GROWUPGROWOLD
HUMAN DEVELOPMENT, BIRTH TO DEATH

Moffitt & Caspi
Genes Environment Health Behavior

Concept Paper Form

Provisional Paper Title: Association of accelerated aging with stress, stressful life events, and PTSD
Proposing Author: Kyle Bourassa
Author's Email: kyle.bourassa@duke.edu
P.I. Sponsor: Terrie Moffitt and Avshalom Caspi
Today's Date: 3/2/2022

Objective of the study:

Stress and stressful events across the lifespan are associated with poorer health [1-3]. This includes subjective feelings of stress[4-7], stressful life events[8-13], and the development of posttraumatic stress disorder (PTSD) after the experience of trauma[14-16]. One way that stress and stressful events could result in poorer health is through accelerating the rate at which people biologically aging age[17]. Accelerated biological aging is associated with a host of poor health outcomes, including risk of chronic disease and early death[18-20]. If stress, stressful life events, or traumatic stress accelerate the aging process, this acceleration would lead to poor health across organ systems and disease states[21-22]. Better understanding these associations could provide evidence as how to best prevent accelerated aging and improve health as a result[21-22].

It remains an open question, however, which aspects of stress and stressful events might result in accelerated biological aging. Is it the subjective feeling of stress, the actual experience of stressful life events, or the mental health sequelae of trauma (i.e., PTSD symptoms) that best predicts accelerated aging? The Dunedin Study is well-suited to address which aspects of stress and stressful events are associated with biological aging, as the study has assessed perceived stress, stressful life events, and PTSD in adulthood from age 32 to 45. The Dunedin Study developed a validated measure assessing the speed of biological aging during this period (i.e., the Pace of Aging), which would allow for direct comparison between associations of biological aging with perceived stress, stressful life events, and PTSD.

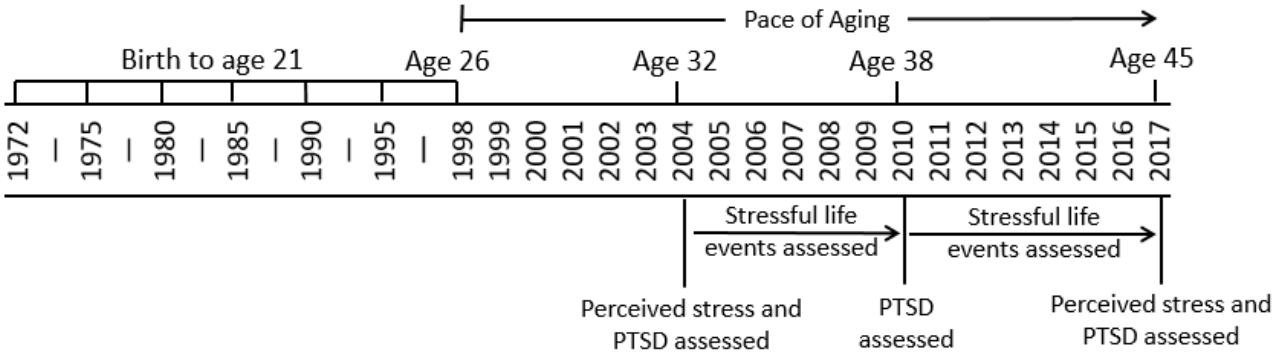

Figure 1. Measurement space for the primary study variables.

Data analysis methods:

Primary Analyses: We propose to investigate the association of stress, stressful life events, and PTSD status with the Pace of Aging (PoA). Participants perceived stress, stressful life events, and PTSD status were

assessed from age 32 to 45. We will estimate the overlap between these 3 ways of ascertaining stress. We will then examine the association between these 3 predictors and the Pace of Aging. Models will include both direct associations of each predictor (perceived stress, stressful life events, and PTSD status) with PoA, as well as associations when all three predictors are in the same model. We hypothesize that each of the three predictors will show associations with accelerated aging in separate models, but PTSD status will show the strongest association with accelerated aging in the combined model.

Sensitivity analyses: We will conduct several sensitivity analyses to supplement the primary analyses.

1. We will run latent class analysis to see if there might be common groups linking the three types of stress, as well as whether these groups are associated with biological aging.
2. We will run our models using counts of phases in which participants had PTSD, as well as the number of PTSD symptom criteria participants met.
3. We will run our models using cut offs for high levels of perceived stress (PSS scores ≥ 10) and stressful life event counts (counts ≥ 20 events
4. We will compare PoA for people with no trauma, traumatic experiences but no PTSD, people with past but not current PTSD, and those with current PSTD to complement the primary analyses

General analysis methods: Participants will be included if they have at least one measure of the 3 predictor variables for least one occasion, as well as PoA assessed. Models will use multiple regression to compare the association between the three predictors: perceived stress, stressful life events, and PTSD. Models will first be run for the three predictors individually, then in a combined model. All models will be run in MPLUS[23] using full information maximum likelihood estimation[24] and including sex as a covariate.

