The Effect of Lifetime Stress on Accelerated Epigenetic Aging

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Background

Allostatic load & Allostasis

- **Allostatic load** is a measure of the biological aging process and the cumulative effect of chronic exposure to stress
- **Allostasis** is the process by which the body alters physiological parameters in response to stress
- The cumulative burden of repeated adaptation to stressful events can **exacerbate the ongoing progression of biological aging** AND **increase** susceptibility to aging-related disease onset.

Epigenetic biomarkers for aging

- DNA methylation (DNAm) characteristically accumulate over time to represent biological progression
- Several studies on accelerated DNAm aging:
  - Associated with aging-related problems, morbidity, and mortality
- Accelerated aging can provide insight on the relationship between allostatic load and biological aging

Lifetime Stress and DNAm Aging

- Lifetime PTSD severity and childhood maltreatment associated with accelerated DNAm age but current PTSD diagnosis and traumatic exposure are not.
- The cumulative effect of stress on biological aging throughout one's lifetime remains to be elucidated.
- Significant stressors may further exacerbate accelerated biological aging and racial disparities in health among Black individuals in the U.S.
- We aim to measure the cumulative effect of a series of life stressors suspected to negatively impact health on accelerated DNAm aging in the **Detroit Neighborhood Health Study (DNHS).**

Detroit Neighborhood Health Study

Project Aims

1. To develop a lifetime stress measure to assess stress burden among DNHS participants.
2. To evaluate the association between a measure of cumulative lifetime stress and accelerated DNAm aging while taking into account gender-related differences in aging biomarkers using two measures of DNAm aging–Horvath's epigenetic clock and Hannum's epigenetic clock.
3. To examine variables that might modify the potential association between lifetime stress burden and accelerated DNAm age.

Methods

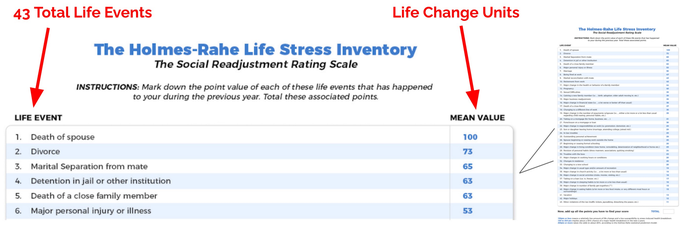

Figure 1. Holmes-Rahe Lifetime Stress Score. Full Lifetime Stress Score (25 Holmes-Rahe life events) and Reduced Lifetime Stress Score (11 Holmes-Rahe life events).

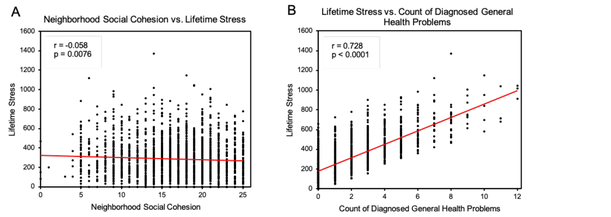

Figure 2. Pearson correlations between A) neighborhood social cohesion and full lifetime stress score and B) count of diagnosed general health problems and full lifetime stress score.

DNA Methylation Assessment

- Genome-wide DNA methylation was measured in whole blood-derived DNA
- DNAm age computed using Horvath and Hannum epigenetic clocks

DNA Methylation Age Acceleration

- Defined as the difference between Horvath/Hannum DNAm age and chronological age
- Positive and negative **residuals** represent accelerated and decelerated DNAm age, respectively.

Statistical Analysis

- Multiple linear regression models of accelerated DNAm age on lifetime stress using Horvath and Hannum epigenetic clocks.
- Models adjusted for smoking status, education, and race.
- Assessed social support as an effect measure modifier.
- **Immune cell proportions** were estimated using the Houseman method and used in sensitivity analyses.
- **Principal component analysis (PCA)** was used to reduce the number of variables in our models by summarizing the proportions of six types of immune cells in the blood.

