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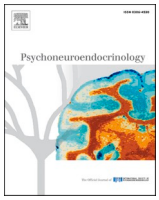

Aging anxiety and epigenetic aging in a national sample of adult women in the United States

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ABSTRACT

Background: Aging anxiety is a multidimensional psychosocial stressor with potential implications for women's long-term health, yet its biological embedding remains poorly understood. This study examined whether domain-specific aging anxieties are associated with accelerated epigenetic aging, using second-generation methylation-based biomarkers.

Methods: Data were drawn from 726 women participating in the Midlife in the United States (MIDUS) study. Aging anxiety was assessed across three domains: declining attractiveness, declining health, and reproductive aging. Epigenetic aging was measured using two complementary second-generation clocks: GrimAge2, which estimates cumulative biological damage and predicts mortality risk, and DunedinPACE, which captures the current pace of biological aging. Multivariable linear regression models tested associations between aging anxiety and epigenetic age acceleration, adjusting sequentially for sociodemographic factors, chronic health conditions, and health behaviors.

Results: Greater declining health anxiety was significantly associated with higher DunedinPACE z-scores (0.07 SD increase, 95 % CI: 0.01, 0.13). This association attenuated to non-significance after adjusting for health behaviors (0.02 SD increase, 95 % CI: −0.04, 0.08), which could be potential mediators on the exposure-outcome association pathway. Higher cumulative aging anxiety was significantly associated with a 0.07 SD increase (95 % CI: 0.01, 0.14) in DunedinPACE, but this association attenuated to non-significance after adjusting for chronic health conditions (0.06 SD increase, 95 % CI: −0.01, 0.13) and health behaviors (0.03 SD increase, 95 % CI: −0.03, 0.08).

Conclusion: Findings indicate that specific domains of aging anxiety, particularly fears about declining health, may manifest biologically and contribute to accelerated aging processes. These results support a biopsychosocial model in which subjective experiences of aging contribute to physiological decline. Future longitudinal studies are needed to clarify whether aging-related anxiety influences epigenetic aging trajectories among women.

1. Introduction

Aging anxiety, a multidimensional construct encompassing fears about physical decline, loss of attractiveness, and reproductive health (Barrett and Robbins, 2008; Brunton and Scott, 2015), is a critical psychosocial stressor (Bergman and Segel-Karpas, 2021), particularly among women navigating sociocultural pressures to maintain youthfulness (Abdou, 2017; Barrett and Robbins, 2008). These gendered pressures reflect internalized ageist narratives that portray women's aging bodies as biologically and socially devalued, fostering chronic self-monitoring and psychological distress (Bergman and Segel-Karpas, 2021; Carrard et al., 2021). Population-based studies consistently indicate that among the various domains of aging anxiety, concerns about declining health are both the most prevalent and the most persistent for women, whereas appearance- and fertility-related anxieties tend to attenuate with age (Barrett and Robbins, 2008; Barrett and Toothman, 2018). Heightened focus on health may stem from women's greater lifetime exposure to chronic illness and functional limitations (Carmel, 2019; Crimmins et al., 2019), compounded by sociocultural expectations that they assume caregiving and health-maintenance roles within families (Sharma et al., 2016). Such demands can reinforce chronic bodily vigilance and amplify perceptions of health-related threats

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(Patwardhan et al., 2024; Schulz and Sherwood, 2008).

While psychosocial distress, in general, is well-established as a contributor to biological aging via epigenetic pathways, such as methylation changes in stress-responsive genes (e.g., *FKBP5*, *NR3C1*) (Mengelkoch et al., 2025; Watkeys et al., 2018), aging anxiety represents a particularly relevant and self-referential stressor that warrants targeted investigation among women (Barrett and Toothman, 2018). Unlike transient or externally driven stress exposures, aging anxiety concerns one's own body and identity and may therefore operate as a recurrent, anticipatory form of stress that can be repeatedly reinforced by sociocultural patterns and daily bodily cues (Barrett and Toothman, 2018; McEwen, 2012; O'Donovan et al., 2012). Such persistent self-focused threat appraisals may sustain stress-responsive systems over time, promoting biological wear and tear (McEwen, 2003). Moreover, the gendered nature of aging anxiety, arising from the internalization of structural and cultural norms that devalue women's bodies, positions it as a potential contributor to sex disparities in aging-related health outcomes (Barrett and Toothman, 2018; Clarke and Griffin, 2008; Sabik, 2015). Finally, because aging anxiety reflects both sociocultural structures and individual cognitive-affective processes (Barrett and Robbins, 2008; Barrett and Toothman, 2018; Bergman and Segel-Karpas, 2021), it provides a theoretically plausible lens for understanding psychosocial pathways through which subjective experiences of aging become biologically embedded (Stephan et al., 2021). Despite these considerations, the biological embedding of aging-related anxieties, particularly through epigenetic mechanisms, remains understudied.

