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Cumulative Stress and Epigenetic Aging: Examining the Role of Psychological Moderators

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Objective: Cellular epigenetic aging has become an important marker of healthy or unhealthy aging. The current study examined whether lifelong cumulative stressors across multiple domains were linked with epigenetic age acceleration (EAA; i.e., epigenetic age greater than chronological age) and whether psychological factors moderated this association. Dimensions of psychological well-being were hypothesized as protective factors, while neuroticism was posited as a vulnerability factor. ***Method:*** Data from the Midlife in the United States (MIDUS) Genomics Project ($N = 1{,}006$) were used, which include deoxyribonucleic acid methylation data from a subset of participants in MIDUS Core Wave 2 and MIDUS Refresher Wave 1. Epigenetic aging values were calculated using the deoxyribonucleic acid methylation profiles at cytosine–phosphate–guanine sites. Cumulative stressors and psychological factors were assessed using the survey data at MIDUS Core Wave 2 and MIDUS Refresher Wave 1. ***Results:*** The results revealed that cumulative stressors were not directly associated with EAA but were contingent on the levels of psychological well-being and neuroticism. Specifically, higher levels of cumulative stressors were significantly linked to EAA, measured by GrimAge2, among those who had lower levels of psychological well-being ($\beta = -.23$ to $-.36$, $SE = .12$ to $.13$, $p = .04$ to $< .01$) or higher neuroticism ($\beta = .26$, $SE = .12$, $p = .03$). Conversely, EAA in individuals who had higher levels of psychological well-being or lower neuroticism was not impacted by the levels of cumulative stressors. ***Conclusions:*** The findings underscore the importance of considering individual psychological assets and vulnerabilities in the pathways linking cumulative stressors to epigenetic aging.

Public Significance Statement
Numerous factors are involved in the pace of biological aging. This study examined the interplay of cumulative stress from childhood to adulthood with psychological factors (assets and vulnerabilities) on epigenetic age acceleration (EAA). Multiple psychological strengths buffered against the adverse effects of cumulative stress on EAA, while neuroticism exacerbated links between such stress and EAA.

Keywords: epigenetic age acceleration, cumulative stressors, psychological well-being, neuroticism

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Deoxyribonucleic acid (DNA) methylation provides an important window on healthy or unhealthy aging. The concept known as epigenetic aging has emerged as predictive of morbidity and mortality (Faul et al., 2023). Individuals exposed to environmental stressors often show older epigenetic age relative to their chronological age, a phenomenon known as epigenetic age acceleration (EAA). Increasingly, researchers have focused on identifying demographic and health factors that contribute to EAA. A recent meta-analysis found that biological sex and health behaviors (e.g., smoking status) were linked to a faster pace of epigenetic aging (Oblak et al., 2021). Childhood socioeconomic status has also been linked with faster epigenetic aging among Black and White women (Brown et al., 2024). Even when accounting for demographic and health factors (e.g., education, childhood

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socioeconomic, and health behaviors), EAA measures remained significant predictors for both (Faul et al., 2023).

Psychosocial stressors also play a key role in EAA. The findings from the Midlife in the United States (MIDUS) study show that both loneliness (Freilich et al., 2024) and experiences of everyday or major discrimination (Cuevas et al., 2024) predict EAA. Similarly, lower social support was positively linked to accelerated aging among older adults in the Health and Retirement Study (Rentscher et al., 2023).

Although much of the existing research focuses primarily on how current single psychosocial stressors affect EAA, individuals often experience multiple stressors simultaneously, including past stressors (e.g., childhood stressors), which have lasting health consequences (D'Amico et al., 2023). Financial stressors are often associated with marital stress that consequently affects mental and physical health (Lee et al., 2021). Accumulated psychosocial stressors have also been linked to increased number and severity of physical symptoms (Haight et al., 2023) as well as increased engagement in adverse health behaviors (e.g., smoking; Slopen et al., 2012). There is, however, limited research on whether cumulative stressors across the lifespan influence EAA (e.g., Harvanek et al., 2021). The current study thus examines cumulative stressors and links them to EAA in a nationally representative sample of Americans. The current research also investigates whether psychological factors (positive and negative) modify how accumulated stress exposures are linked with EAA.

Prior research has shown that psychosocial factors may buffer or exacerbate the effects of stressors on EAA. A supportive family environment was identified as a protective factor (Brody et al., 2016), whereas poor emotion regulation strategies were identified as risk factors that exacerbated stress–EAA linkages (Harvanek et al., 2021). However, little prior work has examined EAA under conditions of cumulative stress, as possibly modified by psychological protective and risk factors (Cuevas et al., 2024).

