Cumulative Stress and Epigenetic Aging: The Moderating Role of Psychological Well-Being and Neuroticism

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MIDUS Midlife in the United States — A National Study of Health & Well-Being

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Introduction

Lifelong cumulative stressors – from childhood adversities (e.g., childhood abuse) to adult challenges (e.g., financial strain) adversely impact one's health (Haight et al., 2024; Slopen et al., 2012). However, its relationship with **epigenetic age acceleration (EAA; i.e., epigenetic age greater than chronological age)** is not well-established. Cellular epigenetic aging has emerged as an important new biomarker of health and is increasingly linked with stress exposures and psychosocial moderating factors.

In this study, we examined how a theoretical model of **psychological well-being, comprised of six distinct dimensions**, was individually ***protective*** against EAA, thus underscoring the idea of resilience in the face of stress (Ryff et al., 2012). Conversely, building on extensive prior research, **neuroticism** was posited as a ***vulnerability*** factor, potentially amplifying the impact of stress on health by heightening negative reactivity to stressors (Bolger & Schilling, 1991).

Research Hypotheses

H1: Higher cumulative stressors will lead to higher EAA.

H2: Psychological well-being will buffer the association between cumulative stressors and EAA.

H3: Neuroticism will exacerbate the association between cumulative stressors and EAA.

Methods

Participants: This study used data from the ***Midlife in the United States*** **(MIDUS)** study, a national longitudinal study of U.S. adults. We included two samples with DNA methylation data: the Core Sample (Wave 2, N = 511) and the Refresher Sample (Wave 1, N = 799). After excluding non-respondents to stressor measures, the final sample included 1,006 participants with an average age of 53.44 years (SD = 12.56), of which 52.68% were female.

Survey data

- **Cumulative stressors** *(Independent variable)*
  Childhood stressors, stressful life events, financial/relationship/neighborhood stress, psychological/physical work stress, work-family conflict, perceived inequality, discrimination, & past-year family problems
- **Psychological well-being** *(moderator 1)*
  Purpose in life, environmental mastery, self-acceptance, autonomy, positive relationships with others, & personal growth (all $\alpha > .69$)
- **Neuroticism** *(moderator 2)*
  worrying, nervous, moody, calm (r) ($\alpha = .73$)
- **Covariates**
  Race/ethnicity, sex, employment status, marital status, children, sample group

Genomics data

- **GrimAge2 epigenetic age acceleration** *(Dependent variable)*
  - 2nd generation epigenetic clock
  - Predictive of healthspan, events related to aging, the onset of disease (e.g., cancer), and all-cause mortality
- **Covariates**
  - Smoking status, alcohol consumption, body-mass-index & age at clinic visit

Analytic Plan

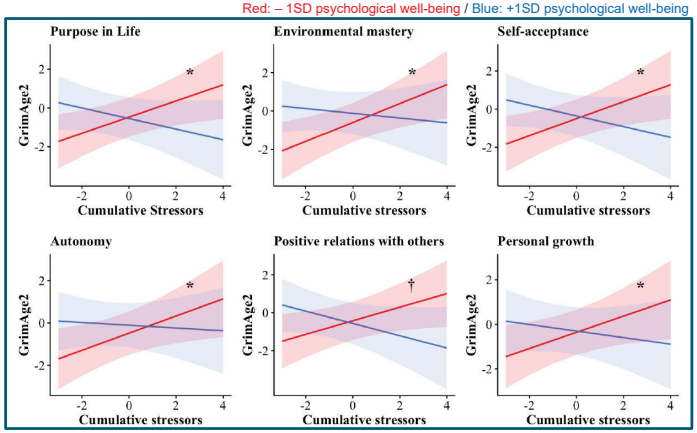
- Multiple linear regression analyses were conducted in R, using cluster-robust standard errors to adjust for clustering within twins & siblings in the analytic sample
- Interaction effect of cumulative stressors X dimensions of psychological well-being/neuroticism were included to test H2 & H3

Study Results

- **H1 : There was No Direct Effect of Cumulative Stressors on Epigenetic Age Acceleration**
  (β = .15, SE = .15, p = .30)

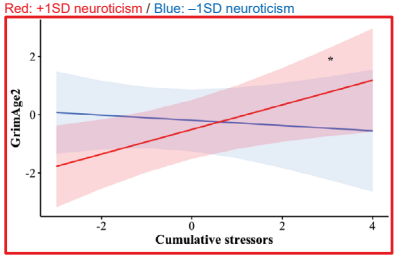
- **H2: Six Dimensions of Psychological Well-Being *Buffered* the Impact of Cumulative Stressors on Epigenetic Age Acceleration**
  - There was a significant interaction effect of cumulative stressors X six dimensions of psychological well-being
    (β = −.23 to −.36, SE = .12 to .13, p = .04 to <.01)

Red: – 1SD psychological well-being / Blue: +1SD psychological well-being



*p < .05, †p = .06

Red: +1SD neuroticism / Blue: –1SD neuroticism



*p < .05

- **H3: Neuroticism *Exacerbated* the Impact of Cumulative Stressors on Epigenetic Age Acceleration**
  - There was a significant interaction effect of cumulative stressors X neuroticism
    (β = .26, SE = .12, p = .03)

Implications & Future Directions

- It is crucial to consider individual psychological assets (psychological well-being) and vulnerabilities (neuroticism) when examining how cumulative stressors affect one's biological aging process.
- People facing multiple stressors may benefit from interventions that enhance well-being and help mitigate the consequences of neuroticism in coping with life stressors.
- Future studies should explore health behaviors (e.g., stress-eating, exercise) as potential mediators in the link between stressors and epigenetic aging.
- Limitation: The current study uses a cross-sectional design, which limits causal inference of the findings.
- Limitation: Longitudinal studies may show selection bias, with participants in the Biomarker project (i.e., those with genomics data) having higher educational attainment.

Link to my website