Second-generation epigenetic clocks, including GrimAge2 and DunedinPACE, offer a compelling framework for examining how psychosocial stress becomes biologically embedded (Christian et al., 2025; Cuevas et al., 2025, 2024; Mulligan, 2025). GrimAge2 estimates cumulative biological damage by integrating DNA methylation surrogates of inflammatory proteins, metabolic risk markers, and smoking history to predict time-to-death (Lu et al., 2022). In contrast, DunedinPACE captures the rate of aging in real time, providing a sensitive measure of ongoing physiological decline (Belsky et al., 2022). While both clocks are responsive to chronic stress and mental health conditions (Christian et al., 2025; Cuevas et al., 2025, 2024; Mulligan, 2025), domain-specific anxieties about aging, particularly those more prevalent among women, have received limited empirical attention.

Different types of aging anxiety may influence epigenetic aging through distinct biobehavioral pathways. Health-related anxiety, rooted in fears of chronic illness or functional decline (Lebel et al., 2020), may activate stress physiology directly via hypothalamic-pituitary-adrenal (HPA) axis dysregulation and inflammatory signaling (Dieleman et al., 2015; Michopoulos et al., 2017), thereby accelerating methylation-based aging. In contrast, anxieties centered on appearance or fertility may trigger behavioral coping strategies, such as smoking, caloric restriction, or sedentariness (Bennett et al., 2017; Iordăchescu et al., 2021; Kruk et al., 2021), that may indirectly increase biological aging through oxidative stress, metabolic dysregulation, and immune compromise (Cardenas et al., 2022; Damiot et al., 2020; Vandercappellen et al., 2022). Internalized ageism may exacerbate both these processes by magnifying subjective threat and diminishing psychological resilience (Bergman and Segel-Karpas, 2021), thus possibly amplifying downstream biological effects. Disentangling these domain-specific pathways is essential for understanding how distinct facets of aging anxiety, such as health-, attractiveness-, and reproductive-related anxiety, may differentially relate to biological aging. Such specificity moves beyond treating stress as a uniform construct and allows for identification of which subjective aging experiences may be most closely embedded within physiological processes in women. Yet, few studies have empirically disaggregated aging anxiety in relation to molecular aging biomarkers.

To address these gaps, we examine whether domain-specific aging anxieties are associated with accelerated epigenetic aging in adult women, using GrimAge2 and DunedinPACE as outcome measures. We additionally evaluated cumulative aging anxiety across all domains to test whether the aggregate burden of aging-related concerns correlates with epigenetic aging acceleration. Based on prior evidence (Bennett et al., 2017; Dieleman et al., 2015; Iordăchescu et al., 2021; Michopoulos et al., 2017), we hypothesized that 1) health-related anxiety will show the strongest association with epigenetic acceleration, given its direct links to stress-responsive biological pathways and its higher prevalence among women; 2) attractiveness- and reproductive-related anxieties will exhibit weaker associations; and 3) these relationships will persist after adjusting for sociodemographic variables and chronic health conditions. By highlighting these pathways, our study aimed to clarify how subjective experiences of aging may become biologically embedded in women.

2. Methods

2.1. Study design and setting

Data come from the Midlife in the United States (MIDUS) study, a national health investigation among English-speaking, community-dwelling U.S. adults aged 25–74 years (Brim et al., 2004). The MIDUS study developed through several recruitment phases. The original cohort (MIDUS 1, n = 7108) was established in 1995–1996 using random digit dialing techniques. To improve African American representation, Wave 2 (MIDUS 2, n = 5555) included an additional 592 participants from Milwaukee, Wisconsin. Recognizing the need to replenish the aging original cohort, investigators launched the MIDUS Refresher Study (MIDUS Refresher 1, 2011–2014), which recruited 4085 new participants, including 508 African American adults from Milwaukee.

