2,901 (78.3%)	1,569 (62.7%)	827 (74.5%)
Single	515 (8.3%)	297 (8.0%)	218 (8.7%)	106 (9.5%)
Divorced/Separated/Widowed	935 (15.1%)	323 (8.7%)	612 (24.4%)	154 (13.9%)
Social isolation index[d], mean (*SD*)	0.72 (0.96)	0.64 (0.93)	0.85 (0.99)	0.69 (0.92)

Note. AHEI-2010 = Alternative Healthy Eating Index 2010; BMI = body mass index; IQR = interquartile range; MET = metabolic equivalent of task; SEIFA = socioeconomic index for areas. All epigenetic aging measures were age-adjusted.

[a]Data presented were for baseline variables unless specified (for age and epigenetic age at follow-up).

[b]Physical activity frequency score was developed according to the frequency of different types of physical activity, including walking, less vigorous activity, and vigorous activity, ranges between 0 and 16, where 0 = none, 1.5 = one or two times per week, 4 = more than 3 times per week, twice the weight was assigned to vigorous activity.

[c]Marital status and social isolation index have a different sample size due to missing values in marital status.

[d]Social isolation index (range: 0–5) was calculated by assigning one point if the participant lived alone, attended no social activities, had no friends or relatives, or was divorced.

Table 2. Cross-sectional associations of social isolation index, living alone, and social activity with epigenetic age ($N = 6{,}208$).

Models	Item		*PCPhenoAge*			*PCGrimAge*			*bAge*			*DunedinPACE*		
		N	β	95% CI	*p*[a]	β	95% CI	*p*	β	95% CI	*p*	β	95% CI	*p*
Social isolation index[b]														
Model 1[c]		5,920	0.02	−0.01, 0.05	.14	0.08	0.05, 0.10	$\mathbf{1\times10^{-9}}$	0.08	0.05, 0.10	$\mathbf{1\times10^{-9}}$	0.07	0.04, 0.09	$\mathbf{1\times10^{-6}}$
Model 2[d]		5,920	0.02	−0.01, 0.04	.22	0.03	0.01, 0.05	.02	0.02	0.00, 0.05	.04	0.03	0.00, 0.05	.04
Living alone														
Model 1	No	5,281	Ref											
	Yes	927	0.01	−0.06, 0.08	.80	0.11	0.04, 0.18	.002	0.11	0.04, 0.18	.001	0.12	0.05, 0.19	.001
Model 2	No	5,281	Ref											
	Yes	927	0.01	−0.07, 0.08	.89	0.01	−0.05, 0.07	.79	0.01	−0.05, 0.06	.86	0.06	−0.01, 0.12	.10
Social activity (hours/week)														
Model 1	Score	6,208	0	−0.01, 0.01	.68	0	−0.01, 0.01	.97	0	−0.01, 0.01	.95	0	−0.01, 0.01	.89
	None	1,045	Ref											
	1–2	881	0.01	−0.08, 0.10	.86	−0.11	−0.20, −0.03	.01	−0.12	−0.21, −0.03	.01	−0.03	−0.12, 0.06	.53
	3–4	1,077	−0.04	−0.13, 0.04	.34	−0.13	−0.21, −0.05	.001	−0.15	−0.23, −0.07	$\mathbf{4\times10^{-4}}$	−0.10	−0.19, −0.02	.02
	5–9	1,367	−0.01	−0.09, 0.07	.75	−0.07	−0.15, 0.00	.06	−0.08	−0.16, −0.01	.03	−0.06	−0.14, 0.02	.17
	10+	1,838	−0.02	−0.09, 0.06	.66	−0.05	−0.13, 0.02	.16	−0.06	−0.13, 0.02	.14	−0.01	−0.09, 0.06	.71
Model 2	Score	6,208	0	−0.01, 0.01	.81	0	−0.00, 0.01	.71	0	−0.00, 0.01	.51	0	−0.00, 0.01	.31
	None	1,045	Ref											
	1–2	881	0.02	−0.07, 0.11	.71	−0.04	−0.11, 0.04	.31	−0.04	−0.11, 0.04	.33	0.04	−0.04, 0.12	.33
	3–4	1,077	−0.04	−0.12, 0.05	.40	−0.07	−0.14, 0.00	.07	−0.07	−0.14, 0.00	.07	−0.03	−0.11, 0.04	.40
	5–9	1,367	−0.01	−0.09, 0.07	.88	−0.01	−0.08, 0.06	.74	−0.01	−0.07, 0.06	.83	0.01	−0.06, 0.09	.75
	10+	1,838	−0.01	−0.09, 0.07	.83	−0.02	−0.08, 0.05	.63	−0.01	−0.07, 0.06	.81	0.04	−0.03, 0.11	.28

