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Social relationships and epigenetic aging in older adulthood: Results from the Health and Retirement Study

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ABSTRACT

Growing evidence suggests that social relationship quality can influence age-related health outcomes, although how the quality of one's relationships directly relates to the underlying aging process is less clear. We hypothesized that the absence of close relationships as well as lower support and higher strain within existing relationships would be associated with an accelerated epigenetic aging profile among older adults in the Health and Retirement Study. Adults (N = 3,647) aged 50–100 years completed ratings of support and strain in relationships with their spouse, children, other family members, and friends. They also provided a blood sample that was used for DNA methylation profiling to calculate *a priori*-specified epigenetic aging measures: Horvath, Hannum, PhenoAge, GrimAge, and Dunedin Pace of Aging methylation (DunedinPoAm38). Generalized linear models that adjusted for chronological age, sex, and race/ethnicity and applied a false discovery rate correction revealed that the absence of marital and friend relationships related to an older GrimAge and faster DunedinPoAm38. Among those with existing relationships, lower support from a spouse, child, other family, and friends and higher strain with friends related to an older PhenoAge and GrimAge and faster DunedinPoAm38. In secondary analyses that further adjusted for socioeconomic and lifestyle factors, lower support from other family members and friends was associated with greater epigenetic aging. Findings suggest that the absence of close relationships and lower support within existing relationships—particularly with family members and friends—relate to accelerated epigenetic aging in older adulthood, offering one mechanism through which social relationships might influence risk for age-related declines and disease.

1. Introduction

A sizeable literature has established that the quality of one's social relationships can have a significant impact on health and well-being across the lifespan. (Holt-Lunstad et al., 2010; Uchino et al., 2018) Current theoretical frameworks posit that social relationships promote health by fulfilling basic needs for social connection and by providing a buffering resource during times of stress; however, they can also be a source of conflict and strain. (Cohen, 2004; Pietromonaco and Collins, 2017; Birmingham and Holt-Lunstad, 2018) Researchers have identified that perceived social support and social strain are distinct dimensions of relationship quality that can influence health. (Cohen, 2004) Whereas social support is defined as the availability of resources, advice, understanding, or acceptance within relationships, (Cohen, 2004) social strain has been described as the presence of criticism, insensitivity, demands, or feelings of being let down by close others. (Brooks and Dunkel, 2011) Although relatively fewer studies have focused on social strain, both lower social support and greater strain have been concurrently and prospectively associated with multiple age-related conditions in middle- and older adulthood, including functional limitations, (Newsom et al., 2008; Mavandadi et al., 2007) poorer physical and cognitive functioning, (Seeman and Chen, 2002; Tun et al., 2013; Seeman et al., 2011) and incidence and progression of cardiovascular disease. (de Vogli et al., 2007; Wang et al., 2005; Orth-Gomer et al., 1993)

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Social support and strain have also been identified as reliable predictors of all-cause mortality (Holt-Lunstad et al., 2010; Kroenke et al., 2013; Birditt and Antonucci, 2008) as well as mortality from cancer, (Pinquart and Duberstein, 2010; Boen et al., 2018) stroke, (Tanne et al., 2004) and cardiovascular disease. (Barth et al., 2010) These findings suggest that social relationships influence aging, although how these qualities of relationships directly relate to the underlying aging process is less clear.

A growing body of evidence has linked social relationship quality to key biological aging processes such as inflammation and telomere shortening, pointing to potential pathways through which relationships may influence these aging-related outcomes. For instance, several studies found that lower social support was associated with elevated peripheral markers of inflammation including interleukin (IL)-6, IL-8, tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) in middle-aged and older adults, (Elliot et al., 2018; Uchino et al., 2018) and increased activation of transcription factor nuclear factor-κB (NF-κB), which regulates the expression of inflammatory genes. (Robles et al., 2018) Social strain has also been associated with greater circulating IL-6 and TNF-α (Whisman and Sbarra, 2012; Kiecolt-Glaser et al., 2005) and NF-κB signaling. (Robles et al., 2018) However, a handful of studies did not find associations between social support and circulating CRP, an indicator of systemic inflammation. (Uchino et al., 2018) Prior research has also suggested that older adults who reported lower social support had shorter telomeres, (Rentscher et al., 2020; Carroll et al., 2013; Zalli et al., 2014) the protective caps at the end of chromosomes that naturally shorten over time but are vulnerable to accelerated shortening and are considered a hallmark of aging. (López-Otín et al., 2013).

Epigenetic markers of aging offer another approach to track the underlying biological aging process. Epigenetic aging refers to age-related alterations to the epigenome (i.e., chemical compounds that modify DNA but do not change its coding sequence), which include histone modifications, chromatin remodeling, and changes in DNA methylation patterns. (López-Otín et al., 2013) One of the most widely used approaches to measuring epigenetic aging, termed the "epigenetic clock," was developed by identifying distinct regions of the DNA that become hypo- or hyper-methylated with age and correlates with chronological age across a range of cell types and tissues. (Horvath, 2013; Hannum et al., 2013) More recent versions of the epigenetic clock, commonly referred to as "second generation" clocks, were developed based on DNA methylation patterns that are associated with multiple biomarkers and are predictive of phenotypic aging outcomes (e.g., morbidity and mortality; PhenoAge) (Levine et al., 2018) and time to death (GrimAge). (Lu et al., 2019) In contrast to the epigenetic clock measures, the Dunedin Pace of Aging methylation (DunedinPoAm38) measure was developed to estimate an individual's *rate* of biological aging at a single point in time, based on data from the Dunedin cohort and changes in 18 biomarkers of organ-system integrity assessed over a 12-year period. (Belsky et al., 2020) Measures of epigenetic age are useful because they assess biological aging in a metric that is intuitive (i.e., years) and can identify individuals who are biologically older or younger than their chronological age. (Crimmins et al., 2021; Ferrucci et al., 2020) They also integrate multiple physiological systems into a single numerical measure of biological age that in turn predicts multiple age-related conditions, including frailty, cognitive decline, and cancer, as well as all-cause and specific-cause (e.g., cancer) mortality, and importantly, may be modifiable by interventions and show feasibility for clinical use (Ferrucci et al., 2020; Fransquet et al., 2019).