This study thus brings psychological well-being to the inquiry, given prior evidence of its protective role on health. On the risk side, neuroticism is examined, which has been identified as a significant risk factor for various health outcomes. Prior evidence documenting these effects is briefly distilled below.

Protective Factors: Dimensions of Psychological Well-Being

Psychological well-being, as formulated by Ryff (1989), has been extensively studied as an influence on health (Ryff, 2024). Purpose in life, for example, has been linked with extended longevity (R. Cohen et al., 2016), reduced risk of Alzheimer's disease pathology (P. A. Boyle et al., 2012), and reduced risk of stroke (Kim et al., 2013). Overall, eudaimonic well-being has also been tied to reward circuitry in the brain as well as reduced diurnal cortisol excretion (Heller et al., 2013). With regard to protective benefits in the face of adversity, aging is known to increase chronic conditions that fuel inflammation, but higher levels of well-being mitigated against elevated Interleukin-6 and C-reactive protein among those with increased chronic conditions (Friedman & Ryff, 2012). Gains in eudaimonic well-being among breast cancer patients have also been linked with gene expression, specifically reduced profiles of proinflammatory genes and increased expression of antiviral and antibody-related genes (C. C. Boyle et al., 2019). In sum, growing evidence documents that psychological well-being has health benefits, leading to the possibility that it may be protective against EAA in the face of cumulative stress.

Risk Factor: Neuroticism

Meta-analytic findings demonstrate that neuroticism is a consistent risk factor for health (Strickhouser et al., 2017), giving it significant implications for public health. For example, neuroticism is associated with elevated inflammation levels (e.g., Interleukin-6; Sutin et al., 2010), physical health conditions 25 years later (Charles et al., 2008), and mortality (Mroczek & Spiro, 2007). Neuroticism may also exacerbate the negative impact of stressors on health. Those with high neuroticism tend to have amplified stress reactivity, making them vulnerable to event-related distress (Bolger & Schilling, 1991). For example, Leger et al. (2016) found that neuroticism had the most significant influence on negative affect when experiencing daily stressors. Likewise, heightened stress reactivity among those with high neuroticism may lead to increased adverse health outcomes, including increased chronic conditions and functional limitations (Leger et al., 2021).

The Present Study

The present study examined whether cumulative stressors are positively associated with EAA and whether psychological well-being (a protective factor) and neuroticism (a vulnerability factor) moderate the relationship between cumulative stressors and biological aging. The guiding hypothesis was that psychological well-being would mitigate the adverse link between cumulative stressors and EAA, while neuroticism would exacerbate such links.

Method

Transparency and Openness

In this article, we report how we determined our sample size, all data exclusions, and all measures that were included in the study. This study was not formally preregistered. The current analysis used publicly available data, which can be assessed through the MIDUS Portal (https://midus.colectica.org/). The data dictionary and analysis codes are available and can be found as the additional online materials (Cha et al., 2025). This study was approved by the Institutional Review Board of the University of Wisconsin-Madison (2006-0612, SE-2011-0350, 2014-0813). All analyses were conducted using SPSS and R (R Core Team, 2023).

Participants and Procedure

This study used the MIDUS investigation, a national longitudinal inquiry of English-speaking adults in the United States. Two samples participated in the MIDUS Genomics Project that included DNA methylation data ($N = 1{,}310$): The MIDUS Core Sample—Wave 2 (M2; $n = 511$; assessed in 2004–2009) and the MIDUS Refresher Sample—Wave 1 (MR1; $n = 799$, assessed in 2012–2016) samples. The Genomics Project was a part of the biomarker project conducted to examine biopsychosocial pathways to health outcomes on a subset of MIDUS Core and Refresher respondents.

Sociodemographic variables, cumulative life stressors, and psychological moderators (psychological well-being and neuroticism)

were drawn from survey data on the Core and Refresher samples. Data were collected via a computer-assisted telephone interview or a computer-assisted personal interview, and a self-administered questionnaire. Those who had missing data on the 11 subdomains of cumulative stressors constructed by Slopen et al. (2018) were excluded from the analyses, thus resulting in 1,006 participants. The average age of the sample was 53.44 ($SD = 12.56$), and 52.68% were female.