From these cohorts, subsets of participants enrolled in biomarker assessment studies: 1255 individuals from the MIDUS 2 cohort participated in the MIDUS 2 Biomarker Project and 863 individuals from the MIDUS Refresher 1 cohort participated in the MIDUS Refresher Biomarker Study (Dienberg Love et al., 2010). These 2118 biomarker study participants underwent comprehensive two-day clinical assessments that collected multiple biological indicators at Georgetown University, the University of Wisconsin-Madison, or the University of California, Los Angeles. Of these participants, 1310 had DNA methylation data available for calculating epigenetic age scores. We excluded 584 men, resulting in a final analytic sample of 726 women. There were no other exclusionary criteria besides the availability of DNA methylation data and being a man.

Biomarker participants were provided with outlines of the biological procedures, $200 for completing the two-day clinic visit, and travel-related expenses (Dienberg Love et al., 2010). In addition to managing the travel logistics, the MIDUS team provided childcare reimbursements and allowed older adults to bring a companion. All participants provided written informed consent. The University of Wisconsin Institutional Review Board approved all MIDUS protocols, with comprehensive methodological details published elsewhere (Brim et al., 2004; Dienberg Love et al., 2010; Radler, 2014). New York University's Institutional Review Board classified this secondary analysis as exempt from review. We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines in reporting this research (von Elm et al., 2008).

2.2. Epigenetic aging

During the second day of clinical assessments, participants provided whole blood samples collected in EDTA-coated BD Vacutainer Tubes, which were subsequently frozen for long-term storage (University of Wisconsin Institute on Aging and UCLA Social Genomics Core Laboratory, 2023). Following extraction, genomic DNA underwent evaluation for quality and quantity before genome-wide methylation analysis using Illumina Methylation EPIC microarray technology. Technical variation

was reduced by applying the noob background correction method from the minfi R package to the raw methylation intensity data. This procedure generated beta values representing methylation proportions at individual CpG sites. These values underwent normalization and were mapped to CpG probes present on the Illumina 450 K methylation array to ensure compatibility with established epigenetic aging algorithms. Rigorous quality control protocols were implemented, encompassing probe detection p-value assessment, sample call rate verification, sex concordance validation, and comparison against reference methylation patterns. All samples met established quality criteria.

The processed methylation data were used to calculate epigenetic age using two specific algorithms: GrimAge2 (Lu et al., 2022) and DunedinPACE (Belsky et al., 2022). These measures were selected over alternative epigenetic clocks available in MIDUS (such as Horvath and Hannum) because GrimAge2 and DunedinPACE were specifically developed to quantify biological aging processes associated with disease and mortality risk (Belsky et al., 2022; Lu et al., 2022), rather than simply estimating chronological age (Irvin et al., 2018). This selection aligned with the research focus on relationships between psychosocial stress and long-term health. For statistical analyses, both epigenetic age measures were standardized to z-scores (mean = 0, SD = 1).

2.3. Aging anxiety

As part of a questionnaire at enrollment for MIDUS 2 and MIDUS Refresher 1, women were shown the following prompt: "Women sometimes worry about the future and getting older. How much do you worry about each of the following?" Three items assessed different dimensions of aging anxiety: (1) Being less attractive as a woman? *(declining attractiveness anxiety)*, (2) Having more illness as you get older? *(declining health anxiety)*, and (3) Being too old to have children? *(reproductive aging anxiety)*. Response options ranged from *(1) A lot* to *(4) Not at all*. We reverse coded each measure so that higher values indicated greater anxiety and transformed them using z-scores. The primary exposures of interest were declining attractiveness anxiety and declining health anxiety. Secondary exposures included reproductive aging anxiety and a cumulative aging anxiety measure. The cumulative measure was created by summing the three standardized anxiety measures and then standardizing the sum to create a z-score. These aging anxiety measures have been used in prior studies (Barrett and Robbins, 2008; Barrett and Toothman, 2018; Kruk et al., 2021).