Study Participant Characteristics

- Majority of study participants were women (61.0%) and identified as Black (82.5%)
- On average, women were 6.6 years older than men
- Completed post-high school education (55.8%)
- Smoked at least once in their lifetime (74.7%)
- On average, the Holmes-Rahe lifetime stress score for women was higher than the score for men using both the full and reduced versions of the lifetime stress score
  - **Full stress score:** Average difference was 106 units
  - **Reduced stress score:** Average difference was 117 units

Results & Discussion

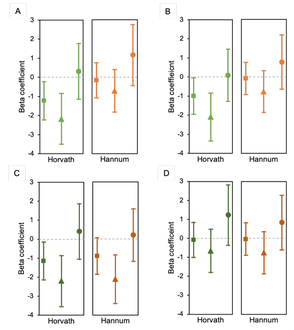

Figure 1. Association between Holmes-Rahe lifetime stress and DNAm age acceleration measures for total sample (square), women (triangle), and men (circle). A, B) Model A adjusted for smoking status, education level, and race; full lifetime stress score used in all analyses. C, D) Model B adjusted for smoking status, education level, race, and immune cell estimates; reduced lifetime stress score used in all analyses.

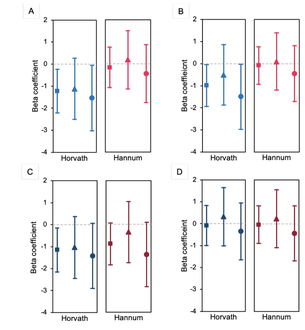

Figure 2. Association between lifetime stress and DNAm age acceleration measures for total sample (square), high social support (triangle), and low social support (circle). A, B) Model A adjusted for smoking status, education level, and race; used full lifetime stress score in all analyses. C, D) Model B adjusted for smoking status, education level, race, and immune cell estimates; used reduced lifetime stress score in all analyses.

- Observed associations between lifetime stress and accelerated DNAm age are **consistent** across analyses using both the full and reduced versions of the Holmes-Rahe lifetime stress score.
- Association appears to be negative, and primarily driven by women using the Horvath clock.
- However, for the reduced version of the stress score, including the estimated proportion of immune cells in the blood also **increases** the negative association among the total sample to the null.
- No evidence of effect measure modification by social support.

Secondary Analyses

- Limitation #1: Holmes-Rahe lifetime stress score cannot measure temporal effects
  - Although the timing of events can't be assessed using this Stress Scale, we **can** measure the frequency/count of Holmes-Rahe life events for each individual.
  - For both Horvath and Hannum epigenetic clocks, we observed that these associations mirror those found in the regression models using the full and reduced lifetime stress scores.
- Limitation #2: Potential ambiguity in Holmes-Rahe Stress Scale
  - Evaluate the association using a reduced Holmes-Rahe lifetime stress score
- Limitation #3: Possible survivorship bias within our sample
  - Examined association between lifetime stress and accelerated DNAm aging using 40-year birth cohorts
  - Examined association between the number of comorbidities and accelerated DNAm aging and Holmes-Rahe lifetime stress
  - Overall, these results provide no evidence that survivors of significant stressful life events are overrepresented in our sample.

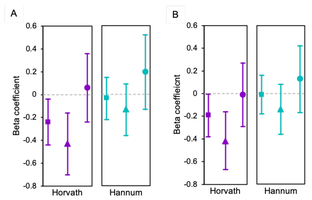

Figure 3. Linear association between count of Holmes-Rahe life events and DNAm age acceleration measures for total sample (square), women (triangle), and men (circle). A, B) Models adjusted for smoking status, education level, race, and immune cell estimates.

Takeaways

- Analyses in this study may be considered somewhat exploratory in nature
- Unclear whether the detected associations between lifetime stress and accelerated DNAm aging are unique to participants in DNHS or whether biases within the study remain to be uncovered
- Future studies should examine other measures of cumulative life stress in DNHS or other similar neighborhood studies to determine the validity of these observed associations.

References

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