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RESEARCH ARTICLE

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Relationship stress and epigenetic age acceleration among older U.S. adults in the Midlife in the United States study

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ABSTRACT

Background: Chronic interpersonal stress has been linked to accelerated biological aging, but questions remain about which relationship stress domains may be most consequential during midlife.

Research design and methods: Linear regression models quantified the cross-sectional associations between domain-specific relationship stressors (marital risk, partner strain, family strain, friendship strain) and next-generation epigenetic clocks (DunedinPACE and GrimAge2) in 1,310 midlife adults from the Midlife in the United States study (mean age = 51, SD = 13).

Results: Controlling for sociodemographic and health behaviors, we found that friendship strain was uniquely associated with accelerated aging (GrimAge2: 0.03 SD increase, 95% CI: 0.01, 0.05, $p = 0.003$; DunedinPACE: 0.05 SD increase, 95% CI: 0.01, 0.09, $p = 0.030$). No statistically significant associations were observed for the other stressors with GrimAge2 or DunedinPACE in fully adjusted models.

Conclusions: These findings identify friendship strain as a potential specific risk factor for accelerated biological aging in midlife. Future research should investigate behavioral and physiological mechanisms linking friendship quality to cellular aging.

PLAIN LANGUAGE SUMMARY

Stress from close relationships can harm health, but it is less clear how different types of relationship stress, such as from family, romantic partners, or friends, affect how the body ages. In this study, we analyzed data from a national sample of midlife adults in the United States to explore the links between relationship stress and the body's aging process. Biological aging was assessed using "epigenetic clocks," blood-based biomarkers that reflect age-related changes at the cellular level. We found that stress from friendships, but not family or romantic relationships, was linked to faster biological aging. These findings suggest that peer relationships may have a unique influence on long-term health. Reducing stress from friendships could be a promising direction for supporting healthy aging.

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KEYWORDS
Biological embedding; interpersonal strain; stress physiology; epigenetic epidemiology; psychobiological processes

1. Background and objectives

Chronic interpersonal stress is recognized as a social determinant of health, with a growing body of evidence linking it to a range of adverse health outcomes, including depression, cardiovascular disease, and immune dysfunction [1,2]. Among adults, the quality of social relationships, especially with romantic partners, family members, and close friends, has been associated with morbidity, mortality, and cognitive decline in later life [3–5]. These associations may be driven by chronic psychosocial stress, which accelerates fundamental biological aging processes through sustained activation of stress-responsive physiological systems [6].

At the physiological level, interpersonal stress may trigger activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, leading to prolonged elevations in glucocorticoids and catecholamines [6–10]. Over time, this persistent activation promotes a cascade of detrimental effects, including systemic inflammation, oxidative stress, and immune dysregulation [6]. These processes collectively contribute to physiological dysregulation that can drive cellular aging [11,12]. Recent advances in epigenetic research have provided powerful new tools to quantify these effects through DNA methylation-based biomarkers of aging, commonly referred to as "epigenetic clocks" [13].

Among the most advanced of these next-generation biomarkers are DunedinPACE [14] and GrimAge2 [15], which reflect distinct approaches to epigenetic aging [14,15]. In particular, DunedinPACE was developed by tracking longitudinal within-person physiological decline (e.g., cardiovascular, metabolic, and immune system dysregulation) to quantify the pace of aging [14,16]. In contrast, GrimAge2 uses DNA methylation surrogates for plasma proteins (e.g., ADM, B2M, Cystatin-C) to predict mortality risk [15]. This methodological distinction explains their differential sensitivity; DunedinPACE has been associated with outcomes such as cognitive decline, dementia, chronic disease incidence (e.g., myocardial infarction and

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Article Highlight

- Chronic interpersonal stress is hypothesized to accelerate biological aging via social and physiological pathways.
- This study examined domain-specific relationship stressors (marital risk, partner strain, family strain, and friendship strain) in relation to epigenetic aging in midlife adults.
- Among all domains, only friendship strain was associated with faster epigenetic aging, as measured by GrimAge2 and DunedinPACE.
- Findings highlight peer relationships as a unique and underrecognized contributor to aging biology.

stroke), and early mortality [14,16,17], while GrimAge2 has demonstrated strong predictive power for all-cause mortality, and age-related outcomes such as coronary heart disease and impaired lung function, outperforming earlier-generation epigenetic clocks [15].