2.4. Covariates

Sociodemographic covariates included age (25−39, 40−49, 50−59), 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-$100,000, $100,000 +), and marital status (married, divorced/separated/widowed, never married). Number of chronic health conditions in the past 12 months was derived as the sum of the following self-reported indicators: (1) asthma, bronchitis, or emphysema, (2) tuberculosis, (3) other lung problems, (4) arthritis, rheumatism, or other bone or joint diseases, (5) sciatica, lumbago, or recurring backache, (6) persistent skin trouble (e.g., eczema), (7) thyroid disease, (8) hay fever, (9) recurring stomach trouble, indigestion, or diarrhea, (10) urinary or bladder problems, (11) being constipated all or most of the time, (12) gall bladder trouble, (13) persistent foot trouble (e.g., bunions, ingrown toenails), (14) trouble with varicose veins requiring medical treatment, (15) AIDS or HIV infection, (16) lupus or other autoimmune disease, (17) persistent trouble with your gums or mouth, (18) persistent trouble with your teeth, (19) high blood pressure or hypertension, (20) anxiety, depression, or some other emotional disorder, (21) alcohol or drug problems, (22) migraine headaches, (23) chronic sleeping problems, (24) diabetes or high blood sugar, (25) multiple sclerosis, epilepsy, or other neurological disorders, (26) stroke, (27) ulcer, (28) hernia, (29) piles or hemorrhoids, and (30) swallowing problems. We grouped the number of chronic health conditions as 0, 1, or 2 + . Self-reported health behaviors included smoking status (never, past, current), past-month alcohol consumption (never, <1 day/week, 1–2 days/week, ≥3 days/week), and body mass index (BMI; continuous). We also controlled for menopausal status. Menopausal status was included as a covariate because the menopausal transition is associated with changes in anxiety symptoms (Bromberger et al., 2013) and may independently influence biological aging and related biomarkers (Levine et al., 2016). Participants self-reported whether their menstrual periods had stopped due to menopause (yes/no).

2.5. Anxiety symptoms

Anxiety symptoms were measured using ten items assessing frequency of experiences in the past 12 months (Wang et al., 2000). Participants reported how often they: (a) felt restless because of worry, (b) felt keyed up, on edge, or had a lot of nervous energy, (c) felt irritable because of worry, (d) had trouble falling asleep, (e) had trouble staying asleep because of worry, (f) had trouble keeping their mind on what they were doing, (g) had trouble remembering things because of worry, (h) felt low on energy, (i) tired easily because of worry, and (j) had sore or aching muscles because of tension. Responses were recorded on a 4-point scale: (1) Most days, (2) Some days, (3) Rarely, and (4) Never. Each item was recoded as binary (1 = most days, 0 = less than most days), and a composite score was created by summing across all ten items. This continuous score was then dichotomized as ≥ 3 versus < 3 to indicate clinically meaningful anxiety symptom burden.

2.6. Statistical analysis

Sample characteristics were expressed as means and SDs for continuous variables and as frequencies and proportions for categorical measures. To examine the associations between aging anxiety and epigenetic age acceleration, we first computed zero-order correlations to measure unadjusted relationships. We then employed multivariable linear regression as the primary analysis (Hidalgo and Goodman, 2013), examining how declining attractiveness anxiety and health anxiety related to epigenetic aging. To understand the influence of potential confounders and mediators, we used a hierarchical approach, adding groups of variables sequentially: Block 1 included sociodemographic factors (age, race/ethnicity, educational attainment, annual household income, marital status, and menopausal status); Block 2 added number chronic health conditions; and Block 3 further controlled for lifestyle factors (smoking status, alcohol use, and BMI). Secondary analyses applied this same tiered modeling strategy to reproductive aging anxiety and cumulative aging anxiety.

We addressed missing data using multivariate imputation by chained equations (Van Buuren and Groothuis-Oudshoorn, 2011), employing logistic regression for dichotomous variables, polytomous regression for non-ordered categorical measures, ordinal regression for ordered categorical variables, and predictive mean matching for continuous variables. Regression coefficients were pooled across ten imputed datasets using Rubin's rules (Rubin, 1987). All statistical analyses were performed in R version 4.5.1 (R Core Team, 2023) with a two-sided $p < 0.05$ considered statistically significant.

3. Results

3.1. Summary statistics

Of the 726 women, the average age was 50.4 years (SD = 12.0), with 61.8 % identifying as non-Hispanic White, 44.8 % holding a college degree, 51.8 % having an annual household income of less than $50,000, and 50.7 % being married (Table 1). Most were premenopausal (70.2 %) and had two or more chronic health conditions (60.2 %).

Table 1
Sample characteristics of 726 women in the Midlife in the United States study.