Note. Epigenetic aging measures were standardized to a mean of 0 and a standard deviation of 1. AHEI-2010 = Alternative Healthy Eating Index - 2010; BMI = body mass index; SEIFA-10 = deciles of socioeconomic index for areas.

[a]Two-sided *p*-values were calculated, and a threshold of $p = 8\times10^{-4}$ to control for type I error was considered, which corresponds to the Bonferroni correction for $N = 64$ tests carried out for each of the cross-sectional and prospective analyses. Significant *p* values by this threshold are highlighted in bold font.

[b]Social isolation index (range: 0–5) was calculated by assigning one point if the participant lived alone, attended no social activities, had no friends or relatives, or was divorced.

[c]Model 1 adjusted for age, sex, country of birth.

[d]Model 2 additionally adjusted for SEIFA-10, education level, smoking status, smoking pack-years, alcohol consumption (spline term), physical activity, BMI, and AHEI-2010.

Table 3. Prospective associations of social isolation index, living alone, and social activity with epigenetic age ($N = 1,110$).

Models	Item	*N*	*PCPhenoAge*			*PCGrimAge*			*bAge*			*DunedinPACE*		
			β	95% CI	*p*[a]	β	95% CI	*p*	β	95% CI	*p*	β	95% CI	*p*
Social isolation index[b]														
Model 1[c]		1,087	0.01	−0.04, 0.06	.69	0.03	−0.01, 0.06	.19	0.02	−0.02, 0.06	.33	0	−0.05, 0.06	.85
Model 2[d]		1,087	0	−0.05, 0.05	.98	0.02	−0.01, 0.06	.23	0.01	−0.02, 0.05	.48	−0.01	−0.06, 0.04	.79
Living alone														
Model 1	No	949	Ref											
	Yes	161	0.01	−0.12, 0.13	.93	0.09	−0.01, 0.19	.08	0.12	0.01, 0.22	.03	0	−0.14, 0.13	.97
Model 2	No	949	Ref											
	Yes	161	−0.01	−0.13, 0.11	.88	0.09	−0.01, 0.18	.09	0.10	0.00, 0.21	.04	−0.03	−0.16, 0.10	.68
Social activity (hours/week)														
Model 1	Score	1,110	0.01	−0.00, 0.02	.14	0	−0.01, 0.01	.38	0.01	−0.00, 0.02	.15	0	−0.01, 0.01	.92
	None	167	Ref											
	1–2	135	−0.14	−0.30, 0.02	.09	−0.19	−0.32, −0.06	.005	−0.10	−0.24, 0.03	.14	−0.12	−0.30, 0.06	.18
	3–4	191	−0.21	−0.36, −0.05	.01	−0.16	−0.28, −0.04	.01	−0.08	−0.21, 0.04	.20	−0.16	−0.32, 0.00	.05
	5–9	261	0.01	−0.14, 0.15	.94	−0.06	−0.18, 0.05	.26	−0.01	−0.13, 0.11	.84	−0.06	−0.21, 0.09	.44
	10+	356	−0.02	−0.16, 0.12	.77	−0.05	−0.16, 0.05	.32	0.01	−0.10, 0.13	.80	−0.07	−0.21, 0.08	.37
Model 2	Score	1,110	0.01	−0.00, 0.02	.17	0	−0.01, 0.01	.40	0.01	−0.00, 0.02	.18	0	−0.01, 0.01	.94
	None	167	Ref											
	1–2	135	−0.11	−0.27, 0.05	.19	−0.17	−0.30, −0.04	.01	−0.08	−0.22, 0.05	.22	−0.10	−0.27, 0.08	.27
	3–4	191	−0.19	−0.34, −0.04	.01	−0.15	−0.27, −0.03	.01	−0.07	−0.20, 0.05	.25	−0.13	−0.29, 0.03	.11
	5–9	261	0.02	−0.13, 0.16	.83	−0.06	−0.17, 0.05	.28	0	−0.12, 0.11	.93	−0.05	−0.20, 0.10	.54
	10+	356	−0.01	−0.15, 0.12	.86	−0.05	−0.16, 0.06	.39	0.02	−0.10, 0.13	.78	−0.06	−0.21, 0.08	.38