The present study extends the literature on social relationships and biological aging by investigating associations between social relationships and epigenetic markers of aging in a large, nationally representative sample of older adults in the Health and Retirement Study (HRS). Whereas most prior research on social relationships and biological aging has focused exclusively on general social support that is non-specific to relationship source or support that is aggregated across sources (e.g., spouse, family, friends), we aimed to examine both positive and negative dimensions of relationship quality in older adults' relationships with their spouse, children, other family members, and friends. One exception to this is a study that assessed support and strain in marital, family, and friend relationships, finding that strain with family members was most robustly associated with a higher inflammatory burden in middle-aged and older adults. (Yang et al., 2014) In addition, a recent study with a subset of HRS participants found that greater support from friends (but not change in support over time) was associated with a slower Dunedin pace of aging up to 10 years later. (Hillmann et al., 2023) Given that not all participants in the HRS sample were married or had other types of close relationships, we first aimed to test whether the presence versus absence of these relationships was associated with epigenetic aging, and among those with existing relationships, whether social support and strain within these relationships related to epigenetic aging. We focused on both support and strain within different relationship types due to the changes in social ties that may occur with aging, whereby some relationships may become more salient and stable and fulfill different purposes or needs (e.g., intimacy, companionship, caregiving) in older adulthood. Finally, we focused on five established, *a priori*-identified epigenetic aging measures derived from DNA methylation profiling to provide insights into how relationship quality may influence the underlying process of aging at the molecular level. These measures are the most commonly assessed in previous research and include the two original "first generation" Horvath and Hannum clocks, as well as the newer "second generation" PhenoAge, GrimAge, and DunedinPoAm38 measures.

Based on previous research linking social relationship quality to age-related conditions and other hallmarks of biological aging (i.e., inflammation and telomere length), we hypothesized that, overall, an absence of close relationships would be associated with an accelerated epigenetic aging profile relative to the presence of close relationships, which provide at least an opportunity for social contact and support in older adulthood. However, we would like to note that previous research has yielded mixed findings regarding parental status and health, (Nomaguchi and Milkie, 2020; Umberson et al., 2010) with some studies suggesting that having children may confer a health benefit in older age. (Modig et al., 2017; Ning et al., 2020; Read and Grundy, 2017; Zhang and Fletcher, 2021) We also hypothesized that among those in existing relationships, lower support and higher strain would be associated with an accelerated epigenetic aging profile. Given that the extant literature is not sufficiently developed, we did not generate hypotheses about whether we would observe differences in the strength of associations between specific relationship types and epigenetic aging, although there is preliminary evidence to suggest that relationships with family and friends may be particularly relevant.

2. Methods

2.1. Ethics statement

This investigation has been conducted in accordance with the ethical standards, the Declaration of Helsinki, and national and international guidelines and has been approved by the Institutional Review Board at the University of Michigan.

2.2. Participants

The present study used data from the University of Michigan Health and Retirement Study (HRS), a longitudinal, nationally representative study of nearly 20,000 U.S. adults over the age of 50. For this study, participants were 4,018 adults aged 50–100 years who provided a blood sample as part of the 2016 Venous Blood Study (VBS) that was used to assess epigenetic aging. (Crimmins et al., 2020) HRS participants were excluded from the VBS if they were not community dwelling (i.e., they were incarcerated or residing in an assisted living setting of any type). The epigenetic aging subsample of the VBS was designed to be

representative of the U.S. population when weighted. For the present analysis, 86 participants were missing data for at least one covariate. To retain participants, analyses included all participants who provided reports of their relationship status, support, or strain for each type of relationship. Thus, the statistical models for each relationship type had different sample sizes (see Tables 2–5 for details). The weighted sample had a mean age of 68.7 years and was 55.1% female. Participants self-identified as Hispanic (7.9%), non-Hispanic Black (9.3%), non-Hispanic of another race (3.3%), and non-Hispanic white (79.5%). The educational distribution of the participants included less than a high school education (13.1%), high school diploma or GED (30.2%), some college (26.0%), and college diploma or higher (30.7%).

2.3. Procedures

Participants in the HRS study completed core interviews every other year, and self-administered psychosocial questionnaires were also given to alternating random halves of the full sample every two years. As part of the self-administered psychosocial questionnaire, participants completed ratings of support and strain in their relationships with their spouse, children, other family members, and friends. If participants were missing social support and strain data from the 2016 or 2014 questionnaire, we used data from the 2012 or 2010 questionnaire, respectively. If participants were missing data from the 2012 or 2010 questionnaire, we used data from 2008 (when the social support and strain measures were first included in the questionnaire). Most social relationship data were obtained from the 2016 or 2014 questionnaire (81.9 to 87.2%), with smaller proportions obtained from 2012 or 2010 (11.5 to 14.8%) and 2008 (1.3 to 3.3%).[1] Participants also provided a blood sample as part of the 2016 Venous Blood Study (VBS) and DNA methylation profiling was performed using the Illumina Infinium Methylation EPIC BeadChip (Illumina, San Diego, CA) to derive the epigenetic aging measures, as described in detail previously. (Crimmins et al., 2020; Crimmins et al., 2017).

2.4. Measures

2.4.1. Social relationship measures

Participants completed ratings of perceived support and strain within four types of relationships: their spouse (husband, wife, or partner with whom they live), child or children, other immediate family members (e.g., brothers, sisters, parents, cousins, grandchildren), and friends. For each relationship type, three items assessed support ("How much do they really understand the way you feel about things?", "How much can you rely on them if you have a serious problem?", and "How much can you open up to them if you need to talk about your worries?") and four items assessed strain ("How often do they make too many demands on you?", "How much do they criticize you?", "How much do they let you down when you are counting on them?", and "How much do they get on your nerves?"). Responses for each item ranged from 1 (*not at all*) to 4 (*a lot*) and items were averaged to create a composite score, with higher scores indicating greater support or strain. We created a relationship status variable for each type of relationship that was coded as "present" (vs. absent) if participants reported having that type of relationship.

2.4.2. Epigenetic aging measures

The epigenetic aging measures for this study included the Horvath, Hannum, PhenoAge, and GrimAge clocks and DunedinPoAm38. The Horvath estimate of epigenetic age is based on DNA methylation levels at 353 cytosine-phosphate-guanine base pair (CpG) sites and was developed as a predictor of chronological age across multiple tissues and cell types. (Horvath, 2013) The Hannum estimate of epigenetic age is based on DNA methylation levels at 71 CpG sites and was developed as a predictor of chronological age in whole blood samples. (Hannum et al., 2013) Phenotypic epigenetic age—also referred to as PhenoAge—is estimated from DNA methylation levels at 513 CpG sites and was developed as a predictor of mortality risk based on 9 markers of tissue and immune function (albumin, creatinine, serum glucose, C-reactive protein [CRP], lymphocyte percent, mean (red) cell volume, red cell distribution width, alkaline phosphatase, and white blood cell count) and chronological age in whole blood samples. (Levine et al., 2018) GrimAge is estimated from DNA methylation levels at 1,030 total CpG sites and was developed as a predictor of time to death based on 7 DNA methylation surrogates of plasma proteins associated with physiological risk and stress factors (adrenomedullin, beta-2 microglobulin, cystatin C, growth differentiation factor 15 [GDF-15], leptin, plasminogen activation inhibitor 1 [PAI-1], tissue inhibitor metalloproteinase 1 [TIMP-1]) and a DNA methylation-based estimator of smoking pack years. (Lu et al., 2019) DunedinPoAm38 is estimated from DNA methylation levels at 46 CpG sites and was developed to estimate an individual's *rate* of biological aging, expressed in years of epigenetic aging per chronological year. DunedinPoAm38 is based on a composite estimate of change in 18 biomarkers of organ-system integrity assessed over a 12-year period in the Dunedin cohort study (Belsky et al., 2020).