Characteristic	N = 726
Age, Mean (SD)	50.4 (12.0)
Age group, No. (%)	
25–39	139 (19.1)
40–49	208 (28.7)
50–59	208 (28.7)
60 +	171 (23.6)
Race/ethnicity, No. (%)	
non-Hispanic White	449 (61.8)
non-Hispanic Black	207 (28.5)
Hispanic	27 (3.7)
non-Hispanic Other	39 (5.4)
Missing	4 (0.6)
Educational attainment, No. (%)	
High school or less	183 (25.2)
Some college/associate's degree	216 (29.8)
College degree or higher	325 (44.8)
Missing	2 (0.3)
Annual household income, No. (%)	
<$50,000	376 (51.8)
$50,000 to $100,000	189 (26.0)
$100,000 +	122 (16.8)
Missing	39 (5.4)
Marital status, No. (%)	
Married	368 (50.7)
Divorced/Separated/Widowed	210 (28.9)
Never married	148 (20.4)
Menopause, No. (%)	
No	510 (70.2)
Yes	216 (29.8)
Number of chronic health conditions, No. (%)	
0	136 (18.7)
1	150 (20.7)
2 +	437 (60.2)
Missing	3 (0.4)
Anxiety symptoms in the past year (continuous), Mean (SD)	0.3 (1.3)
Anxiety disorder in the past year (binary), No. (%)	
No	696 (95.9)
Yes	30 (4.1)
Anxiety, depression, or some other emotional disorder in the past 12 months, No. (%)	
No	534 (73.6)
Yes	189 (26.0)
Missing	3 (0.4)
Sample characteristics of 726 women in the Midlife in the United States study.	
Characteristic	N = 726
Smoking status, No. (%)	
Never	437 (60.2)
Past	188 (25.9)
Current	101 (13.9)
Alcohol consumption, No. (%)	
Never	276 (38.0)
< 1 day a week	214 (29.5)
1–2 days a week	117 (16.1)
3 + days a week	119 (16.4)
Body mass index, Mean (SD)	29.2 (7.7)
Missing, No. (%)	19 (2.6)
Reproductive aging anxiety, Mean (SD)	1.3 (0.7)
Missing, No. (%)	15 (2.1)
Declining attractiveness anxiety, Mean (SD)	2.0 (0.9)
Missing, No. (%)	11 (1.5)
Declining health anxiety, Mean (SD)	2.4 (0.9)
Missing, No. (%)	9 (1.2)
Cumulative aging anxiety, Mean (SD)	5.7 (1.9)
Missing, No. (%)	17 (2.3)
GrimAge2, Mean (SD)	61.5 (9.6)
DunedinPACE, Mean (SD)	1.0 (0.1)

Thirty-eight percent had never consumed alcohol, 60.2 % never smoked, and the mean BMI was 29.2 (SD = 7.7). In the past year, 4.1 % had an anxiety disorder and 26.0 % had a history of anxiety, depression, or some other emotional disorder. The response distribution for each aging anxiety measure is presented in Table 2. Eighty-one percent did not have reproductive aging anxiety, 34.0 % had no declining attractiveness anxiety, and 18.3 % did not report declining health anxiety.

Table 3 presents the zero-order correlations. GrimAge2 moderately correlated with declining attractiveness anxiety (r = -0.175), reproductive aging anxiety (r = -0.308), and cumulative aging anxiety (r = -0.219). By comparison, DunedinPACE exhibited a small correlation with declining health anxiety (r = 0.084).

Table 2
Response distribution for aging anxiety measures among 726 women in the Midlife in the United States study.

Characteristic	N = 726
Reproductive aging anxiety, No. (%)	
A lot	26 (3.6)
Some	39 (5.4)
A little	58 (8.0)
Not at all	588 (81.0)
Missing	15 (2.1)
Declining attractiveness anxiety, No. (%)	
A lot	64 (8.8)
Some	138 (19.0)
A little	266 (36.6)
Not at all	247 (34.0)
Missing	11 (1.5)
Declining health anxiety, No. (%)	
A lot	100 (13.8)
Some	205 (28.2)
A little	279 (38.4)
Not at all	133 (18.3)
Missing	9 (1.2)

3.2. Primary analysis

Table 4 reports the primary analysis results. Model 1 indicated that controlling for sociodemographic factors, higher anxiety about declining health was significantly associated with a 0.08 SD increase in DunedinPACE (95 % CI: 0.02, 0.15). Model 2 demonstrated that this association remained robust even after adjusting for chronic health conditions (0.07 SD increase, 95 % CI: 0.01, 0.13). However, introducing health behaviors in Model 3 reduced the strength and statistical significance of this association (0.02 SD increase, 95 % CI: −0.04, 0.08), suggesting that smoking status, alcohol consumption, and BMI may mediate the aging anxiety-epigenetic aging relationship. Sensitivity analyses stratified by recent history of anxiety, depression, or other emotional disorders (past 12 months) showed that associations between health anxiety and DunedinPACE were slightly stronger among those with a psychiatric history compared to those without (Table 5). Among those with a history, the association was 0.12 (95 % CI: −0.01, 0.24) in Model 1, 0.10 (95 % CI: −0.02, 0.23) in Model 2, and 0.07 (95 % CI: −0.05, 0.19) in Model 3. Among those without a history, the association was 0.06 (95 % CI: −0.02, 0.14) in Model 1, 0.05 (95 % CI: −0.03, 0.13) in Model 2, and 0.01 (95 % CI: −0.07, 0.08) in Model 3. DunedinPACE did not significantly vary across levels of anxiety about declining attractiveness. We also did not find statistically significant associations of anxiety about declining health or attractiveness with GrimAge2.