Measures

Cumulative Stressors

The cumulative stress measure (Slopen et al., 2012) is a composite index that captures stress accumulation across an individual's life course. Drawing from multiple domains, it integrates stressors from different life stages available in the MIDUS dataset to provide a comprehensive assessment of an individual's total stress burden. Unlike measures that assess individual life stressors, this approach emphasizes the wider scope of stress exposures across time. This cumulative stress index has been linked with a range of health outcomes, including smoking (Slopen et al., 2012), daily health symptoms (Haight et al., 2023), and cognitive functioning (D'Amico et al., 2023). Although prior studies vary in their inclusion of stressor domains, the current study examined all 11 domains: childhood stressors, stressful life experiences in adulthood, financial stress, relationship stress, neighborhood stress, psychological work stress, physical work stress, work–family conflict, perceived inequality, discrimination, and past year family problems (i.e., spouse/partner, parents, and children). If a life stress measure was irrelevant to a participant due to their demographic characteristics, missing data were substituted with the lowest possible value, and cumulative stressor value was not computed if participants did not respond to one or more of the 11 stressor domains. All values for 11 domains were standardized and summed to make a single index of cumulative stressors (for more details on the constructs, see the online supplemental materials, pp. 2–4).

The cumulative stress index demonstrated good convergent validity, as evidenced by its positive and significant correlations with well-established measures of stress and emotional distress, including the Perceived Stress Scale ($r = .44$, $p < .001$; S. Cohen et al., 1983) and the Center for Epidemiologic Studies Depression Scale ($r = .40$, $p < .001$; Radloff, 1977). In addition, the index exhibited discriminant validity, demonstrating low correlations with constructs that are theoretically distinct from stress. Specifically, the cumulative stress index was unrelated to the self-construal scale (Singelis, 1994) for both independent self-construal ($r = .01$, $p = .84$) and weakly related to interdependent self-construal ($r = -.10$, $p < .01$). Cumulative stress index was also only weakly related to openness ($r = -.05$, $p = .10$), agreeableness ($r = -.10$, $p < .01$), extraversion ($r = -.13$, $p < .001$), and conscientiousness ($r = -.19$, $p < .001$). Neuroticism, however, exhibited a moderate correlation with cumulative stress ($r = .30$, $p < .001$), which is consistent with its theoretical relationship to stress.

Protective Factor: Psychological Well-Being

Psychological well-being was assessed using Ryff's Well-Being Scale (Ryff, 1989). Each of the six components was measured with seven items, resulting in a total of 42 items: purpose in life (e.g., "I have a sense of direction and purpose in life"; $\alpha = .72$), environmental mastery (e.g., "In general, I feel I am in charge of the situation in which I live"; $\alpha = .82$), self-acceptance (e.g., "I like most parts of my personality"; $\alpha = .85$), autonomy (e.g., "I judge myself by what I think is important, not by the values of what others think is important"; $\alpha = .69$), positive relations with others (e.g., "Most people see me as loving and affectionate"; $\alpha = .79$), and personal growth (e.g., "I have the sense that I have developed a lot as a person over time"; $\alpha = .75$). Participants rated the extent to which they agreed to the items on a 7-point Likert scale (1 = *strongly agree* to 7 = *strongly disagree*). The scales were summed to make six separate dimensions, and the scores were reverse coded so that higher scores indicate higher standing in the measure. The combined psychological well-being measure was calculated as the average of the standardized scores across the six dimensions of psychological well-being.

Risk Factor: Neuroticism

Participants' neuroticism was measured as one of the Big Five personality traits. Four adjectives, worrying, nervous, moody, and calm (reverse-coded), were presented and asked to be rated on a 4-point Likert scale (1 = *a lot* to 4 = *not at all*). The four scores were aggregated to make a single index of neuroticism, and values were computed so that higher scores indicate higher neuroticism ($\alpha = .73$).

EAA

Fasting blood draws obtained from participants during the biomarker project were subject to genome-wide methylation profiling using Illumina Methylation EPIC microarrays, after testing for suitable DNA yield and integrity. The resulting beta values representing the approximate percentage of methylation at each assayed cytosine–phosphate–guanine site were noob normalized to control for technical variability. These values were then matched with the cytosine–phosphate–guanine sites on the Illumina Methylation 450K microarray, commonly used for calculating epigenetic age scores, and were screened using standard quality control metrics and scored. For detailed information, see data documentation on the MIDUS Colectica Portal (https://midus.wisc.edu/midus_genetic_data.php).

The analyses used second- and third-generation epigenetic clocks—GrimAge2 (a current version of GrimAge), PhenoAge, and DunedinPACE, which are the EAA parameters most predictive of healthspan, all-cause mortality, and the onset of diseases, such as cancer (Levine et al., 2018). GrimAge2 incorporates DNA methylation-based estimators of multiple plasma proteins and other characteristics (e.g., smoking) and is predictive of time to death and events related to aging (McCrory et al., 2021). PhenoAge is a phenotypic clock derived from biomarkers that outperformed prior epigenetic clocks (i.e., Hannum and Horvath) and reflected age-related immune system decline (Levine et al., 2018). Both GrimAge2 and PhenoAge generate an epigenetic age in years that can be contrasted with chronological age (Levine et al., 2018). DunedinPACE is distinct from GrimAge2 and PhenoAge in that it reflects the relative pace of aging as a multiplicative factor, which indicates the ratio of biological age per calendar year of chronologic age and serves as a direct measure of EAA (Belsky et al., 2022). To calculate EAA from the other epigenetic age measures, we regressed GrimAge2 and PhenoAge on chronological age and computed residuals to index how much older one is

biologically compared to one's chronological age. Thus, a positive value indicated EAA.