In addition to their predictive power, DunedinPACE and GrimAge 2 are recognized for their sensitivity to social exposure, particularly psychosocial stressors [14,18]. For example, individuals reporting higher levels of discrimination exhibited faster epigenetic aging as measured by both DunedinPACE and GrimAge2 compared to those reporting lower levels [18]. These associations were particularly robust for DunedinPACE [18]. Similarly, exposure to childhood trauma has been linked with faster GrimAge acceleration [19]. Despite substantial evidence linking early-life adversity and other psychosocial stressors to accelerated epigenetic aging [20–22], few studies have examined the role of relationship stressors in adulthood, particularly in large, population-based samples. Existing literature has predominantly focused on marital quality or partner strain, often overlooking the potential cumulative and domain-specific effects of stress occurring in other important relational contexts, such as familial or friendship networks [23,24]. This represents a significant gap in scientific literature, as negative interactions across multiple relationship domains may independently, and perhaps synergistically, contribute to accelerated biological aging through distinct or overlapping pathways.

Recent work by Rentscher et al. [4] has begun to address this gap using Health and Retirement Study data and analyzing composite support/strain scores across relationships (spouse, child, family, friends) in older adults. They found that both lower support and higher strain predicted accelerated epigenetic aging (i.e., DunedinPACE/GrimAge), independent of sociodemographic and behavioral factors [4]. While these findings highlight the importance of relationship quality for biological aging in later life, examining these associations in a cohort encompassing a broader age range, including middle-aged adults, would enhance the generalizability of these observations. Furthermore, the original study assessed only the presence or absence of strain. To achieve a more informative dose-response understanding of how social strain influences epigenetic aging, research should prioritize assessing the quantitative levels or cumulative burden of these negative social exposures. Building on this foundation, we examined relationship stress and epigenetic aging in the Midlife in the United States (MIDUS) study using domain-specific measures of relationship stress (marital risk, partner strain, family strain, friendship strain) and next-generation epigenetic clocks (DunedinPACE and GrimAge2) with enhanced sensitivity to distinct aging processes. To ensure broad generalizability, we prioritized relationship stressors that are broadly applicable across our study population, specifically, those involving family and friends, as our primary exposures. Marital and romantic partner strain were examined as secondary exposures, allowing us to assess whether similar associations extended to this relationship context. This approach enabled us to (a) disentangle unique stressor associations across relationship domains, and (b) examine both the pace of aging (DunedinPACE) and mortality-related aging (GrimAge2), two distinct but complementary epigenetic biomarkers, to provide a more nuanced understanding of how different aspects of biological aging may be influenced by relationship stressors.

2. Research design and methods

2.1. Study design and setting

We analyzed data from the MIDUS, a national health cohort of English-speaking, non-institutionalized U.S. adults aged 25–74 years [25]. MIDUS included several phases. The original cohort ($n = 7,108$) was recruited between 1995–1996 using random digit dialing. During Wave 2, MIDUS enhanced African American representation by enrolling an additional 592 participants from Milwaukee, Wisconsin. Between 2011–2014, the MIDUS Refresher Study was initiated to replenish the original cohort, recruiting 4,085 new adult participants. This refresher sample included 508 African American adults from Milwaukee, Wisconsin.

Subsets of participants from both MIDUS cohorts enrolled in follow-up biomarker projects: the MIDUS Biomarker Project (2004–2009; $n = 1,255$) from the original cohort and the MIDUS Refresher Biomarker Study (2012–2016; $n = 863$) from the refresher cohort [26]. Of the 2,118 biomarker participants, 1,310 had available DNA methylation epigenetic age scores. These participants completed comprehensive health assessments during a 2-day clinic visit that collected various bioindicators. All participants provided informed consent. Complete MIDUS study protocols have been detailed elsewhere and received approval from the University of Wisconsin Institutional Review Board [25–27]. The New York University Institutional Review Board classified our secondary analysis as exempt from review. The current investigation followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [28].