3.3. Secondary analysis

Secondary analyses indicated that, after adjusting for sociodemographic characteristics, greater cumulative aging anxiety was significantly associated with a 0.07 SD increase in DunedinPACE (95 % CI: 0.01, 0.14; Table 4). This association's magnitude attenuated in Model 2 (0.06 SD increase, 95 % CI: −0.01, 0.13) and further reduced in Model 3 (0.03 SD increase, 95 % CI: −0.03, 0.09). Conversely, cumulative aging anxiety was not significantly associated with changes in GrimAge2 across all three models. The multivariable models did not provide evidence of a significant relationship between reproductive aging anxiety and either epigenetic aging measure.

4. Discussion

This study is the first, to our knowledge, to demonstrate that domain-specific aging anxiety is associated with accelerated epigenetic aging in women, as measured by DunedinPACE. Our findings suggest that aging-related distress, particularly anxiety about health decline, is not merely a psychological concern, but may be a biologically embedded stressor with measurable consequences for molecular aging. Importantly, we show that the associations between aging anxiety and biological aging differ across anxiety domains and epigenetic clocks, offering new insight into the biopsychosocial determinants of aging.

Consistent with our hypotheses, health-related aging anxiety exhibited the strongest and most consistent associations with epigenetic aging. This form of anxiety, centered on concerns about physical decline and vulnerability to illness with age (Krautwurst et al., 2014), may operate as a chronic stressor, not only because of its persistence over time but also because it is often accompanied by a heightened sensitivity to internal bodily cues (Krautwurst et al., 2014).

For some individuals, these concerns are not merely cognitive or emotional but are experienced somatically, creating a feedback loop in which the perception of aging and the fear of health deterioration heighten bodily awareness (Krautwurst et al., 2014). This intensified awareness reinforces a current state of psychological distress, which may, in turn, trigger sustained physiological arousal (e.g., via HPA axis activation and inflammatory signaling; Chen et al., 2017). Over time, this recurrent cycle of cognitive-affective distress and physiological responses may become biologically embedded, for instance through cumulative DNA methylation changes, contributing to a faster pace of epigenetic aging as captured by DunedinPACE (Belsky et al., 2022; Harvanek et al., 2021; O'Donovan et al., 2012; Stephan et al., 2021; Wu et al., 2024). The health-related anxiety association persisted even after adjusting for sociodemographic factors, menopausal status, and chronic health conditions, suggesting a potentially unique biophysiological pathway. Although the effect sizes were modest (0.07 SD increase), they are similar to those observed for other psychosocial stressors in epigenetic aging research (Protsenko et al., 2023; Rodrigues et al., 2025), and may be clinically meaningful given DunedinPACE's established links to morbidity and mortality risk (Belsky et al., 2022).

By contrast, attractiveness-related anxiety showed no significant associations with either epigenetic clock. This may reflect measurement limitations (e.g., underreporting due to social desirability), or it may indicate that concerns about physical appearance, while psychologically meaningful, do not sufficiently engage systemic stress responses or behavioral risks robustly enough to influence biological aging. Similarly, reproductive-related anxiety was not significantly associated with DunedinPACE in either unadjusted or adjusted models. Although these findings suggest that fertility-related stress may not exert robust effects on biological aging, it remains possible that its influence operates indirectly through behavioral coping mechanisms (e.g., poor sleep quality), particularly among women navigating perceived reproductive urgency and engaging in health-related behaviors to manage stress or

Table 3
Zero-order correlations among aging anxiety and epigenetic aging measures.

	1	2	3	4	5
1. Declining attractiveness anxiety					
2. Declining health anxiety	0.525***				
3. Reproductive aging anxiety	0.211***	0.136***			
4. Cumulative aging anxiety	0.826***	0.796***	0.548***		
5. GrimAge2	-0.175***	-0.029	-0.308***	-0.219***	
6. DunedinPACE	-0.067	0.084*	0.040	0.018	0.441***

*p < 0.05; **p < 0.01; ***p < 0.001

Table 4
Standardized beta coefficients (and 95 % confidence intervals) from a series of linear regression models quantifying the association between aging anxiety and epigenetic aging among 726 women in the Midlife in the United States study.