Covariates

Demographic covariates included age (participants' age at the biomarker data collection), sex (0 = *male*, 1 = *female*), education (years), race (0 = *White*, 1 = *Black*, 2 = *Others*), employment status (0 = *not working*, 1 = *working*), marital status (0 = *not married*, 1 = *currently married or cohabitating*), and whether one has children (0 = *no children*, 1 = *one or more children*). Health covariates included smoking status (0 = *never smoker*, 1 = *former smoker*, 2 = *current smoker*), alcohol consumption (the number of alcoholic drinks consumed per week past month), and body mass index (BMI). Sample (0 = *Core*, 1 = *Refresher*) was also accounted for to adjust for the potential sample differences. All health covariates and participants' ages were from the biomarker data collection, consistent with the DNA methylation data, while other variables were from M2 and MR1 survey data, respectively.

Data Analytic Strategy

Hypotheses were tested by multiple linear regressions, with all continuous variables standardized before the analyses. Psychological well-being as a moderator was examined by regressing EAA on cumulative stressors, psychological well-being, and the interaction term between these two measures. To examine whether neuroticism aggravated the relationship between cumulative stressors and EAA, cumulative stressors, neuroticism, and their interaction were included as predictors. All regression models used cluster-robust standard errors to adjust for the 45 sets of twins or siblings in the analytic sample, and simple slope analyses were conducted with 1 *SD* above and below for the identified moderators.

Results

Cumulative Stressors and EAA

The results showed that the marginal effect of cumulative stressors was not significantly related to DunedinPACE, PhenoAge, and GrimAge2 (all $ps > .30$; see Table S1 in the online supplemental materials). f^2_p indicated that cumulative stressors explained .1% of the total variance of three epigenetic clocks. Regarding demographic covariates, education was a significant predictor for DunedinPACE and GrimAge2 in that those who had higher education showed lower EAA. Being employed was related to lower GrimAge2, and males were more likely to experience higher DunedinPACE and GrimAge2. For health behavior covariates, smoking status was significantly related to all EAA measures such that former smokers and current smokers had higher EAA than nonsmokers. Alcohol consumption was also related to PhenoAge and GrimAge2, such that more alcohol consumption was linked to higher EAA. The BMI was associated with all EAA measures, as higher BMI was linked to higher EAA. Overall, health behavior covariates aligned with previous meta-analytic findings (Oblak et al., 2021).

Protective Factor: Psychological Well-Being

Overall psychological well-being was a significant moderator in the association of cumulative stressors with GrimAge2 ($\beta = -.38$, $SE = .12$, $p < .01$, $f^2_p = .01$) but not with DunedinPACE ($\beta = -.00$, $SE = .00$, $p = .23$) or PhenoAge ($\beta = -.13$, $SE = .17$, $p = .44$). Simple slope analysis revealed that individuals with low psychological well-being experienced heightened GrimAge2 levels in response to higher cumulative stressors ($\beta = .47$, $SE = .19$, $p = .02$), whereas this association was not observed among those with high psychological well-being ($\beta = -.28$, $SE = .21$, $p = .18$).

Next, we explored each dimension of psychological well-being as a moderator (see Model 1 of Table 1 and Figure 1). Purpose in life moderated the association of cumulative life stressors on GrimAge2 ($\beta = -.35$, $SE = .13$, $p < .01$, $f^2_p = .01$) but not on DunedinPACE and PhenoAge (all $ps > .22$). Simple slope analyses revealed that among those who had a higher purpose in life, cumulative stressors were not significantly associated with GrimAge2 ($\beta = -.27$, $SE = .20$, $p = .18$), whereas higher levels of cumulative stressors were significantly linked to an increase in GrimAge2 among those who had lower levels of purpose in life ($\beta = .42$, $SE = .20$, $p = .04$). For specific results of DunedinPACE and PhenoAge, see Tables S2 and S3 in the online supplemental materials.