Note. Epigenetic aging measures were standardized to a mean of 0 and a standard deviation of 1. AHEI-2010 = Alternative Healthy Eating Index - 2010; BMI = body mass index; SEIFA-10 = deciles of socioeconomic index for areas.

[a]Two-sided *p*-values were calculated, and a threshold of $p = 8 \times 10^{-4}$ to control for type I error was considered, which corresponds to the Bonferroni correction for $N = 64$ tests carried out for each of the cross-sectional and prospective analyses. Significant *p* values by this threshold are highlighted in bold font.

[b]Social isolation index (range: 0–5) was calculated by assigning one point if the participant lived alone, attended no social activities, had no friends or relatives, or was divorced.

[c]Model 1 adjusted for age, sex, country of birth, and the corresponding epigenetic aging measure at baseline.

[d]Model 2 additionally adjusted for SEIFA-10, education level, smoking status, smoking pack-years, alcohol consumption (spline term), physical activity, BMI, and AHEI-2010.

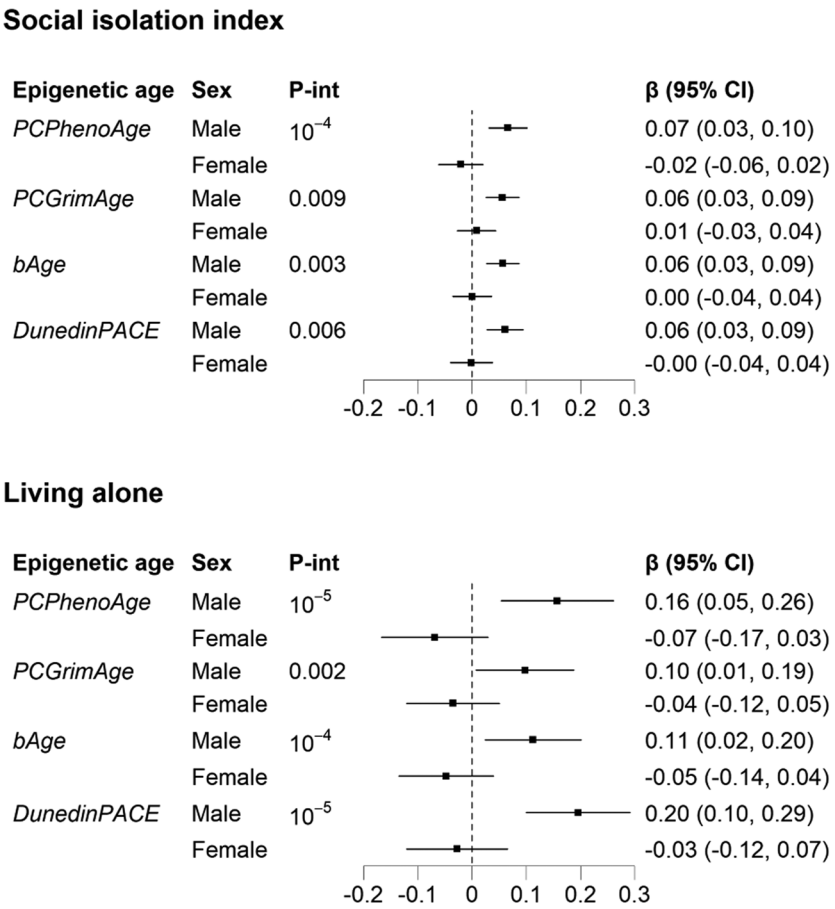

Figure 1. Subgroup analysis of the effect modification by sex for the associations of social isolation and living alone with epigenetic age ($N = 6{,}208$). The models adjusted for age, country of birth, SEIFA-10, education level, smoking status, smoking pack-years, alcohol consumption, physical activity, BMI, AHEI-2010. *p*-int stands for the *p* values for interaction calculated from the likelihood ratio tests comparing models with and without interaction terms. Two-sided *p*-values were calculated, and a threshold of $p = .006$ to control for type I error was considered, which corresponds to the Bonferroni correction for $N = 8$ tests carried out. 7/8 tests for interaction passed this threshold. AHEI-2010 = Alternative Healthy Eating Index - 2010; BMI = body mass index; SEIFA-10 = deciles of socioeconomic index for areas.