2.5. Covariates

Several variables that might affect epigenetic aging estimates were evaluated as covariates in the main analyses based on previous research, (Beach et al., 2015; Crimmins et al., 2021; Levine et al., 2018; Lu et al., 2019; Oblak et al., 2021) including chronological age, biological sex (female, with male as the reference group), and self-identified race/ethnicity (non-Hispanic Black, Hispanic, and non-Hispanic other race, with non-Hispanic white as the reference group). Secondary analyses also considered educational attainment (less than high school, high school diploma or GED, and some college, with a college diploma or higher as the reference group), body mass index (BMI; kg/m^2) category (25 to < 30 as overweight, 30 to < 35 as obese I, and ≥ 35 as obese II, with < 25 as normal or underweight as the reference group), smoking status (current and past, with never as the reference group), and alcohol use (1–4 drinks per day, and 5 + drinks per day, with none as the reference group). Post-hoc sensitivity analyses evaluated physical activity as an additional covariate: Participants reported how often they engaged in mild, moderate, and vigorous physical activity, with responses ranging from 1 (*hardly ever or never*) to 4 (*more than once a week or every day*), and items were averaged to create a composite score representing the frequency of any type of physical activity. Given that variations in blood cell composition may influence the estimation of and account for some age-related differences in epigenetic aging, (Crimmins et al., 2021; Crimmins et al., 2017) an additional set of post-hoc sensitivity analyses evaluated the percentage of monocyte, natural killer (NK) cell, B cell, and T cell (CD4 total, CD8 naïve, CD8 total) subsets assessed using flow cytometry and neutrophils assessed using hematology complete blood count.

2.6. Data analysis plan

To examine whether having a specific type of social relationship (spouse, children, other family, friends) was associated with epigenetic aging, we first conducted generalized linear models (GLMs) for each epigenetic aging measure that included participants' relationship status for each relationship type (present vs. absent) as separate predictors, adjusting for chronological age, biological sex, and self-identified race/ethnicity. Next, to examine whether social relationship quality was associated with epigenetic aging, we conducted a second set of models that included each social support or strain measure as separate predictors, adjusting for chronological age, biological sex, and self-

[1] A post-hoc sensitivity analysis that excluded participants who provided social relationship data in 2008 suggested a similar overall pattern of findings.

identified race/ethnicity. We then applied a 5% false discovery rate (FDR) correction for multiple testing (Benjamini and Hochberg, 1995) across the five epigenetic aging measures for each social domain.

We performed an additional set of models as secondary analyses that further adjusted for educational attainment and lifestyle factors, including BMI category, smoking status, and alcohol use, and post-hoc analyses that adjusted for physical activity and cell subsets. Observations were weighted to be nationally representative of community dwelling older U.S. adults using sampling weights provided by HRS. For participants who did not have specific weights for the 2016 Venous Blood Sample, weights from the 2016 HRS core interview were used. All analyses were conducted in R 4.1.3 "One Push-Up" using the tidyverse, jtools, and survey packages. (Wickham et al., 2019; Long, 2020; Lumley, 2004).

3. Results

3.1. Preliminary analyses

Sample characteristics appear in Table 1. Approximately two thirds of participants were married (65.1%), and a majority had children (85.9%), other family members (93.4%), and friends (91.2%). On average, participants reported slightly higher support than strain for all relationship types. The average epigenetic age for the clock measures (Horvath, Hannum, PhenoAge, GrimAge) ranged from 54.0 to 67.2 years and the average DunedinPoAm8 was 1.1 years of epigenetic age for each year of chronological age. Social support and strain variables were moderately correlated (r = 0.10–0.51; Supplemental Table 1). Epigenetic aging variables were low to highly correlated (r = 0.12–0.77; Supplemental Table 2), which is consistent with other studies (Belsky et al., 2018; Li et al., 2020).

3.2. Spousal relationship status and quality

Consistent with hypotheses, being married was associated with a younger GrimAge (unstandardized $b = -0.822$, $SE = 0.219$, $p < .001$) and a slower DunedinPoAm38 ($b = -0.012$, $SE = 0.004$, $p = .004$), and these associations remained statistically significant following FDR correction (Table 2). Being married was not associated with the Horvath, Hannum, or PhenoAge measures.

Among those who were married, greater spousal support was associated with a younger Hannum age ($b = -0.380$, $SE = 0.184$, $p = .04$), PhenoAge ($b = -0.604$, $SE = 0.248$, $p = .02$), and GrimAge ($b = -0.333$, $SE = 0.125$, $p = .01$) and a slower DunedinPoAm38 ($b = -0.008$, $SE = 0.003$, $p = .02$), and associations with GrimAge and DunedinPoAm38 remained statistically significant following FDR correction (Fig. 1; Table 2). In secondary analyses that further adjusted for educational attainment and lifestyle factors (BMI category, smoking status, and alcohol use), greater spousal support was associated with a younger PhenoAge ($b = -0.528$, $SE = 0.248$, $p = .04$; however, this association was reduced to non-significance following FDR correction. Spousal support was not associated with the Horvath measure.

Among those who were married, greater spousal strain was associated with an older Hannum age ($b = 0.348$, $SE = 0.142$, $p = .02$); however, this association was reduced to non-significance following FDR correction (Fig. 2; Table 2). In secondary analyses that further adjusted for educational attainment and lifestyle factors, greater spousal strain was also associated with an older Hannum age ($b = 0.294$, $SE = 0.138$, $p = .04$), but the association was not significant following FDR correction. Spousal strain was not associated with the Horvath, PhenoAge, GrimAge, or DunedinPoAm38 measures.

3.3. Child relationship status and quality

Consistent with hypotheses, having a child was associated with a younger Hannum age ($b = -0.582$, $SE = 0.286$, $p = .047$) and GrimAge ($b = -0.588$, $SE = 0.292$, $p = .0496$); however, these associations were reduced to non-significance following FDR correction (Table 3). In secondary analyses that further adjusted for educational attainment and lifestyle factors, having a child was associated with a younger GrimAge ($b = -0.583$, $SE = 0.240$, $p = .02$), but the association was not significant following FDR correction. Having a child was not associated with the Horvath, PhenoAge, or DunedinPoAm38 measures.