<u>Variables needed at which ages:</u>

- Biological aging outcome
    - Pace of Aging at phase 45
- Stress measure observation period: age 32 to age 45
    - Perceived stress predictor
        - Perceived stress scale scores at age 32 and 45 (perceived stress was not assessed at aged 38).
    - Stressful life events predictor
        - Count via the life history calendar at 38 and 45 covers the period from age 32-45.
    - PTSD predictor
        - PTSD status at age 32, 38, and 45 covering the observation period from age 32 to 45.
        - Lifetime traumas reported at age 45
        - Lifetime prior PTSD at age 26 and 32, for PTSD prior to the observation period
- Sex as a demographic covariate

<u>Significance of the Study (for theory, research methods or clinical practice)</u>:

This study will help provide new knowledge about the relevance of stress, stressful life events, and trauma to accelerated biological aging. Although there is some prior evidence linking each of the 3 measures of stress to accelerated aging previously, it is unclear whether it is the degree to which someone subjectively feels stressed, the absolute number of stressful life events they experience, or the experience of trauma leading to mental health symptoms that is most relevant to aging. This knowledge could support future research on stress and health by providing evidence as to which measures are most predictive of aging and health outcomes. In addition, this work could be used in the future to better understand when, how, and for whom to intervene to address the potential effect of stress, stressful life events, and trauma on people's biological aging, with the hope of preventing accelerated aging and improving health.

References

1. Kalmakis, K.A. and Chandler, G.E. Health consequences of adverse childhood experiences: a systematic review. *J Am Assoc Nurse Pract*, 2015;27(8):457-465.
2. Farrell AK, Simpson JA, Carlson EA, Englund MM, Sung S. The impact of stress at different life stages on physical health and the buffering effects of maternal sensitivity. *Health Psychol*, 2017;36(1):35.
3. Horn Mallers M, Almeida DM, Neupert SD. Women's daily physical health symptoms and stressful experiences across adulthood. *Psychol Health*, 2005;20(3):389-403
4. Cohen S, Williamson GM. Stress and infectious disease in humans. *Psychol Bull*. 1991;109(1):5-24.
5. Glaser R, Rabin B, Chesney M, Cohen S, Natelson B. Stress-induced immunomodulation: Implications for infectious diseases?. JAMA. 1999;281(24):2268-70.
6. Phillips DP, Liu GC, Kwok K, et al. The Hound of the Baskervilles effect: Natural experiment on the influence of psychological stress on timing of death. *BMJ*. 2001;323(7327):1443-46.
7. Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. *JAMA*. 2007;298(14):1685-87.
8. Russ TC, Stamatakis E, Hamer M, et al. Association between psychological distress and mortality: Individual participant pooled analysis of 10 prospective cohort studies. *BMJ*. 2012;345:e4933.
9. Noelke C, Avendano M. Who suffers during recessions? Economic downturns, job loss, and cardiovascular disease in older Americans. *Am J Epidemiol*. 2015;182(10):873-82.
10. Browning M, Heinesen E. Effect of job loss due to plant closure on mortality and hospitalization. J Health Econ. 2012;31(4):599-616.
11. Moon JR, Kondo N, Glymour MM, Subramanian SV. Widowhood and mortality: A meta-analysis. *PloS One*. 2011;6(8):e23465.
12. Noelke C, Beckfield J. Recessions, job loss, and mortality among older US adults. *Am J Pub Health*. 2014;104(11):e126-e134.
13. Niiyama M, Tanaka F, Nakajima S, et al. Population-Based Incidence of Sudden Cardiac and Unexpected Death Before and After the 2011 Earthquake and Tsunami in Iwate, Northeast Japan. *J Am Heart Assoc.* 2014;3(3):e000798.
14. Boscarino JA. Posttraumatic stress disorder and mortality among US Army veterans 30 years after military service. *Ann Epidemiol*. 2006;16(4):248-56.
15. Boscarino JA. A prospective study of PTSD and early-age heart disease mortality among Vietnam veterans: Implications for surveillance and prevention. Psychosom Med. 2008;70(6):668.
16. Sledjeski EM, Speisman B, Dierker LC. Does number of lifetime traumas explain the relationship between PTSD and chronic medical conditions? Answers from the National Comorbidity Survey-Replication (NCS-R). *J Behav Med*. 2008;31(4):341-9.
17. Wolf EJ, Logue MW, Stoop TB, Schichman SA, Stone A, Sadeh N, Hayes JP, Miller MW. Accelerated DNA methylation age: Associations with PTSD and mortality. *Psychosom Med*. 2018;80(1):42.
18. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell.* 2013;153(6):1194-217.
19. Kaeberlein M. Longevity and aging. *F1000prime reports*. 2013;5,5.
20. Strong K, Mathers C, Leeder S, Beaglehole R. Preventing chronic diseases: how many lives can we save?. *The Lancet*. 2005;366(9496):1578-82.
21. Barzilai N, Cuervo AM, Austad S. Aging as a biological target for prevention and therapy. *JAMA*. 2018;320(13):1321-2.
22. Kennedy BK, Berger SL, Brunet A, et al. Geroscience: linking aging to chronic disease. *Cell.* 2014;159(4):709-13.

23. Muthén LK. & Muthén BO. Mplus User's Guide. Seventh Edition. Los Angeles, CA: Muthén & Muthén. 1998-2012.
24. Graham JW. Missing data analysis: Making it work in the real world. *Annu Rev Psychol*. 2009;60, 549-576.