effect sizes of social relationship components we investigated were generally weaker than those for other major lifestyle-related factors such as smoking, weight, and diet for which we previously found per *SD* increases were associated with 0.1 – 0.3 *SD* changes in epigenetic age (Li et al., 2024), but were similar or even slightly stronger than for blood glucose (Li, Hodge, et al., 2025) and physical activity (Zheng et al., 2025). Previous studies reported that social isolation and loneliness are associated with unhealthy behaviors such as smoking, being physically inactive, and eating a poorer diet (Shankar et al., 2011; Steptoe et al., 2024), which are associated with older epigenetic age (Dugué et al., 2022; Fiorito et al., 2019; Li et al., 2024; Zheng et al., 2025). These analyses were adjusted for baseline epigenetic age, therefore suggesting that the health-related benefits of positive social relationships accumulate over a long period of time (a decade in our study). Although some differences between cross-sectional and prospective analyses were observed, the follow-up sample of our study was not large enough to discern true differences from random variability.

The social isolation index we used was calculated using a similar set of items as the index created by Shankar et al. (2011), which has generated insights into age-related traits in a number of studies (Shankar et al., 2011; Steptoe et al., 2013, 2024). In our baseline sample, the distribution of the social isolation index (mean = 0.72, *SD* = 0.96) was very similar to that observed in their study, including participants with similar characteristics (mean = 0.75, *SD* = 0.85). At follow-up, the index was slightly lower (mean = 0.69), suggesting less highly isolated participants, possibly due to healthier attendees.

Previous studies exploring the associations of social relationships with aging or health-related factors tended to focus on medical conditions and inflammation biomarkers such as CRP. A previous study of 5,512 MCCS participants found no association between social relationships and successful aging (defined as being disease-free, having no impairment or difficulty in physical functioning, and having no severe psychological distress after 70 years old) (Hodge et al., 2013). Steptoe et al. (2013) analyzed data of 6,500 participants from the English Longitudinal Study of Ageing and reported that both social isolation and loneliness were associated with elevated risks of death. Another study using participants from the same cohort found that isolated individuals had higher blood pressure, and higher CRP and fibrinogen levels (Shankar et al., 2011). The epigenetic aging measures we considered are increasingly recognized to be powerful indicators of biological aging, showing stronger associations with disease and mortality risk than CRP or other aging/inflammation markers, and may therefore provide a more comprehensive account of the effect of social relationships on health and aging.

Our results confirmed our hypothesis of an effect modification by sex in the associations of social isolation and living alone with epigenetic age. Other studies also observed such sex differences in health-related aspects of social relationships. Wang et al. (2023) synthesized results from 90 studies and reported a higher risk of mortality in socially isolated individuals, more so in men than women. Another study including 1,715 older adults found that being married was associated with lower CRP levels, particularly in men (Sbarra, 2009). A study of 46,054 participants living across over 200 countries found that men feel lonely more often than women (Barreto et al., 2021). Therefore, it is possible that men who lived alone or were socially isolated were more likely to feel lonely than women, which could accumulate over time and lead to unhealthy behaviors that accelerate their epigenetic age. This might be explained by the different experiences of men and women in their social relationships and types of activities (Calasanti, 2009; Dury et al., 2021; Fuhrer & Stansfeld, 2002), which could therefore influence their mental health and well-being, and eventually contribute to their health and aging processes.

The strengths of our study included the use of prospective data from a large sample of middle-aged and older adults with detailed information on a broad range of quantitative aspects of social relationships. House et al. (1988) conceptualized that social relationships exert not just a direct impact on health but also indirect effects, for example, via buffering of psychosocial stress. Our study investigated the quantity and frequency of various types of social relationships, offering a fairly comprehensive quantification of the role of objective social relationships in the aging process. We used four up-to-date, powerful measures of epigenetic age that, to our knowledge, provide the most accurate quantification of biological age. In addition, the sex difference in the associations of living alone and social isolation with epigenetic age has potential implications in informing future health prevention and sex-specific needs of social support. Our study therefore added robust epidemiological evidence and valuable insights to understanding the health impacts of social relationships.