Among those who had a child, greater support from one's child was associated with a younger PhenoAge ($b = -0.464$, $SE = 0.201$, $p = .03$) and GrimAge ($b = -0.389$, $SE = 0.120$, $p = .002$) and a slower DunedinPoAm38 ($b = -0.008$, $SE = 0.003$, $p = .003$), and the associations remained statistically significant following FDR correction (Fig. 1; Table 3). In secondary analyses that further adjusted for educational attainment and lifestyle factors (BMI category, smoking status, and alcohol use), greater support from one's child was associated with a younger GrimAge ($b = -0.247$, $SE = 0.107$, $p = .03$) and slower DunedinPoAm38 ($b = -0.006$, $SE = 0.002$, $p = .01$); however, the

Table 1
Sample characteristics for older adults in the Health and Retirement Study with epigenetic aging data (N = 3,647).

	Mean / %	SD	Range
Chronological age, years	68.7	9.3	50–100
Biological sex			
Female	55.1		
Male	44.9		
Self-identified race/ethnicity			
Black, non-Hispanic	9.3		
Hispanic	7.9		
Other race, non-Hispanic	3.3		
White, non-Hispanic	79.5		
Educational attainment			
Less than high school	13.1		
High school diploma or GED	30.2		
Some college	26.0		
College diploma or higher	30.7		
BMI category			
Normal or underweight (<25)	27.0		
Overweight (25 to < 30)	37.3		
Obese I (30 to < 35)	22.3		
Obese II (>35)	13.4		
Smoking status			
Never	44.7		
Current	10.4		
Former	44.8		
Alcohol use			
None	56.2		
1–4 drinks per day	41.2		
5+ drinks per day	0.03		
Physical activity	2.9	0.9	1–4
Relationship status			
Has a spouse	65.1		
Has children	85.9		
Has other family	93.4		
Has friends	91.2		
Social support			
Spousal support	3.4	0.7	1–4
Child support	3.2	0.8	1–4
Other family support	2.8	0.9	1–4
Friend support	3.0	0.8	1–4
Social strain			
Spousal strain	2.0	0.7	1–4
Child strain	1.7	0.7	1–4
Other family strain	1.6	0.6	1–4
Friend strain	1.4	0.5	1–4
Epigenetic aging variables			
Horvath	65.2	9.4	29.9–114.5
Hannum	54.0	8.9	32.0–107.8
PhenoAge	56.8	9.9	27.4–101.7
GrimAge	67.2	8.5	45.6–99.6
DunedinPoAm38	1.1	0.1	0.8–1.4

Note. DunedinPoAm38 = Dunedin Pace of Aging methylation; BMI = body mass index.

Table 2
Generalized linear models with spousal relationship status, support, and strain predicting epigenetic aging.

	Horvath			Hannum			PhenoAge			GrimAge			DunedinPoAm38		
Model	*β*	*b(SE)*	*p*	*β*	*b(SE)*	*p*	*β*	*b(SE)*	*p*	*β*	*b(SE)*	*p*	*β*	*b(SE)*	*p*
Spousal status (has a spouse)															
Model 1	−0.001	−0.018 (0.250)	0.94	−0.001	−0.021 (0.203)	0.92	−0.018	−0.386 (0.282)	0.18	**−0.045**	**−0.822 (0.219)**	**<0.001***	**−0.065**	**−0.012 (0.004)**	**0.004***
Model 2	−0.002	−0.031 (0.272)	0.91	0.004	0.078 (0.205)	0.70	−0.011	−0.233 (0.280)	0.41	−0.009	−0.165 (0.217)	0.45	−0.015	−0.003 (0.004)	0.40
Spousal support															
Model 1	0.002	0.035 (0.228)	0.88	**−0.028**	**−0.380 (0.184)**	**0.04**	**−0.041**	**−0.604 (0.248)**	**0.02***	**−0.026**	**−0.333 (0.125)**	**0.01***	**−0.064**	**−0.008 (0.003)**	**0.02***
Model 2	0.002	0.030 (0.221)	0.89	−0.025	−0.339 (0.172)	0.06	**−0.036**	**−0.528 (0.248)**	**0.04**	−0.008	−0.096 (0.123)	0.44	−0.035	−0.005 (0.003)	0.15
Spousal strain															
Model 1	0.001	0.014 (0.221)	0.95	**0.026**	**0.348 (0.142)**	**0.02**	0.012	0.167 (0.215)	0.44	−0.012	−0.150 (0.136)	0.28	0.026	0.003 (0.003)	0.32
Model 2	−0.002	−0.026 (0.221)	0.91	**0.022**	**0.294 (0.138)**	**0.04**	0.007	0.105 (0.218)	0.63	−0.017	−0.208 (0.115)	0.08	0.018	0.002 (0.003)	0.46

Note. *b* = unstandardized coefficient. Bold font denotes statistically significant associations. Asterisks indicate statistically significant associations following false discovery rate correction. Model 1 adjusts for chronological age, biological sex, and self-identified race/ethnicity. Model 2 adjusts for Model 1 variables as well as educational attainment, body mass index category, smoking status, and alcohol use. The sample size for the spousal status models is $n = 3{,}646$ (Model 1) and $n = 3{,}571$ (Model 2), for the spousal support models is $n = 2{,}714$, and for the spousal strain models is $n = 2{,}699$.

Table 3
Generalized linear models with child relationship status, support, and strain predicting epigenetic aging.

	Horvath			Hannum			PhenoAge			GrimAge			DunedinPoAm38		
Model	*β*	*b(SE)*	*p*	*β*	*b(SE)*	*p*	*β*	*b(SE)*	*p*	*β*	*b(SE)*	*p*	*β*	*b(SE)*	*p*
Child status (has a child)															
Model 1	−0.022	−0.653 (0.413)	0.12	**−0.021**	**−0.582 (0.286)**	**0.047**	−0.020	−0.627 (0.406)	0.13	**−0.022**	**−0.588 (0.292)**	**0.0496**	−0.026	−0.007 (0.006)	0.24
Model 2	−0.023	−0.684 (0.427)	0.12	−0.020	−0.570 (0.310)	0.07	−0.024	−0.725 (0.415)	0.09	**−0.022**	**−0.583 (0.240)**	**0.02**	−0.025	−0.007 (0.005)	0.20
Child support															
Model 1	−0.012	−0.156 (0.214)	0.47	−0.012	−0.144 (0.159)	0.37	**−0.035**	**−0.464 (0.201)**	**0.03***	**−0.034**	**−0.389 (0.120)**	**0.002***	**−0.063**	**−0.008 (0.003)**	**0.003***
Model 2	−0.010	−0.124 (0.216)	0.57	−0.008	−0.102 (0.158)	0.52	−0.029	−0.390 (0.203)	0.06	**−0.022**	**−0.247 (0.107)**	**0.03**	**−0.046**	**−0.006 (0.002)**	**0.01**
Child strain															
Model 1	0.014	0.213 (0.187)	0.26	0.012	0.163 (0.151)	0.28	0.032	0.493 (0.283)	0.09	**0.024**	**0.319 (0.136)**	**0.02**	**0.044**	**0.006 (0.003)**	**0.02**
Model 2	0.011	0.163 (0.190)	0.40	0.006	0.085 (0.144)	0.56	0.024	0.373 (0.291)	0.21	0.005	0.063 (0.110)	0.57	0.015	0.002 (0.002)	0.39