2.2. DNA methylation epigenetic age acceleration

On the second day of the clinic visit, whole blood samples were collected in EDTA-containing BD Vacutainer Tubes and frozen for storage [29]. Genomic DNA was later extracted and assessed for yield and integrity prior to genome-wide DNA methylation profiling using Illumina Methylation EPIC microarrays [29]. Raw methylation intensity data were processed using the noob background correction method implemented

in the minfi R package to reduce technical variation [29]. Resulting beta values – denoting an estimated methylation percentage at each CpG site – were normalized and mapped to the CpG probes found on the Illumina Methylation 450K microarray to align with existing epigenetic age algorithms [29]. Standard quality control procedures were applied, including checks for probe detection p-values, sample call rate, sex concordance, and comparison to reference methylation profiles; all samples passed the quality control thresholds [29]. Processed methylation values were used to calculate epigenetic age scores using published algorithms for GrimAge2 [15] and DunedinPACE [14], both of which yield measures of epigenetic age acceleration. Other epigenetic clocks available in MIDUS (e.g., Horvath, Hannum) primarily estimate chronological age [30]. As such, we selected DunedinPACE and GrimAge 2 given their design to capture biological aging processes linked to morbidity and mortality [14,15], aligning with our interest in how psychosocial stress may be associated with long-term health outcomes. Scores were standardized (z-scores: mean = 0, SD = 1) for analyses.

2.3. Relationship stress

2.3.1. Family strain

We used four items to assess family strain [31]. Participants were asked "Thinking about the members of your family, not including your spouse/partner, how often" (1): do they make too many demands on you? (2) do they criticize you? (3) do they let you down when you are counting on them? (4) do they get on your nerves? Response options ranged from *(1) never* to *(4) often* and were averaged such that higher scores indicated greater family strain (Cronbach's α = 0.80).

2.3.2. Friend strain

Four items measured friend strain [31]: (1) "How often do your friends make too many demands on you?" (2) "How often do they criticize you?" (3) "How often do they let you down when you are counting on them?" (4) "How often do they get on your nerves?" Response options ranged from *(1) never* to *(4) often* and were averaged such that higher scores denoted higher friend strain (Cronbach's α = 0.80).

2.3.3. Marital risk

The 5-item Marital Risk Scale measured marital risk [31,32]. The questionnaire asked respondents: (1) "During the past year, how often have you thought your relationship might be in trouble?" (2) "It is always difficult to predict what will happen in a relationship, but realistically, what do you think the chances are that you and your partner will eventually separate?" (3) "How much do you and your spouse or partner disagree on the following issues?" (3a) "Money matters such as how much to spend, save, or invest." (3b) "Household tasks, such as what needs doing and who does it." (3c) "Leisure time activities, such as what to do and with whom." Response options ranged from *(1) never* to *(5) all the time* for the first question; from *(1) not likely at all* to *(4) very likely* for the second question; and from *(1) not at all* to *(4) a lot* for the third question. We summed scores such that higher values indicated greater marital risk (Cronbach's α = 0.84). Non-married individuals were assigned the lowest value for each item, aligning with scoring systems used in prior research [33].

2.3.4. Spouse/Partner strain

Six items evaluated spouse/partner strain [31]: (1) "How often does your spouse or partner make too many demands on you?" (2) "How often does he or she argue with you?" (3) "How often does he or she make you feel tense?" (4) "How often does he or she criticize you?" (5) "How often does he or she let you down when you are counting on him or her?" (6) "How often does he or she get on your nerves?" Response options ranged from *(1) never* to *(4) often* and were averaged such that higher scores reflected higher spouse/partner strain (Cronbach's α = 0.87). Like the marital risk measure, non-married individuals were assigned the lowest value for each spouse/partner strain item, aligning with scoring systems used in prior research [33]. All relationship stress measures were standardized into z-scores (mean = 0, SD = 1).

2.4. Covariates

We controlled for several sociodemographic characteristics and health behaviors. Sociodemographic factors included age (measured continuously), sex (male vs. female), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, non-Hispanic Other), educational attainment (high school or less, some college/associate's degree, college degree or higher), annual household income (<$50,000, $50,000 to $100,000, $100,000+), and marital status (married, divorced/separated/widowed, never married). Health behaviors included smoking status (never, past, current), alcohol consumption (never, < 1 day a week, 1–2 days a week, 3+ days a week), and body mass index (BMI, measured continuously).

2.5. Analytic strategy

We described sample characteristics using counts and percentages for categorical variables and means and SDs for continuous measures. Zero-order correlations were computed to assess interrelationships among the relationship stress domains. To examine associations between relationship stress domains and epigenetic aging, we conducted a series of linear regression models with GrimAge2 and DunedinPACE as outcomes. Primary analyses focused on family strain and friend strain as exposures. For each exposure-outcome combination, we fit three models: Model 1 expressed the epigenetic age outcome as a linear function of the relationship stress measure (unadjusted model); Model 2 controlled for sociodemographic characteristics; and Model 3 further controlled for health behaviors. Secondary analyses repeated this modeling approach using marital risk and spouse/partner strain as exposures. Regression coefficients were interpreted as the SD change in the epigenetic age outcome for every one SD increase in the relationship stress measure.