Environmental mastery significantly interacted with cumulative life stressors on GrimAge2 ($\beta = -.31$, $SE = .12$, $p < .01$, $f^2_p = .01$) but not on other EAA measures (all $ps > .23$). The simple slopes showed similar patterns as the test of purpose in life, such that high environmental mastery buffered the association of cumulative stressors with GrimAge2 ($\beta = -.12$, $SE = .21$, $p = .56$), while those with low levels of environmental mastery showed higher GrimAge2 with increasing cumulative stressors ($\beta = .49$, $SE = .19$, $p = .01$).

Self-acceptance also significantly moderated cumulative life stressors on GrimAge2 ($\beta = -.36$, $SE = .12$, $p < .01$, $f^2_p = .01$) but not DunedinPACE and PhenoAge (all $ps > .16$). Those with higher levels of self-acceptance did not show a significant relationship between cumulative stressors on GrimAge2 ($\beta = -.28$, $SE = .21$, $p = .17$), but those with low self-acceptance showed higher GrimAge2 ($\beta = .45$, $SE = .20$, $p = .02$).

Autonomy significantly interacted with cumulative stressors in relation to GrimAge2 ($\beta = -.23$, $SE = .12$, $p = .04$, $f^2_p = .004$) but not DunedinPACE and PhenoAge (all $ps > .77$). Having high autonomy buffered the relationship of cumulative stressors with GrimAge2 ($\beta = -.06$, $SE = .20$, $p = .75$), while those with low autonomy showed that cumulative stressor accelerated GrimAge2 ($\beta = .41$, $SE = .18$, $p = .02$).

Positive relations with others significantly moderated the association of cumulative stressors with GrimAge2 ($\beta = -.34$, $SE = .13$, $p < .01$, $f^2_p = .01$) but not DunedinPACE and PhenoAge (all $ps > .37$). Those who maintained positive relations with others showed that cumulative stressors were not related to GrimAge2 ($\beta = -.32$, $SE = .22$, $p = .15$). However, those who had lower levels of positive relations had accelerated GrimAge2 in the presence of higher cumulative stressors despite its marginal significance ($\beta = .36$, $SE = .19$, $p = .055$).

Personal growth significantly moderated the association of cumulative stressors with GrimAge2 ($\beta = -.26$, $SE = .12$, $p = .04$, $f^2_p = .005$) but not DunedinPACE and PhenoAge (all $ps > .26$). Those with low personal growth showed accelerated GrimAge2 ($\beta = .36$, $SE = .18$, $p = .05$) but those with high personal growth showed that cumulative stressors were unrelated to GrimAge2 ($\beta = -.15$, $SE = .20$, $p = .46$).

Table 1
The Interaction of Cumulative Stressors With Risk and Protective Factors on GrimAge2 Acceleration

Interaction terms	Without covariates		With covariates	
	β (*SE*)	*p*	*b* (*SE*)	*p*
Model 1: Psychological well-being				
Cumulative Stressors × Purpose in Life	−.48 (.18)	.008	−.35 (.13)	.009
Cumulative Stressors × Environmental Mastery	−.48 (.17)	.005	−.31 (.12)	.008
Cumulative Stressors × Self-Acceptance	−.49 (.17)	.005	−.36 (.12)	.003
Cumulative Stressors × Autonomy	−.47 (.17)	.006	−.23 (.12)	.043
Cumulative Stressors × Positive Relations With Others	−.40 (.18)	.030	−.34 (.13)	.008
Cumulative Stressors × Personal Growth	−.42 (.18)	.018	−.26 (.12)	.037
Model 2: Neuroticism				
Cumulative Stressors × Neuroticism	.40 (.16)	.011	.26 (.12)	.027

