Association of Symptoms of Posttraumatic Stress Disorder and GrimAge, an Epigenetic Marker of Mortality Risk, in US Military Veterans

Peter J. Na, MD, MPH[a,b,*]; Janitza L. Montalvo-Ortiz, PhD[a,b]; Sheila T. Nagamatsu, PhD[a,b]; Steven M. Southwick, MD[b]; John H. Krystal, MD[b,c]; Joel Gelernter, MD[b,c]; and Robert H. Pietrzak, PhD, MPH[b,c,d]

Posttraumatic stress disorder (PTSD) is prevalent in US military veterans and has been linked to premature mortality, which can be predicted by accelerated epigenetic aging, a marker of biological aging.[1]

Recent studies have reported associations between PTSD and accelerated epigenetic aging.[1] GrimAge, a composite of DNA methylation (DNAm)-based markers linked to health- and lifespan, is the strongest predictor of various age-related metrics (eg, time to death, to coronary heart disease, and to cancer) relative to other measures of epigenetic aging.[1] We examined the relationship between PTSD and its specific symptoms, other medical and psychiatric conditions, and GrimAge in a large, nationally representative sample of male US veterans.

METHODS

Participants

The sample included 1,132 male European-American US veterans who participated in the National Health and Resilience in Veterans Study, which surveyed a nationally representative sample of US veterans (see Supplementary Material).

Assessments

GrimAge. GrimAge is a composite measure of epigenetic aging based on 8 DNAm surrogates of plasma proteins that are associated with mortality or morbidity, and a DNAm-based estimator of smoking pack-years. Accelerated GrimAge (ie, greater epigenetic than actual age) was operationalized as a residual GrimAge acceleration ≥ 5 years relative to chronologic age (mean = 8.3 years, standard deviation = 2.2, range = 5–16).

PTSD symptoms. PTSD symptoms were assessed using the PTSD Checklist-Specific Stressor Version (PCL-S); scores ≥ 35 were indicative of probable PTSD.

Methodological details are available in the Supplementary Methods.

Data Analysis

Multivariable relative regression analyses were conducted to examine the relationship between PTSD and accelerated GrimAge (see Supplementary Material).

RESULTS

A total of 18.3% (95% confidence interval [CI] = 16.0%–20.8%) of the sample had accelerated GrimAge. Relative to veterans without accelerated GrimAge, those with accelerated GrimAge were less likely to be married/partnered and to have an annual household income > $60,000/year and more likely to be combat veterans, obese, and current smokers and to screen positive for current alcohol use disorder and PTSD; they also reported more cumulative traumas and medical conditions (Table 1).

When these variables were entered into a relative regression analysis, PTSD was associated with 2-fold greater odds of accelerated GrimAge while college graduate or higher education was associated with lower odds of this outcome; none of the other variables were significant (all *P* values > 0.20). PTSD remained significantly associated with accelerated GrimAge even after additionally adjusting for smoking status (risk ratio = 2.00, 95% CI = 1.01–3.99).

PTSD was specifically associated with an acceleration in DNAm surrogates of tissue inhibitor metalloproteinase-1 (TIMP-1), β-2 microglobulin (B2M), and growth differentiating factor-15 (GDF-15) (Supplementary Table 1).

Greater severity of trauma-related detachment (ie, feeling distant or cut off from others, OR = 1.73, 95% CI = 1.22–2.45, *P* = .002; Supplementary Figure 1) and sleep disturbance (OR = 1.51, 95% CI = 1.16–1.95, *P* = .002) were independently associated with accelerated GrimAge.

[a]VA Connecticut Healthcare System, West Haven, Connecticut
[b]Department of Psychiatry, Yale School of Medicine, New Haven, Connecticut
[c]US Department of Veterans Affairs National Center for PTSD, VA Connecticut Healthcare System, West Haven, Connecticut
[d]Department of Social and Behavioral Sciences, Yale School of Public Health, New Haven, Connecticut
**Corresponding author:* Peter J. Na, MD, MPH, 300 George St, Ste 901, New Haven, CT 06511 (peter.na@yale.edu).
J Clin Psychiatry 2022;83(4):21br14309