Note. *b* = unstandardized coefficient. Bold font denotes statistically significant associations. Asterisks indicate statistically significant associations following false discovery rate correction. Model 1 adjusts for chronological age, biological sex, and self-identified race/ethnicity. Model 2 adjusts for Model 1 variables as well as educational attainment, body mass index category, smoking status, and alcohol use. The sample size for the child status models is $n = 3{,}676$ (Model 1) and $n = 3{,}602$ (Model 2), for the child support models is $n = 3{,}306$, and for the child strain models is $n = 3{,}314$.

Table 4
Generalized linear models with other family relationship status, support, and strain predicting epigenetic aging.

	Horvath			Hannum			PhenoAge			GrimAge			DunedinPoAm38		
Model	*β*	*b(SE)*	*p*	*β*	*b(SE)*	*p*	*β*	*b(SE)*	*p*	*β*	*b(SE)*	*p*	*β*	*b(SE)*	*p*
Other family status (has other family)															
Model 1	0.018	0.683 (0.506)	0.18	**−0.019**	**−0.691 (0.341)**	**0.048**	−0.021	−0.825 (0.448)	0.07	−0.015	−0.494 (0.419)	0.24	−0.033	−0.012 (0.008)	0.18
Model 2	0.020	0.737 (0.513)	0.16	**−0.020**	**−0.701 (0.339)**	**0.045**	−0.021	−0.818 (0.453)	0.08	−0.008	−0.266 (0.347)	0.45	−0.021	−0.008 (0.008)	0.35
Other family support															
Model 1	0.003	0.030 (0.137)	0.83	−0.016	−0.164 (0.118)	0.17	0.00003	0.0003 (0.136)	0.998	**−0.024**	**−0.237 (0.113)**	**0.04**	**−0.060**	**−0.006 (0.002)**	**0.004***
Model 2	0.006	0.069 (0.136)	0.61	−0.012	−0.125 (0.114)	0.28	0.005	0.061 (0.136)	0.66	**−0.019**	**−0.187 (0.082)**	**0.03**	**−0.051**	**−0.005 (0.002)**	**0.002***
Other family strain															
Model 1	0.009	0.138 (0.241)	0.57	0.014	0.207 (0.167)	0.22	−0.001	−0.015 (0.244)	0.95	0.016	0.219 (0.148)	0.15	0.032	0.005 (0.003)	0.16
Model 2	0.007	0.098 (0.238)	0.68	0.010	0.146 (0.169)	0.39	−0.007	−0.107 (0.258)	0.68	0.002	0.024 (0.123)	0.85	0.007	0.001 (0.003)	0.72

Note. b = unstandardized coefficient. Bold font denotes statistically significant associations. Asterisks indicate statistically significant associations following false discovery rate correction. Model 1 adjusts for chronological age, biological sex, and self-identified race/ethnicity. Model 2 adjusts for Model 1 variables as well as educational attainment, body mass index category, smoking status, and alcohol use. The sample size for the other family status models is n = 3,710 (Model 1) and n = 3,635 (Model 2), for the other family support models is n = 3,570, and for the other family strain models is n = 3,569.

associations were reduced to non-significance following FDR correction. Support from one's child was not associated with the Horvath or Hannum measures.

Among those who had a child, greater strain with one's child was associated with an older GrimAge (b = 0.319, SE = 0.136, p =.02) and faster DunedinPoAm38 (b = 0.006, SE = 0.003, p =.02); however, the associations were reduced to non-significance following FDR correction (Fig. 2; Table 3). Strain with one's child was not significantly associated with the Horvath, Hannum, or PhenoAge measures in these models. In secondary models that further adjusted for educational attainment and lifestyle factors (BMI category, smoking status, and alcohol use), strain with one's child was not associated with any of the epigenetic aging measures.

3.4. Other family member relationship status and quality

Consistent with hypotheses, having other family members was associated with a younger Hannum age (b = −0.691, SE = 0.341, p =.048); however, this association was reduced to non-significance following FDR correction (Table 4). In secondary analyses that further adjusted for educational attainment and lifestyle factors, having other family members was associated with a younger Hannum age (b = −0.701, SE = 0.339, p =.045), but the association was not significant following FDR correction. Having other family members was not associated with the Horvath, PhenoAge, GrimAge, or DunedinPoAm38 measures.

Among those who had other family members, greater family support was associated with a younger GrimAge (b = −0.237, SE = 0.113, p =.04) and a slower DunedinPoAm38 (b = −0.006, SE = 0.002, p =.004), and the association with DunedinPoAm38 remained statistically significant following FDR correction (Fig. 1; Table 4). In secondary analyses that further adjusted for educational attainment and lifestyle factors, greater support from other family members was associated with a younger GrimAge (b = −0.187, SE = 0.082, p =.03) and a slower DunedinPoAm38 (b = −0.005, SE = 0.002, p =.002) and the association with DunedinPoAm38 remained statistically significant following FDR correction. Family support was not associated with the Horvath, Hannum, or PhenoAge measures.

Among those who had other family members, strain within family relationships was not associated with any of the epigenetic aging measures (Fig. 2; Table 4).

3.5. Friend relationship status and quality

Consistent with hypotheses, having friends was associated with a younger GrimAge (b = −1.624, SE = 0.344, p <.001) and a slower DunedinPoAm38 (b = −0.019, SE = 0.006, p =.005), and these associations remained statistically significant following FDR correction (Table 5). In secondary analyses that further adjusted for educational attainment and lifestyle factors, having friends was associated with a younger GrimAge (b = −0.814, SE = 0.312, p =.01), but the association was reduced to non-significance following FDR correction. Having friends was not associated with the Horvath, Hannum, or PhenoAge measures.