One of the limitations of our study is that the MCCS participants were generally healthier than the general Australian population (Giles & English, 2002) and thus likely more socially connected. Our prospective analyses were based on a smaller subset of participants who were randomly selected from controls in seven nested cancer case-control studies and therefore were considered representative of the entire cohort. However, we acknowledge that this could limit the generalizability of our prospective findings. The MCCS is a large prospective omnibus cohort study that was designed to address a broad range of research questions, in particular the roles of lifestyle factors in the development of cancer and other chronic health conditions (Milne et al., 2017), and therefore lacked the collection of detailed data on gender-specific or social science-specialized and qualitative information. Our study nevertheless provided a fairly comprehensive assessment of the associations of quantitative, objective aspects of social relationships, in particular, companionship, with aging in a well-powered population-based sample. Future studies could investigate more qualitative and subjective aspects of social relationships, particularly perceived loneliness, social support, or social distress (Cyranowski et al., 2013; Umberson & Montez, 2010) and compare these with the quantitative aspects, as well as other markers of aging and health, to provide a more comprehensive picture of the effects of social relationships on biological age. Additionally, as our study focused on middle-aged and older adults, their contact frequencies and participation in social activity were likely affected by their health status, which we could not control for as we had limited data on medical conditions. Social relationships are likely to influence health both directly and indirectly via other mechanisms such as influencing mental health and reducing stress, receiving external supports, and increasing health awareness (Cohen, 2004; House et al., 1988). Epigenetic aging measures are powerful biological aging indicators because their development is based on capturing multiple health-related aspects, including lifestyle via smoking pack-years in *GrimAge* and obesity in *DunedinPACE* (Belsky et al., 2022; Dugué et al., 2021; Li et al., 2024; Lu et al., 2019). Therefore, the attenuation in the effect estimates in Model 2 is likely attributable to both confounding and mediation effects. Health and social behaviors are intricately related and influence each other, which guided our choice of covariates. In our study, the associations between social relationships and epigenetic age were relatively weak and similar across epigenetic aging measures, as were the amounts of attenuation after adjustment for a range of health-related variables. We acknowledge that formal mediation analyses would be beneficial for further quantification of the pathways by which social relationships influence epigenetic age, in terms of lifestyle, inflammation, or other factors. Our study tested a wide range of social relationship variables with four up-to-date epigenetic aging measures both cross-sectionally and prospectively, and the results were overall consistent with our hypothesis and previous studies that found social relationships to be weakly positively associated with epigenetic age (Hillmann et al., 2023; Joshi et al., 2024; Rentscher et al., 2023). Our findings were also consistent with our hypothesis and previous findings that social isolation and living alone may show sex-specific associations with health-related traits, with stronger associations in males than in women (Qi et al., 2023; Sbarra, 2009; Wang et al., 2023; Zhao et al., 2022). Nevertheless, we cannot discard the possibility that some of our results may have been false positives; additional studies are required to confirm our findings. We considered p-value thresholds based on the Bonferroni correction separately for cross-sectional and prospective analyses. These thresholds are nevertheless considered stringent and do not account for the relatively strong correlations between the tests carried out. Even though many tests failed to pass the thresholds, most results were consistent with our a priori hypotheses, and our study offers a valuable quantification of the associations between social relationships and epigenetic age as a potential pathway by which these may be beneficial to healthy aging.

To conclude, positive social relationships in middle-aged and older Australians showed some associations with younger epigenetic age cross-sectionally and a decade later. Social isolation and living alone were associated with older epigenetic age in men only. Our study therefore confirms, via the use of epigenetic aging markers, that being socially active is beneficial to physiological health.

Supplementary material

Supplementary data are available at *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences* online.

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Conflict of interest

None declared.

Data availability

Due to ethical constraints related to the consent of participants, we cannot share the full deidentified data set. For most participants included in this study, the data are publicly available under controlled access at dbGaP (#phs003213.v1.p1, for which more details can be found at https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi? study_id=phs003213.v1.p1).

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