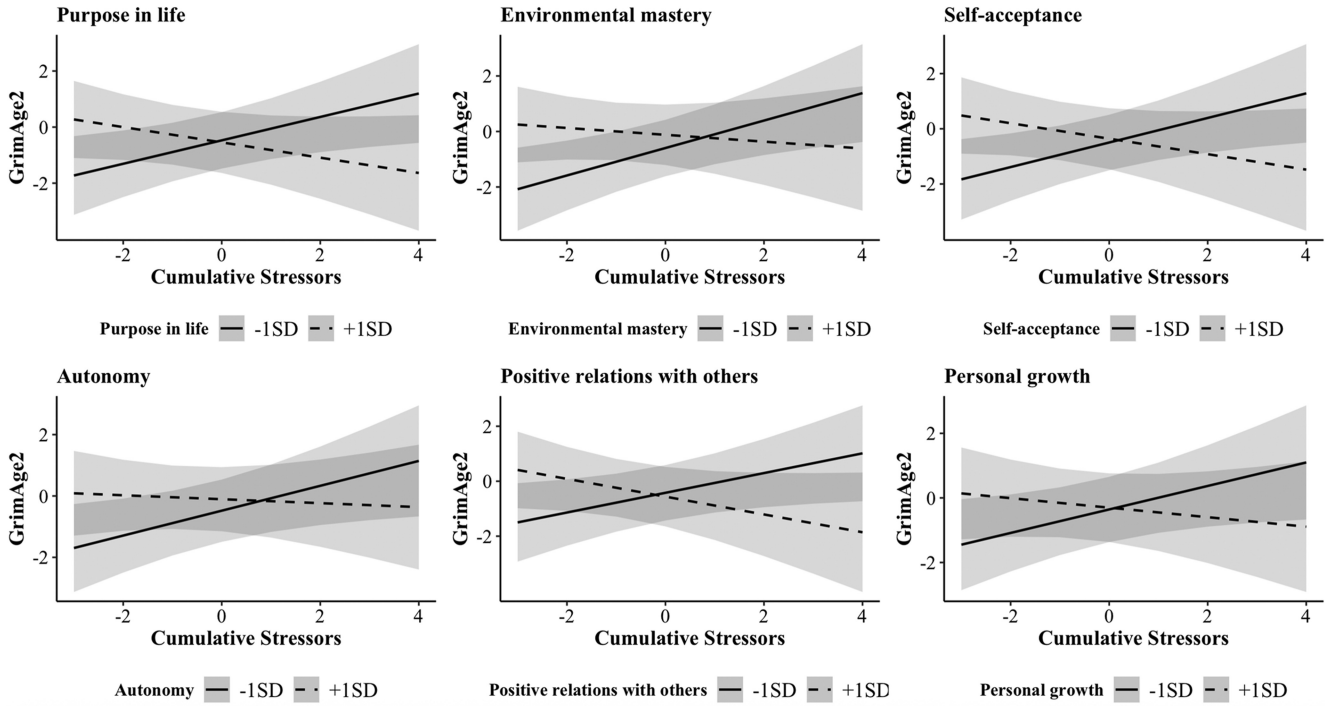
Risk Factor: Neuroticism

To examine whether neuroticism is a vulnerability factor, neuroticism and its interaction term with cumulative stressors were entered into the models predicting EAA. Neuroticism was a significant moderator in the association between cumulative stressors and GrimAge2 ($\beta = .26$, $SE = .12$, $p = .03$, $f^2_p = .01$) but not DunedinPACE or PhenoAge (all $ps > .09$; see Model 2 of Table 1 and Figure 2). Simple slope analysis revealed that those with high neuroticism experienced accelerated GrimAge2 with greater cumulative stress ($\beta = .42$, $SE = .18$, $p = .02$) but those with low neuroticism showed no significant relationship between cumulative stressors and GrimAge2 ($\beta = -.09$, $SE = .20$, $p = .65$).

Post Hoc Analyses

An additional model including both interaction terms of Cumulative Stress × Psychological Well-Being and Cumulative Stress × Neuroticism were examined to investigate how competing factors influence EAA. The results showed that although the protective benefits of psychological well-being remained for GrimAge2

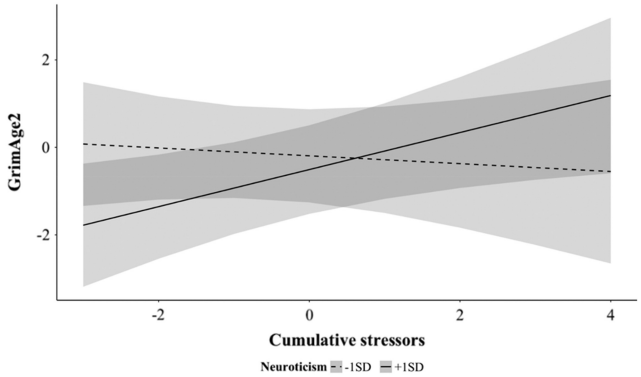
Figure 1
Predicted GrimAge2 Contingent on Levels of Cumulative Stressors and Components of Psychological Well-Being



Note. Dashed lines indicate 1 *SD* above the mean, and solid lines indicate 1 *SD* below the mean. The shaded area indicates 95% confidence intervals.

Figure 2

Predicted GrimAge2 Contingent on the Levels of Cumulative Stressors and Neuroticism



Note. The solid line indicates 1 *SD* above the mean, and the dashed line indicates 1 *SD* below the mean. The shaded area indicates 95% confidence intervals.

($\beta = -.35$, $SE = .15$, $p = .02$, $f_p^2 = .01$), the moderation of neuroticism was no longer significant ($\beta = .05$, $SE = .14$, $p = .72$). For the six dimensions of psychological well-being, the buffering effect remained significant for purpose in life, self-acceptance, and positive relations with others. This effect persisted even when the interaction with neuroticism was included in the model, with neuroticism itself remaining nonsignificant throughout.