Among those who had friends, greater friend support was associated with a younger GrimAge (b = −0.379, SE = 0.105, p <.001) and slower DunedinPoAm38 (b = −0.005, SE = 0.002, p =.02), and these associations remained statistically significant following FDR correction (Fig. 1; Table 5). In secondary analyses that further adjusted for educational attainment and lifestyle factors, the association with GrimAge remained statistically significant (b = −0.264, SE = 0.090, p =.006), including following FDR correction. Friend support was not associated with the Horvath, Hannum, or PhenoAge measures.

Among those who had friends, greater strain with friends was associated with an older GrimAge (b = 0.432, SE = 0.204, p =.04) and a faster DunedinPoAm38 (b = 0.013, SE = 0.004, p =.003), and the association with DunedinPoAm38 remained statistically significant following FDR correction (Fig. 2; Table 5). Strain with friends was not associated with the Horvath, Hannum, or PhenoAge measures in these models. In secondary analyses that further adjusted for educational attainment and lifestyle factors, strain with friends was not associated with epigenetic aging.

Table 5
Generalized linear models with friend relationship status, support, and strain predicting epigenetic aging.

	Horvath			Hannum			PhenoAge			GrimAge			DunedinPoAm38		
Model	*β*	*b(SE)*	*p*	*β*	*b(SE)*	*p*	*β*	*b(SE)*	*p*	*β*	*b(SE)*	*p*	*β*	*b(SE)*	*p*
Friend status (has friends)															
Model 1	−0.005	−0.167 (0.409)	0.68	−0.009	−0.270 (0.312)	0.39	−0.013	−0.453 (0.562)	0.42	**−0.056**	**−1.624 (0.344)**	**<0.001***	**−0.060**	**−0.019 (0.006)**	**0.005***
Model 2	−0.002	−0.066 (0.408)	0.87	−0.004	−0.110 (0.294)	0.71	−0.008	−0.273 (0.594)	0.65	**−0.028**	**−0.814 (0.312)**	**0.01**	−0.016	−0.005 (0.006)	0.44
Friend support															
Model 1	−0.014	−0.180 (0.170)	0.29	0.002	0.030 (0.137)	0.83	−0.006	−0.077 (0.204)	0.71	**−0.033**	**−0.379 (0.105)**	**<0.001***	**−0.045**	**−0.005 (0.002)**	**0.02***
Model 2	−0.013	−0.163 (0.173)	0.35	0.007	0.090 (0.145)	0.54	0.002	0.024 (0.215)	0.91	**−0.023**	**−0.264 (0.090)**	**0.006***	−0.030	−0.004 (0.002)	0.09
Friend strain															
Model 1	0.002	0.039 (0.306)	0.90	0.009	0.163 (0.229)	0.48	−0.016	−0.328 (0.347)	0.35	**0.025**	**0.432 (0.204)**	**0.04**	**0.071**	**0.013 (0.004)**	**0.003***
Model 2	−0.002	−0.029 (0.301)	0.92	0.002	0.036 (0.214)	0.87	−0.025	−0.511 (0.330)	0.13	−0.005	−0.088 (0.165)	0.60	0.024	0.004 (0.004)	0.21

Note. *b* = unstandardized coefficient. Bold font denotes statistically significant associations. Asterisks indicate statistically significant associations following false discovery rate correction. Model 1 adjusts for chronological age, biological sex, and self-identified race/ethnicity. Model 2 adjusts for Model 1 variables as well as educational attainment, body mass index category, smoking status, and alcohol use. The sample size for the friend status models was $n = 3{,}702$ (Model 1) and $n = 3{,}627$ (Model 2), for the friend support models is $n = 3{,}475$, and for the friend strain models is $n = 3{,}473$.

3.6. Post-hoc sensitivity analyses with adjustment for physical activity and cell subsets

In post-hoc sensitivity analyses that further adjusted for physical activity, the pattern of findings remained the same with two exceptions (Supplemental Table 3). Specifically, the association between support from one's children and a younger GrimAge ($b = -0.169$, $SE = 0.103$, $p = .11$) was reduced to non-significance and the association between support from friends and a younger GrimAge ($b = -0.217$, $SE = 0.093$, $p = .03$) was no longer statistically significant with the FDR correction.

In a second set of post-hoc sensitivity analyses that adjusted for cell subsets, the overall pattern of findings was similar, and the magnitude of associations with epigenetic aging increased for some of the relationship variables (Supplemental Table 4). Specifically, several associations that were statistically or marginally significant in previous models increased in magnitude such that they remained statistically significant following FDR correction. For instance, having other family members was associated with a younger Hannum age ($b = -0.847$, $SE = 0.332$, $p = .02$) and PhenoAge ($b = 1.261$, $SE = 0.476$, $p = .01$), and having friends was associated with a younger GrimAge ($b = -0.795$, $SE = 0.259$, $p = .004$). In addition, lower support from one's child was associated with an older PhenoAge ($b = -0.544$, $SE = 0.202$, $p = .01$) and faster DunedinPoAm38 ($b = -0.006$, $SE = 0.002$, $p = .01$), whereas greater strain with one's spouse was associated with an older Hannum age ($b = 0.415$, $SE = 0.136$, $p = .004$). Also of note, the association between lower support from other family members and a faster DunedinPoAm38 ($b = -0.005$, $SE = 0.002$, $p = .01$) was reduced to marginal significance following FDR correction in models that adjusted for cell subsets.

4. Discussion

The present study investigated associations between social relationships and epigenetic aging in a nationally representative sample of older adults in the Health and Retirement Study. Specifically, we examined whether the absence of close relationships as well as lower perceived support and higher strain in existing relationships with one's spouse, children, other family members, and friends were associated with an accelerated epigenetic aging profile. As hypothesized, older adults who did not have a spouse or friend relationships were biologically older based on GrimAge and DunedinPoAm38 estimates than their peers who were married or had friendships. Individuals who reported lower support—feeling less understood, that they could not rely upon, and/or that they could not open up—in relationships with their spouse, children, family members, or friends had an accelerated epigenetic aging profile based on PhenoAge, GrimAge, and DunedinPoAm38 estimates relative to same-aged peers who experienced greater support. Specifically, the difference in epigenetic age between older adults who reported the lowest and highest levels of support ranged from 1.02 to 1.83 years, depending on the relationship type and the epigenetic measure. In addition, individuals who reported that their friends made too many demands on them, criticized them, let them down, and/or got on their nerves had an accelerated aging profile based on DunedinPoAm38 estimates relative to same-aged peers who experienced less strain. It was somewhat surprising that social support and strain were less consistently or not at all associated with the "first generation" Horvath and Hannum clocks, although these measures were developed to predict chronological age alone and are likely capturing different aspects of the aging process than the "second generation" PhenoAge, GrimAge, and DunedinPoAm38 measures, which were developed based on biomarkers that are predictive of morbidity and mortality. (Oblak et al., 2021) Given that previous research has linked relationship quality to age-related conditions such as functional limitations, (Newsom et al., 2008; Mavandadi et al., 2007) poorer physical and cognitive functioning, (Seeman and Chen, 2002; Tun et al., 2013; Seeman et al., 2011) cardiovascular disease, (de Vogli et al., 2007; Wang et al., 2005; Orth-Gomer et al., 1993) and mortality, (Holt-Lunstad et al., 2010; Kroenke