To cite: Na PJ, Montalvo-Ortiz JL, Nagamatsu ST, et al. Association of symptoms of posttraumatic stress disorder and GrimAge, an epigenetic marker of mortality risk, in US military veterans. *J Clin Psychiatry.* 2022;83(4):21br14309.
To share: https://doi.org/10.4088/JCP.21br14309

Table 1. Bivariate and Multivariable Correlates of Accelerated GrimAge in US Military Veterans[a]

	No Accelerated GrimAge N = 957 (weighted 81.7%)	Accelerated GrimAge N = 178 (weighted 18.3%)	Bivariate test of difference, t or χ^2	Multivariable relative regression analysis, risk ratio (95% CI)
AgeAccelGrim (years), weighted mean (SD)	−1.4 (3.3)	8.4 (2.2)	38.79***	
Age, weighted mean (SD), y	63.1 (14.2)	63.3 (13.0)	0.22	…
Married/partnered	765 (77.2%)	128 (70.2%)	4.14*	0.69 (0.44–1.08)
College graduate or higher education	497 (38.0%)	55 (20.1%)	21.72***	0.51 (0.31–0.86)*
Household income > $60,000	524 (45.3%)	60 (26.1%)	23.41***	1.39 (0.87–2.22)
Combat veteran	334 (31.1%)	70 (38.6%)	4.01*	1.07 (0.69–1.66)
Cumulative trauma burden, weighted mean (SD)	3.2 (2.7)	3.9 (2.9)	3.53***	0.96 (0.89–1.04)
Childhood abuse			0.60	…
None	754 (81.2%)	135 (83.6%)		
Physical abuse	139 (16.4%)	28 (14.1%)		
Physical and sexual abuse	21 (2.4%)	5 (2.3%)		
Years since index trauma, weighted mean (SD)	22.3 (18.6)	24.0 (18.1)	1.05	…
No. of medical conditions, weighted mean (SD)	2.8 (1.9)	3.2 (2.3)	2.31*	1.06 (0.95–1.18)
Obesity	287 (28.6%)	64 (39.7%)	8.94**	1.41 (0.93–2.16)
Current smoker[b]	92 (10.3%)	32 (20.7%)	15.58***	…
Current major depressive disorder	45 (4.9%)	21 (8.5%)	3.23	1.30 (0.51–3.31)
Current alcohol use disorder	124 (12.9%)	38 (20.2%)	6.63*	1.24 (0.81–1.89)
Current posttraumatic stress disorder	77 (9.3%)	36 (21.4%)	22.16***	2.11 (1.06–4.23)*

[a]Values expressed as n (weighted %) unless otherwise noted.
[b]Current smoking status was excluded from the multivariable relative regression analysis as it is redundant with the DNAm PACKYRS surrogate marker of smoking pack-years. In a model that additionally adjusted for current smoking status, posttraumatic stress disorder remained significantly associated with accelerated GrimAge (risk ratio = 2.00, 95% CI = 1.01–3.99).
**P* < .05. ***P* < .001. ****P* < .001.

DISCUSSION

Results of this nationally representative study of male European-American US veterans revealed that PTSD is associated with 2-fold greater odds of accelerated GrimAge, which averaged nearly a full decade. This association was independent of a broad range of other factors, including smoking.

PTSD was associated with an acceleration in DNAm surrogates of TIMP-1, B2M, and GDF-15. TIMP-1 has been linked to abnormalities in long-term potentiation in the prefrontal cortex[2]; B2M, with increased stress-induced gene expression in individuals with psychiatric disorders[3]; and GDF-15, a stress-induced cytokine, with inflammation and physical dysfunction.[4]

Greater severity of 2 specific PTSD symptoms—detachment and sleep disturbance—were independently associated with accelerated GrimAge. Potential mechanisms linking these particular symptoms to accelerated GrimAge include dysregulation of hypothalamic-pituitary-adrenal axis, neuroendocrine, and inflammatory responses.[5,6] While larger and prospective studies are needed to disentangle temporal and mechanistic associations between PTSD and accelerated GrimAge, these findings underscore the utility of transdiagnostic, symptom-level approaches to identifying dimensions of psychopathology linked to epigenetic aging.[6]

Collectively, the results of this study extend prior work[1] to suggest that PTSD is associated with accelerated epigenetic aging in veterans. Limitations of our study include the cross-sectional design; focus on male, European-American veterans, which may limit generalizability of the findings; and use of self-report assessment instruments. Further research is needed to replicate these results in larger, more diverse samples and evaluate the efficacy of interventions for PTSD in forestalling premature biological aging in veterans and other high-risk populations.