General Discussion

Life stressors are known to accelerate biological aging, but the role of psychological characteristics as protective or vulnerability factors remains largely unexplored. We examined whether different aspects of psychological well-being and neuroticism independently influence pathways between cumulative stressors and EAA. Utilizing data from the MIDUS national longitudinal study, the results showed that the six dimensions of psychological well-being dampened the association of cumulative stressors on EAA, whereas neuroticism exacerbated the negative effect. However, post hoc analyses revealed that the detrimental impact of neuroticism was no longer significant when the interaction term with psychological well-being was in the model. The sustained protective effect of psychological well-being highlights that actively striving to realize one's potential may help mitigate the role of neuroticism as an accelerator of stress on biological aging. Taken together, psychological well-being is consistently protective against EAA, while neuroticism, though weaker, served as a risk factor. All findings were observed using EAA measured by the GrimAge2 epigenetic clock.

Importantly, cumulative stressors showed no significant marginal association with EAA, though cumulative stressors combined with other psychological characteristics were positively associated with EAA. The absence of the main effect on the associations between stressors and EAA underscores that the detrimental health effects of stressors can be amplified or ameliorated by individuals' characteristics, such as psychosocial resources, which are congruent with previous findings. For example, Brody et al. (2016) found that racial discrimination did not have a main effect on EAA, but the interaction of racial discrimination with family support showed decelerated EAA in the presence of discrimination if respondents had high family support. Similarly, the current findings demonstrated that the impact of cumulative stressors on EAA is evident via interaction with individuals' psychological well-being and neuroticism profiles.

The moderating effect of psychological well-being was evident across all six dimensions in the main analyses. Such patterns might suggest conceptual and empirical overlap among the dimensions, although extensive psychometric work has previously supported the distinctiveness of the measures (Ryff, 1989). Prior work has also shown that the six dimensions of psychological well-being sometimes have disparate health outcomes. For example, three dimensions of well-being (purpose in life, self-acceptance, and personal growth) were significant predictors of fewer components of metabolic syndrome, whereas three other dimensions were not (Boylan & Ryff, 2015). The present findings show that, while the six dimensions are empirically distinct, all aspects of eudaimonia constitute protective assets in the context of cumulative life stressors and EAA.

It is notable that the moderating effects of psychological resources on the associations between cumulative stressors and EAA were evident only for the GrimAge2 epigenetic clock but not the other epigenetic clocks (i.e., PhenoAge or DunedinPACE). This distinctive pattern may stem from the unique derivation of GrimAge, which was developed as an epigenetic proxy of multiple health/aging/mortality-related biomarkers and health characteristics (e.g., smoking). GrimAge outperforms earlier generation epigenetic clocks in predicting age-related declines (McCrory et al., 2021), and some prior research has shown that psychological factors are distinctively related to GrimAge. For instance, Cuevas et al. (2024) found that everyday discrimination was associated with GrimAge2 and DunedinPACE, while major lifetime discrimination was only linked to DunedinPACE. These patterns suggest that epigenetic clocks may vary in their sensitivity to distinct types of stress exposures and/or protective factors. Furthermore, principal component (PC) analysis of DNA methylation data may enhance the precision of epigenetic clocks (Higgins-Chen et al., 2022); however, PC-based epigenetic clocks are not currently available in MIDUS. Additionally, there is no simple score-generating algorithm for PC–PhenoAge, which means that the generalizability of any PC–clock results derived from this approach may not extend to other samples and could be prone to overfitting. Future research is needed to clarify why various stress exposures relate to specific EAA measures, along with the moderation of psychosocial factors in these relationships.

How psychological resources might be mobilized to deter the effects of cumulative stressors is an important future direction, given that psychological well-being has been shown to be changeable and modifiable (Ruini & Ryff, 2016). Ostafin and Proulx (2023), for example, found that those who reflected on their life goals had lower levels of anxiety after exposure to a stressful film compared to the control group. Implementing person-level interventions to improve psychological well-being, particularly among those with high cumulative stress, may be particularly beneficial.

Limitations and Future Directions

The cross-sectional design of this inquiry limits causal inference regarding temporal relationships between cumulative stressors and psychological factors. Selection bias may also be evident in MIDUS biomarker participants; those who participated tend to

have higher education levels compared to those who did not. This bias suggests that the impact of cumulative stressors on epigenetic aging might have been more pronounced if more disadvantaged individuals participated in the study. Although sociodemographic variables were treated as control variables in the analyses, these factors may matter in understanding the interplay of cumulative stress, psychosocial factors, and EAA. When sample size allows, examining three-way interactions could offer valuable insights.