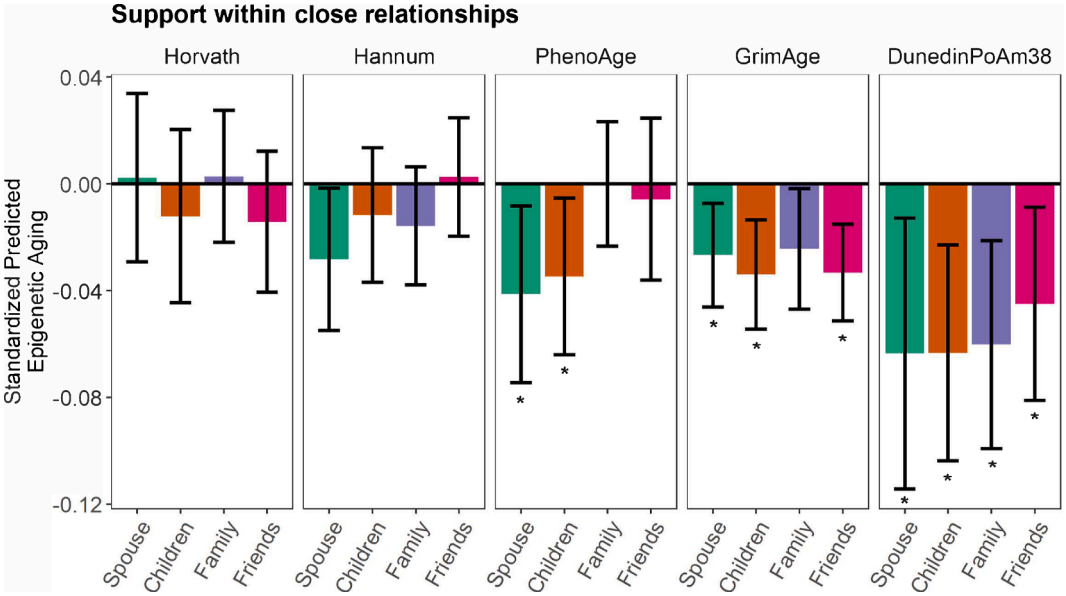

Fig. 1. Associations between social support and epigenetic aging in the Health and Retirement Study. Generalized linear models (GLMs) with standardized coefficients (relationship and epigenetic aging variables were *z*-scored) showing associations between perceived support from one's spouse, children, other family members, and friends and epigenetic aging. Models adjusted for chronological age, biological sex, and self-identified race/ethnicity. Error bars represent 95% confidence intervals for each point estimate. Asterisks denote associations that remained statistically significant following false discovery rate correction for multiple testing. Associations between support from friends and family members and GrimAge and DunedinPoAm38, respectively, remained statistically significant in secondary models that further adjusted for educational attainment and lifestyle factors.

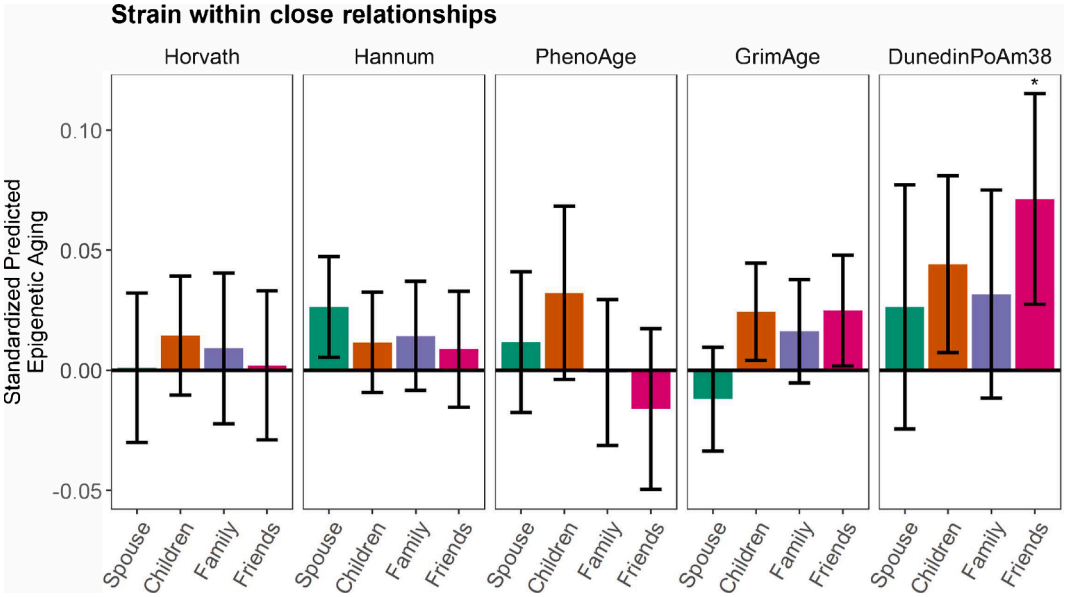

Fig. 2. Associations between social strain and epigenetic aging in the Health and Retirement Study. Generalized linear models (GLMs) with standardized coefficients (relationship and epigenetic aging variables were *z*-scored) showing associations between perceived strain with one's spouse, children, other family members, and friends and epigenetic aging. Models adjusted for chronological age, biological sex, and self-identified race/ethnicity. Error bars represent 95% confidence intervals for each point estimate. Asterisks denote associations that remained statistically significant following false discovery rate correction for multiple testing. Social strain was not associated with epigenetic aging in secondary models that further adjusted for educational attainment and lifestyle factors.

et al., 2013; Birditt and Antonucci, 2008) these findings suggest that the DNA methylation patterns captured by these "second generation" clocks may serve as a plausible mechanism through which relationship processes influence aging and health.