We conducted an exploratory analysis to investigate whether cumulative exposure across all four relationship stress domains was associated with each epigenetic age outcome. For this analysis, we summed the four standardized relationship stress measures (family strain, friend strain, marital risk, and spouse/partner strain) to create a cumulative strain score,

which was subsequently standardized (mean = 0, SD = 1) for consistency with the individual domain analyses. All statistical analyses were performed using R version 4.4.3 [34]. Statistical significance was assessed as a 2-sided $p < .05$.

To address missing data, we employed multivariate imputation by chained equations using the mice R package [35]. For continuous measures (BMI, relationship strain measures, and GrimAge2), we used predictive mean matching. Categorical variables required different approaches based on their structure: multinomial logistic regression for unordered categories (race/ethnicity and marital status) and ordinal logistic regression for ranked categories (educational attainment and annual household income). Following Rubin's rules [36], we generated 10 complete datasets through imputation and pooled the results from the regression analyses across all datasets to obtain final estimates.

3. Results

3.1. Descriptive statistics

Of the 1,310 participants (mean age 51 years, SD 13), 55% were female, 67% were non-Hispanic White, and 59% were married (Table 1). Table 2 shows the zero-order correlations among the relationship domains. Primary exposure domains

Table 1. Summary statistics on 1,310 participants from the midlife in the United States study.

Characteristic	N = 1,310
Age, Mean (SD)	51.3 (12.5)
Range	25 to 82
Sex, No. (%)	
Male	584 (44.6)
Female	726 (55.4)
Race/ethnicity, No. (%)	
Non-Hispanic White	879 (67.1)
Non-Hispanic Black	309 (23.6)
Hispanic	43 (3.3)
Non-Hispanic Other	71 (5.4)
Missing	8 (0.6)
Educational attainment, No. (%)	
High school or less	296 (22.6)
Some college/associate's degree	387 (29.5)
College degree or higher	625 (47.7)
Missing	2 (0.2)
Annual household income, No. (%)	
<$50,000	626 (47.8)
$50,000 to $100,000	349 (26.6)
$100,000+	273 (20.8)
Missing	62 (4.7)
Marital status, No. (%)	
Married	776 (59.2)
Divorced/Separated/Widowed	292 (22.3)
Never married	239 (18.2)
Missing	3 (0.2)
Smoking status, No. (%)	
Never	756 (57.7)
Past	380 (29.0)
Current	174 (13.3)
Alcohol consumption, No. (%)	
Never	426 (32.5)
< 1 day a week	353 (26.9)
1–2 days a week	228 (17.4)
3+ days a week	303 (23.1)
Body mass index, Mean (SD)	28.9 (6.8)
Missing, No. (%)	33 (2.5)
Family strain, Mean (SD)	2.1 (0.7)
Missing, No. (%)	8 (0.6)
Friend strain, Mean (SD)	1.9 (0.6)
Missing, No. (%)	10 (0.8)
Marital risk, Mean (SD)	7.4 (3.1)
Missing, No. (%)	12 (0.9)
Spouse/Partner strain, Mean (SD)	1.7 (0.7)
Missing, No. (%)	12 (0.9)
Cumulative strain, Mean (SD)	13.0 (3.8)
Missing, No. (%)	26 (2.0)
GrimAge2, Mean (SD)	62.7 (10.7)
Missing, No. (%)	1 (0.1)
DunedinPACE, Mean (SD)	1.0 (0.1)

Table 2. Zero-order correlations among relationship domains, midlife in the United States study.

	Family strain	Friend strain	Marital risk	Spouse/Partner strain
Family strain				
Friend strain	0.439***			
Marital risk	−0.017	−0.057*		
Spouse/Partner strain	−0.059*	−0.070*	0.837***	
Cumulative strain	0.220***	0.168***	0.957***	0.848***

*$p < 0.05$; **$p < 0.01$;***$p < 0.001$.