Future studies could also benefit from longitudinal designs to illuminate within-person dynamics of how epigenetic age responds to stressors and psychological factors. The relationship between cumulative stressors and psychological well-being or neuroticism may also shift with repeated assessments of epigenetic age, potentially revealing amplified effects over time. As MIDUS is ongoing, future research will be able to explore these questions.

A better understanding is also needed of the underlying mechanisms through which stressors interact with psychosocial assets to influence EAA, including the role of health behaviors. For instance, stressors are associated with smoking status—those experiencing the highest levels of stress were 3.74 times more likely to be current smokers (Slopen et al., 2012). Although smoking is a well-established risk factor for EAA (Oblak et al., 2021), how it matters for the interplay between cumulative stress and well-being in predicting EAA warrants greater study. Other health behaviors—such as food and alcohol consumption or physical activity—may also mediate the relationships between stressors, psychosocial factors, and EAA.

Future research also might usefully explore how protective and vulnerability factors work in tandem to shape one's EAA. That is, individuals may exhibit both high or low protective and vulnerability psychological traits, or combinations of high and low. A person-centered approach, such as developing typologies that integrate protective and vulnerability factors, could provide deeper insight into their combined influence. For example, Uchino et al. (2012) categorized social relationships into distinct groups by examining both positive and negative aspects, offering a nuanced framework for understanding their impact on telomeres. Similarly, applying typological methods to psychological risk and protective factors may clarify their combined influence on biological aging.

Finally, epigenetic aging clocks are ever evolving. Thus, the epigenetic clocks used in the current analyses are not definitive, and future research needs to replicate these findings with next-generation epigenetic clocks and/or other measures of biological aging in order to establish the health significance of the effects we observed.

Conclusion

The current study demonstrates how individual psychosocial factors may modify the effects of cumulative stressors on biological aging. Psychological well-being appears to be a significant protective factor, whereas neuroticism appears to represent a risk factor in the acceleration of epigenetic aging. Notably, these moderating effects were evident only for the GrimAge2 epigenetic clock and not for DunedinPACE or PhenoAge. This distinctive pattern may reflect the sensitivity of GrimAge to stressors, as it integrates multiple health- and aging-related characteristics. These findings warrant further replication, including the exploration of newly identified epigenetic clocks. Overall, the results suggest that biological aging was not uniformly impacted by stressors but can be significantly altered depending on an individual's psychological assets and vulnerabilities.

Resumen

Objetivos: El envejecimiento epigenético celular se ha convertido en un marcador importante del envejecimiento saludable o no saludable. El presente estudio examinó si los factores estresantes acumulados a lo largo de la vida en múltiples dominios se relacionaban con la aceleración de la edad epigenética (EAA, por sus siglas en inglés; es decir, una edad epigenética mayor que la edad cronológica) y si los factores psicológicos moderaban esta asociación. Se planteó la hipótesis de que las dimensiones del bienestar psicológico eran factores protectores, mientras que el neuroticismo se postuló como un factor de vulnerabilidad. ***Métodos:*** Se utilizaron datos del proyecto Genómico de la Mediana Edad en Estados Unidos (MIDUS, por sus siglas en inglés) ($N = 1{,}006$), que incluye datos de metilación del ADN de un subgrupo de participantes en el "MIDUS Core Wave 2 (M2)" y el "MIDUS Refresher Wave 1 (MR1)". Los valores de envejecimiento epigenético se calcularon utilizando los perfiles de metilación del ADN en los sitios de Citosina-fosfato-Guanina. Se evaluaron los factores estresantes acumulativos y los factores psicológicos utilizando los datos de la encuesta en M2 y MR1. ***Resultados:*** Los resultados revelaron que los estresores acumulativos no se asociaron directamente con la EAA, sino que dependían de los niveles de bienestar psicológico y neuroticismo. Específicamente, niveles más altos de estresores acumulativos se vincularon significativamente con la EAA, medida mediante GrimAge2, en quienes presentaron niveles más bajos de bienestar psicológico ($\beta = .23$ a $.36$, $SE = .12$ a $.13$, $p = .04$ a $< .01$) o mayor neuroticismo ($\beta = .26$, $SE = .12$, $p = .03$). Por el contrario, la EAA en individuos con niveles más altos de bienestar psicológico o menor neuroticismo no se vio afectada por los niveles de estresores acumulativos. ***Conclusiones:*** Los hallazgos subrayan la importancia de considerar los activos y las vulnerabilidades psicológicas individuales en las vías que vinculan los factores estresantes acumulativos con el envejecimiento epigenético.

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