In secondary analyses that also adjusted for educational attainment and lifestyle factors (BMI, smoking status, and alcohol use) that have been associated with epigenetic aging in prior research, (Beach et al., 2015; Crimmins et al., 2021; Levine et al., 2018; Lu et al., 2019) relationship quality was more robustly associated with epigenetic aging than relationship status, with stronger effects for social support than for social strain. Specifically, lower support from friends and family members (other than a spouse or children) was associated with an older GrimAge and faster DunedinPoAm38, respectively, over and above these well-established health risk factors, although the effect sizes for associations with social support ($\beta = -0.023$ and -0.051, respectively) were typically smaller than the effect sizes for educational attainment (0.122 to 0.199) and lifestyle factors (BMI: 0.004 to 0.358; smoking status: 0.229 to 1.349; alcohol use: −0.029 to 0.157) in models that

adjusted for all the factors. In post-hoc sensitivity analyses that further adjusted for physical activity, the magnitude of the association between support from friends and GrimAge was reduced slightly and did not remain statistically significant with FDR correction. Overall, the pattern of findings from these secondary analyses suggest that lifestyle factors may mediate associations between social relationship status and quality and epigenetic aging, although this remains to be empirically tested. Interestingly, adjustment for cell subsets strengthened some of the associations, such that having other family members was significantly associated with a younger Hannum age and PhenoAge and having friends was associated with a younger GrimAge. In addition, lower support from one's child was associated with an older PhenoAge and faster DunedinPoAm38, whereas greater strain with one's spouse was associated with an older Hannum age. These results suggest that individual variations in blood cell composition observed in whole blood (particularly neutrophils, B cells, and CD8 naïve cells)—which fluctuate in response to biological and psychosocial conditions and the aging process itself (Hawkley and Cacioppo, 2004; Dhabhar, 2014; Schedlowski et al., 1993; Herbert and Cohen, 1993)—can influence estimation of epigenetic aging, and that not accounting for these variations may in some cases obscure associations with social factors.

These findings point to the importance of friend and family relationships for older adults and are consistent with prior research with population-based samples of middle-aged and older adults, which found that strain with family members was more strongly associated with a higher inflammatory burden than strain within other relationships (Yang et al., 2014) and support from friends (but not other relationship types) predicted a slower DunedinPoAm38 approximately 10 years later in a smaller sample of HRS participants (effect size: $\beta = -0.07$). (Hillmann et al., 2023) Our results that GrimAge and DunedinPoAm38 were most robustly associated with relationship quality are particularly noteworthy in a sample of older adults who may be experiencing or beginning to experience declines in their health, given that these measures are predictive of multiple age-related conditions such as declines in cognitive and physical function, cancer, and cardiovascular disease, as well as time to death. (Levine et al., 2018; Lu et al., 2019) In addition, relationships with close others become more salient, and in some cases, more stable or involuntary (e.g., more difficult to choose to exit) in older adulthood as individuals who experience health declines may rely more on others for support. (Uchino, 2009; Wrzus et al., 2013) Therefore, the experience of being in close relationships—particularly with family and friends—that are characterized by lower support may have a particular influence on the health and well-being of older adults—and epigenetic aging may be one mechanism through which this occurs.

Results from this study contribute to a growing literature on the influence of social relationships on key biological aging processes. Previous research has linked social support and strain to peripheral markers of inflammation, activation of transcription factor NF-κB, which regulates the expression of inflammatory genes, and telomere length. These findings also extend an emerging literature on psychosocial stress and epigenetic aging, which has linked exposure to early life adversity (Palma-Gudiel et al., 2020) and traumatic experiences (Wolf et al., 2018) to accelerated epigenetic aging in adulthood. Given that the absence of close relationships, as well as low social support and high strain are considered to be forms of social stress, the presence and quality of social relationships may affect epigenetic aging through similar stress-related pathways; however, the specific cellular and molecular mechanisms through which stress may impact epigenetic aging are not well understood. In response to stress, chronic or repeated activation of the sympathetic nervous system (SNS) and the hypothalamus-adrenal–pituitary (HPA) axis releases neuroendocrine mediators (e.g., catecholamines, glucocorticoids) that interact with receptors on the surface of cells. Mounting evidence suggests that this stress signaling cascade can initiate multiple biological aging pathways within cells, including those that contribute to DNA damage, telomere attrition, cellular senescence, and inflammation. (Polsky et al., 2022) It will be important for future research to begin to delineate the specific biological pathways through which experiences of stress and social adversity (and associated neuroendocrine mediators) may modify DNA methylation and other epigenetic processes to alter rates of aging.

Our results should be considered in light of study limitations, which suggest directions for future research. Most notably, at this time, the Health and Retirement Study has measured epigenetic aging at a single timepoint, which limited the present analyses to concurrent associations and precluded the investigation of the influence of social relationships on *changes* in epigenetic aging over time. On account of this, we were also unable to test an alternative hypothesis that epigenetic aging, as a marker of an underlying aging process, might influence changes in social relationship status and quality. It will be important for future research to examine the directionality of the observed effects and to link these associations with age-related health outcomes at future timepoints. In addition, the social support measures for this study focused primarily on emotional support and did not address other forms of support, such as tangible or informational support. Although this study accounted for the potential contributions of lifestyle factors such as smoking, alcohol use, and physical activity to epigenetic aging, whether these and other behavioral and psychological factors (e.g., depression, stress appraisals) (Uchino et al., 2018) mediate associations between social relationships and epigenetic aging in older adulthood remains a question for future investigation. Finally, although the HRS 2016 Venous Blood Study includes several validated measures of epigenetic aging, the whole genome DNA methylation data are not currently available, which precluded an analysis of specific or novel DNA methylation sites that may be associated with social relationship status and quality beyond the epigenetic aging measures.

Despite these limitations, the present study extends the literature on social relationships and biological aging by demonstrating that the absence of close relationships as well as lower support and higher strain in existing relationships are associated with an accelerated epigenetic aging profile in older adults. Furthermore, lower support from family and friends was associated with an accelerated aging profile over and above well-established lifestyle factors such as smoking status and alcohol use. These findings suggest that epigenetic aging may be a plausible biological mechanism through which social relationship quality might influence aging and age-related health outcomes such as cancer, cardiovascular disease, dementia, and early mortality. In addition, this investigation involved a large, socioeconomically diverse, and nationally representative sample of community dwelling older adults in the United States, which increases generalizability of the findings. In light of emerging evidence that these epigenetic aging mechanisms may be sensitive to and modifiable by behavioral interventions, (Brody et al., 2016; Waziry et al., 2023) these results suggest that close relationship quality—particularly with family members and friends—may represent a behavioral target for intervention in older adulthood that has the potential to prevent, slow, or reverse accelerated aging and extend the healthspan (number of years free from age-related disease and disability) and lifespan.

CRediT authorship contribution statement

Kelly E. Rentscher: Conceptualization, Writing – original draft. **Eric T. Klopack:** Conceptualization, Formal analysis, Writing – review & editing. **Eileen M. Crimmins:** Conceptualization, Writing – review & editing. **Teresa E. Seeman:** Writing – review & editing. **Steve W. Cole:** Writing – review & editing. **Judith E. Carroll:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data are publicly available from the Health and Retirement Study at https://hrs.isr.umich.edu/

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2023.09.001.

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