(family and friend strain) showed a moderate positive correlation ($r = 0.44$), and secondary exposure domains (marital risk and spouse/partner strain) were highly correlated ($r = 0.84$). Cross-domain correlations between primary and secondary exposures were minimal.

3.2. Primary analyses

Primary analyses revealed that greater friend strain consistently tracked with changes in epigenetic aging according to the GrimAge2 and DunedinPACE metrics (Table 3). In the unadjusted model (Model 1), a 1-SD increase in friend strain was associated with a 0.06 SD decrease in GrimAge2 score (95% CI: −0.11 to −0.01, $p = 0.037$) and a 0.12 SD increase in DunedinPACE score (95% CI: 0.07 to 0.17, $p < 0.001$). After adjusting for sociodemographic factors (Model 2), the association was a 0.06 SD increase for GrimAge2 (95% CI: 0.03 to 0.08, $p < 0.001$) and a 0.08 SD increase for DunedinPACE (95% CI: 0.04 to 0.13, $p = 0.001$). The magnitudes of these associations attenuated when additionally controlling for health behaviors (Model 3): GrimAge2 (0.03 SD increase, 95% CI: 0.01 to 0.05, $p = 0.003$) and DunedinPACE (0.05 SD increase, 95% CI: 0.01 to 0.09, $p = 0.030$). Supplementary analyses did not suggest that these associations significantly varied by sex or annual household income (Supplemental Document). We found no evidence that family strain was significantly associated with either epigenetic aging measure after accounting for health behaviors. Full model outputs are available in the Supplemental Document.

3.3. Secondary analyses

Secondary analyses examined associations between other relationship stress measures and epigenetic aging (Table 3). Higher marital risk was significantly associated with lower GrimAge2 (0.08 SD decrease, 95% CI: −0.14 to −0.03, $p = 0.003$) and lower DunedinPACE (0.13 SD decrease, 95% CI: −0.19 to −0.08, $p < 0.001$). However, these associations were attenuated to non-significance after adjusting for sociodemographic factors in Model 2 (GrimAge2: 0.03 SD increase, 95% CI: −0.01 to 0.06, $p = 0.087$; DunedinPACE: 0.04 SD increase, 95% CI: −0.03 to 0.10, $p = 0.27$) and health behaviors in Model 3 (GrimAge2: 0.00 SD change, 95% CI: −0.02 to 0.03, $p = 0.74$; DunedinPACE: 0.01 SD decrease, 95% CI: −0.06 to 0.05, $p = 0.78$). Similarly, spouse/partner strain demonstrated a significant negative association with DunedinPACE in the unadjusted model (0.18 SD decrease, 95% CI: −0.23 to −0.13, $p < 0.001$) but not with GrimAge2 (0.04 SD decrease, 95% CI: −0.09 to 0.02, $p = 0.17$). The association with DunedinPACE was substantially reduced and became non-significant after sociodemographic adjustment (Model 2: 0.02 decrease, 95% CI: −0.09 to 0.06, $p = 0.68$).

Cumulative strain, representing total relationship stress across domains, was significantly associated with lower GrimAge2 in the unadjusted model (0.13 SD decrease, 95% CI: −0.19 to −0.08, $p < 0.001$). This association reversed direction and became positive after adjusting for sociodemographic factors (0.05 SD increase, 95% CI: 0.02 to 0.08, $p < 0.001$) but was no longer significant in the fully adjusted model (0.02 SD increase, 95% CI: −0.01 to 0.04, $p = 0.12$). Cumulative strain was not significantly associated with DunedinPACE after health behavior adjustment.

4. Discussion and implications

The current study examined associations between multiple domains of relationship stress and epigenetic aging in

Table 3. Unadjusted and adjusted associations between relationship stress and epigenetic age acceleration among 1,310 participants from the midlife in the Unites States study.