	Model 1		Model 2		Model 3	
	β (95 % CI)	p value	β (95 % CI)	p value	β (95 % CI)	p value
GrimAge2						
Declining attractiveness anxiety	0.01 (-0.03, 0.06)	0.50	0.01 (-0.03, 0.05)	0.57	-0.02 (-0.05, 0.02)	0.42
Declining health anxiety	0.02 (-0.02, 0.06)	0.37	0.02 (-0.03, 0.06)	0.47	-0.02 (-0.06, 0.02)	0.24
Reproductive aging anxiety	-0.02 (-0.07, 0.02)	0.33	-0.02 (-0.07, 0.02)	0.31	-0.01 (-0.05, 0.03)	0.48
Cumulative aging anxiety	0.01 (-0.04, 0.05)	0.76	0.00 (-0.04, 0.05)	0.88	-0.03 (-0.06, 0.01)	0.21
DunedinPACE						
Declining attractiveness anxiety	0.02 (-0.04, 0.08)	0.55	0.01 (-0.05, 0.07)	0.77	-0.01 (-0.07, 0.05)	0.68
Declining health anxiety	**0.08 (0.02, 0.15)**	**0.009**	**0.07 (0.01, 0.13)**	**0.032**	0.02 (-0.04, 0.08)	0.49
Reproductive aging anxiety	0.05 (-0.02, 0.12)	0.17	0.05 (-0.03, 0.12)	0.21	0.06 (-0.01, 0.12)	0.079
Cumulative aging anxiety	**0.07 (0.01, 0.14)**	**0.030**	0.06 (-0.01, 0.13)	0.079	0.03 (-0.03, 0.09)	0.34

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

Table 5
Standardized beta coefficients (and 95 % confidence intervals) from a series of linear regression models quantifying the association between aging anxiety and DunedinPACE among 726 women in the Midlife in the United States study, stratified by history of anxiety, depression, or some other emotional disorder in the past 12 months.

	Model 1		Model 2		Model 3	
	β (95 % CI)	p value	β (95 % CI)	p value	β (95 % CI)	p value
No history of anxiety, depression, or some other emotional disorder in the past 12 months (n = 534)						
Declining attractiveness anxiety	0.02 (-0.06, 0.10)	0.70	0.01 (-0.07, 0.09)	0.77	0.01 (-0.07, 0.08)	0.82
Declining health anxiety	0.06 (-0.02, 0.14)	0.12	0.05 (-0.03, 0.13)	0.22	0.01 (-0.07, 0.08)	0.84
Reproductive aging anxiety	0.02 (-0.06, 0.11)	0.58	0.02 (-0.07, 0.10)	0.67	0.03 (-0.04, 0.11)	0.40
Cumulative aging anxiety	0.05 (-0.03, 0.13)	0.23	0.04 (-0.04, 0.12)	0.35	0.02 (-0.05, 0.10)	0.55
History of anxiety, depression, or some other emotional disorder in the past 12 months (n = 189)						
Declining attractiveness anxiety	-0.01 (-0.12, 0.11)	0.89	-0.02 (-0.14, 0.09)	0.72	-0.04 (-0.15, 0.07)	0.44
Declining health anxiety	0.12 (-0.01, 0.24)	0.061	0.10 (-0.02, 0.23)	0.094	0.07 (-0.05, 0.19)	0.26
Reproductive aging anxiety	0.07 (-0.05, 0.19)	0.23	0.08 (-0.04, 0.20)	0.20	0.08 (-0.03, 0.20)	0.15
Cumulative aging anxiety	0.08 (-0.04, 0.20)	0.18	0.07 (-0.05, 0.19)	0.23	0.05 (-0.06, 0.16)	0.40

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

maintain a sense of reproductive fitness (Bryant et al., 2012). Consistent with previous studies (Barrett and Toothman, 2018), the majority of participants (81 %) reported no reproductive anxiety. The relatively low prevalence of reproductive aging anxiety in this cohort may partially account for the absence of an observed association with epigenetic aging and aligns with prior evidence that reproductive concerns tend to decrease with age and are less salient for women in midlife (Barrett and Barbee, 2022; Barrett and Toothman, 2018).