	Model 1			Model 2			Model 3		
	Beta	95% CI	p-value	Beta	95% CI	p-value	Beta	95% CI	p-value
Grimage2									
Family strain	**−0.14**	**(−0.20, −0.09)**	**< 0.001**	**0.03**	**(0.01, 0.06)**	**0.023**	0.01	(−0.01, 0.03)	0.40
Friend strain	**−0.06**	**(−0.11, −0.01)**	**0.037**	**0.06**	**(0.03, 0.08)**	**< 0.001**	**0.03**	**(0.01, 0.05)**	**0.003**
Marital risk	**−0.08**	**(−0.14, −0.03)**	**0.003**	0.03	(−0.01, 0.06)	0.087	0.00	(−0.02, 0.03)	0.74
Partner strain	−0.04	(−0.09, 0.02)	0.17	0.01	(−0.03, 0.05)	0.65	−0.01	(−0.04, 0.02)	0.45
Cumulative strain	**−0.13**	**(−0.19, −0.08)**	**< 0.001**	**0.05**	**(0.02, 0.08)**	**< 0.001**	0.02	(−0.01, 0.04)	0.12
DunedinPACE									
Family strain	**0.08**	**(0.02, 0.13)**	**0.005**	**0.05**	**(0.01, 0.10)**	**0.040**	0.01	(−0.03, 0.06)	0.53
Friend strain	**0.12**	**(0.07, 0.17)**	**< 0.001**	**0.08**	**(0.04, 0.13)**	**0.001**	**0.05**	**(0.01, 0.09)**	**0.030**
Marital risk	**−0.13**	**(−0.19, −0.08)**	**< 0.001**	0.04	(−0.03, 0.10)	0.27	−0.01	(−0.06, 0.05)	0.78
Partner strain	**−0.18**	**(−0.23, −0.13)**	**< 0.001**	−0.02	(−0.09, 0.06)	0.68	−0.04	(−0.11, 0.02)	0.19
Cumulative strain	−0.05	(−0.10, 0.01)	0.084	**0.07**	**(0.02, 0.13)**	**0.007**	0.02	(−0.03, 0.07)	0.45

Results were pooled across ten datasets.
Bold indicates $p < 0.05$.
Model 1 was unadjusted.
Model 2 controlled for age, sex, race/ethnicity, educational attainment, annual household income, and marital status.
Model 3 controlled for age, sex, race/ethnicity, educational attainment, annual household income, marital status, smoking status, alcohol use, and body mass index.

a large sample of midlife adults. Our findings revealed that after adjusting for sociodemographic covariates and health behaviors, friend strain remained significantly associated with accelerated biological aging as measured by GrimAge2 and DunedinPACE. Strain in other relational domains, including family, marital, and partner relationships, showed no significant associations with epigenetic aging in fully adjusted models.

These results highlight the distinctive importance of friendship strain for biological aging processes during midlife. While existing literature has primarily emphasized the health effects of romantic and family relationships [3,37–39], our findings reveal that friendship stress may exert unique effects on cellular aging during this life stage. Our results both contrast with and extend those of Rentscher et al. [4], who found that relationship quality across multiple domains predicted accelerated aging in older adults. While the authors identified significant associations with various types of relationship strain, we observed a significant association only with friend strain in midlife. This divergence may reflect developmental differences, as friendships may play a particularly salient role during midlife compared to later life stages examined by Rentscher et al. [4] Additionally, our use of advanced next-generation epigenetic clocks (GrimAge2 and DunedinPACE) may have provided greater sensitivity to stress-related biological aging. However, differences in findings may also stem from variations in sample characteristics.

This particular vulnerability of midlife adults to friendship strain may stem from several psychosocial factors. Unlike family relationships, which are often obligatory, friendships in adulthood are typically voluntary relationships that are more sensitive to quality and reciprocity [40]. The voluntary nature of these ties means that strained friendships may represent particularly significant stressors, as they often involve conflicts in relationships that individuals have actively chosen to maintain. In addition, friendships often serve as important sources of emotional support, belonging, and social integration during midlife [40], a period when individuals may be navigating multiple role transitions (e.g., career advancement, parenting adolescents, caring for aging parents) [41]. As such, when these supportive relationships become sources of stress rather than support, the psychological and physiological consequences may be particularly severe. The fact that friend strain was associated with both DunedinPACE and GrimAge2 further underscores this vulnerability, as these measures capture distinct dimensions of biological aging. DunedinPACE reflects the current pace of physiological decline, capturing progressive changes in organ system integrity that occur before clinical disease develops [14] whereas GrimAge2 was designed to predict mortality risk based on cumulative epigenetic alterations linked to lifespan [15]. Therefore, associations with both measures reinforce the idea that friendship strain may influence aging in multiple ways, affecting both the pace of current decline and the buildup of risks that impact lifespan.