Cumulative aging anxiety, a broader, multidimensional index, was significantly associated with DunedinPACE, but not GrimAge2. This divergence may reflect fundamental differences between the epigenetic clocks. For instance, while GrimAge2 captures accumulated damage and exposure (Lu et al., 2022), DunedinPACE reflect the current rate of physiological decline (Belsky et al., 2022). Our findings suggest that generalized and cumulative aging anxiety may influence ongoing, dynamic biological wear-and-tear, as captured by DunedinPACE, but does not appear to shape long-term cumulative risk in the absence of domain-specific distress or behavioral mediators.

Our results are consistent with prior literature showing that health-related aging anxiety is the most prevalent domain of aging anxiety for women and is strongly linked to psychological and physical outcomes (Barrett and Robbins, 2008; Barrett and Toothman, 2018). Indeed, previous studies have found that health-related concerns predict higher depressive symptoms, loneliness, and poorer self-rated health in midlife and older adulthood (Barrett and Robbins, 2008; Bergman and Segel-Karpas, 2021; Westerhof et al., 2023). The present findings extend this body of work by demonstrating a similar association at the molecular level, as indicated by epigenetic aging biomarkers (Belsky et al., 2022). While earlier studies have not examined domain-specific aging anxiety in relation to epigenetic clocks, our results align with broader evidence linking psychological distress to accelerated biological aging (Verhoeven et al., 2014, 2015).

Taken together, our findings substantially extend prior research on aging anxiety by demonstrating its potential biological embedding. While earlier work has established the psychosocial contours of domain-specific aging anxieties (Barrett and Robbins, 2008; Barrett and Toothman, 2018; Bergman and Segel-Karpas, 2021), our study is the first, to our knowledge, to show that different domains of aging-specific anxiety are associated with accelerated epigenetic aging, particularly when

health-related. Furthermore, by employing second-generation epigenetic clocks, GrimAge2 and DunedinPACE, we provide molecular evidence that aging-specific anxieties are associated with accelerated biological aging, advancing theoretical models of stress embodiment within the context of geroscicence.

5. Limitations and future directions

While this study offers novel insights into the potential biological embedding of aging anxiety, several limitations warrant consideration. First, the cross-sectional design precludes causal inference. It is possible that the observed association between aging anxiety and accelerated epigenetic aging is driven, in part, by unmeasured factors, such as lifetime history of exposure to chronic stressors or an underlying trait vulnerability to anxiety, which may predispose individuals to both higher aging anxiety and accelerated biological aging. Nonetheless, our analytic approach is grounded in the conceptualization of aging anxiety as a distinct, self-referential stressor, rather than a proxy for cumulative adversity, supported by theoretical and empirical evidence of its unique relevance to women's health and biological aging (Barrett and Toothman, 2018; Chrisler et al., 2016; Fredrickson and Roberts, 1997; Lasher and Faulkender, 1993; Stephan et al., 2021). Second, although epigenetic clocks capture cumulative exposure (GrimAge2) and dynamic biological change (DunedinPACE) (Belsky et al., 2022; Lu et al., 2022), longitudinal designs are needed to determine temporal precedence and assess whether anxiety-related epigenetic acceleration is reversible. Third, although our sample was sociodemographically diverse, larger and more intersectionally representative cohorts are needed to assess whether associations may vary by race, socioeconomic status, or menopausal stage. Fourth, we could not compute reliability coefficients because each aging anxiety measure consisted of a single item (Barrett and Toothman, 2018). Future investigations are needed to validate these measures in different cohorts and to develop multiple items for each aging anxiety domain. Finally, we were unable to account for women experiencing perimenopause, who may have exacerbated anxiety symptoms.

6. Conclusions

This study provides novel evidence that women's aging anxiety, particularly fears related to health decline, is associated with accelerated epigenetic aging. Domain-specific distress appears to exert differential biological effects, with health-related anxiety potentially linked to accelerated pace of aging (DunedinPACE). This finding supports a biopsychosocial model in which subjective experiences of aging may become biologically embedded, potentially contributing to physiological decline and increased disease vulnerability. By identifying aging anxiety as a measurable and modifiable psychosocial determinant, this work advances geroscience research by highlighting upstream psychological pathways that may shape aging biology and influence healthspan trajectories across the lifespan.

CRediT authorship contribution statement

Mariana Rodrigues: Writing – original draft, Investigation, Conceptualization. **Adolfo G. Cuevas:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization. **Jemar R. Bather:** Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Consent to participate

All participants in the MIDUS study provided written informed consent.

Clinical trial number

Not applicable.

Ethics approval declaration

The MIDUS study protocols received institutional review board approval by the University of Wisconsin Institutional Review Board 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's Institutional Review Board.

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Declaration of Competing Interest

None.

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Data availability statement

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

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