Interestingly, while marital risk and partner strain were each associated with epigenetic aging in unadjusted models, these associations attenuated substantially after accounting for sociodemographic factors such as annual household income, educational attainment, and marital status. This pattern of attenuation suggests that apparent links between these types of relationship stress and biological aging may be partially confounded by broader social determinants of health. For instance, individuals experiencing economic hardship may be more likely to experience strain across multiple relationship domains while simultaneously facing other stressors that accelerate biological aging. These findings align with prior research emphasizing the fundamental role of structural factors in shaping both relationship quality and health outcomes across the life course [42].

Several limitations of the current study should be noted, however. First, the cross-sectional design precludes causal inferences about the directionality of our observed associations. While it is plausible that relationship stress accelerates biological aging, it is also possible that individuals who are aging faster biologically may experience more strain in their social relationships, or that other variables influence both processes. As such, longitudinal studies with repeated measures of both relationship quality and epigenetic aging are needed to disentangle these possibilities. Second, relationship stress was measured via self-report, which may be subject to reporting biases. Third, although we controlled for several important sociodemographic and health-related covariates, there may be other unmeasured confounders (e.g., childhood adversity) that could have influenced our results. Fourth, while we focused on specific types of relationship stress, other forms of stress (e.g., neighborhood and/or workplace stress) that were not examined in this study may also contribute to epigenetic aging. Fifth, we could not adjust for blood cell-type composition due to a lack of available data in the MIDUS methylation release. This is an important limitation because DNA methylation profiles are highly cell-type specific [43], and bulk blood measures inevitably reflect underlying variation in leukocyte subtypes. Such variation can strongly influence epigenetic clock estimates. For instance, naïve CD8+ T cells exhibit markedly younger epigenetic ages than memory T-cell subsets [44], meaning that age-related immune shifts such as immunosenescence can confound associations between psychosocial stress and biological aging [45]. More broadly, cell-type heterogeneity has been shown to account for a substantial fraction of DNA methylation variability across individuals, often exceeding the variance attributable to exposures like smoking or age [46]. Thus, lack of adjustment for cell composition may bias associations or obscure cell-intrinsic aging signals. Future studies should prioritize the inclusion of estimated cell-type proportions, via reference-based deconvolution of methylation arrays or other approaches, to better isolate biological aging effects from immune cell composition. Sixth, while the MIDUS sample is ethnically diverse, genetic principal components were not available for the subsample with epigenetic aging data, limiting our ability to adjust for population stratification. Future studies that integrate genetic and epigenetic data could help clarify the extent to which ancestry-related variation may confound associations between social stress and biological aging. Finally, although the MIDUS sample is diverse, our findings may not generalize to younger or older populations, or to individuals from different cultural

contexts where the meaning and importance of various relationship types may differ.

Despite these limitations, our study makes several important contributions to the growing literature on social determinants of biological aging. By examining multiple domains of relationship stress simultaneously, we identified friendship strain as a potentially unique correlate of accelerated epigenetic aging in midlife adults. This finding expands our understanding of the social determinants of health by highlighting an understudied relational context that may be particularly relevant for midlife health and aging. Future research should build on these findings by examining the specific mechanisms linking friendship strain to biological aging, as well as potential moderators of these associations.

5. Conclusion

Overall, the current study makes three key contributions to understanding the association between relationship stress and biological aging. First, we demonstrated that friendship strain remains significantly associated with accelerated aging in midlife adults, even after comprehensive adjustment for potential confounders. Second, our domain-specific approach revealed that while marital, partner, and family strain were associated with epigenetic aging in unadjusted models, only friendship strain remained significant after full covariate adjustment, suggesting particular robust biological embedding. Third, our application of next-generation epigenetic clocks in this context showed GrimAge2's and DunedinPACE's responsiveness to psychosocial stressors in midlife. Future research should examine the behavioral and physiological mechanisms linking friendship strain to accelerated epigenetic aging.

Author contributions

Mariana Rodrigues: Conceptualization, Investigation, Writing (Original Draft). **Jemar R. Bather**: Conceptualization, Methodology, Formal Analysis, Investigation, Supervision, Writing (Original Draft), Project Administration. **Adolfo G. Cuevas**: Conceptualization, Investigator, Supervision, Writing (Review & Editing), Project Administration, Funding Acquisition.

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Data availability statement

The data that support this study's findings are publicly available on the MIDUS Colectica Portal.

Ethical conduct of research

The MIDUS study protocols received institutional review board approval and all participants provided informed consent. The present analyses used de-identified, publicly available MIDUS data and were determined exempt by the New York University Institutional Review Board.

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