Published online: July 6, 2022.

Relevant financial relationships: **Dr Gelernter** is paid for editorial work on the journal *Complex Psychiatry*. **Dr Krystal** is a scientific advisor to Biohaven Pharmaceuticals, BioXcel Therapeutics, Inc., Cadent Therapeutics (Clinical Advisory Board), PsychoGenics, Inc., Stanley Center for Psychiatric research at the Broad Institute of MIT and Harvard, Lohocla Research Corporation. He owns stock and/or stock options in Biohaven Pharmaceuticals, Sage Pharmaceuticals, Spring Care, Inc., BlackThorn Therapeutics, Inc., Terran Biosciences, Inc. He reports income < $10,000 per year from AstraZeneca Pharmaceuticals, Biogen, Idec, MA, Biomedisyn Corporation, Bionomics, Limited (Australia), Boehringer Ingelheim International, Concert Pharmaceuticals, Inc., Epiodyne, Inc., Heptares Therapeutics, Limited (UK), Janssen Research & Development, L.E.K. Consulting, Otsuka America Pharmaceutical, Inc., Perception Neuroscience Holdings, Inc. Spring Care, Inc., Sunovion Pharmaceuticals, Inc., Takeda Industries, and Taisho Pharmaceutical Co., Ltd. He reports income > $10,000 per year from *Biological Psychiatry* (Editor). Dr Krystal received the drug Saracatinib from AstraZeneca and Mavoglurant from Novartis for research related to National Institute on Alcohol Abuse and Alcoholism grant "Center for Translational Neuroscience of Alcoholism [CTNA-4]" from AstraZeneca Pharmaceuticals. He holds the following patents: (1) Seibyl JP, Krystal JH, Charney DS. Dopamine and Noradrenergic Reuptake Inhibitors in Treatment of Schizophrenia. US Patent #5447948. September 5, 1995; (2) Coric V, Krystal JH, Sanacora G. Glutamate Modulating Agents in the Treatment of Mental Disorders. US Patent #8778979 B2 patent issue date: July 15, 2014. US Patent Application No. 15/695164 filed on 09/05/2017; (3) Charney D, Krystal JH, Manji H, Matthew S, Zarate C. Intranasal Administration of Ketamine to Treat Depression. United States Application No. 14/197767 filed on March 5, 2014; United States application or Patent Cooperation Treaty (PCT) International application No. 14/306382 filed on June 17, 2014; (4) Zarate C, Charney DS, Manji HK, Mathew SJ, Krystal JH, Department of Veterans Affairs "Methods for Treating Suicidal Ideation," Patent Application No. 14/197.767 filed on March 5, 2014, by Yale University Office of Cooperative Research; (5) Arias A, Petrakis I, Krystal JH. Composition and Methods to Treat Addiction. Provisional Use Patent Application no. 61/973/961. April 2, 2014. Filed by Yale University Office of Cooperative Research; (6) Chekroud A, Gueorguieva R, Krystal JH. Treatment Selection for Major Depressive Disorder filed on June 3, 2016, USPTO docket number Y0087.70116US00. Provisional patent submission by Yale University; (7) Gihyun Y, Petrakis I, Krystal JH—Compounds, Compositions and Methods for Treating or Preventing Depression and Other Diseases. US Provisional Patent Application No. 62/444552, filed on January 10, 2017, by Yale University Office of Cooperative Research OCR 7088 US01; and (8) Abdallah C, Krystal JH, Duman R, Sanacora G. Combination Therapy for

Treating or Preventing Depression or Other Mood Diseases. US Provisional Patent Application No. 62/719935 filed on August 20, 2018, by Yale University Office of Cooperative Research OCR 7451 US01. The other authors report no competing interests.

Funding/support: The National Health and Resilience in Veterans Study is supported by the US Department of Veterans Affairs National Center for Posttraumatic Stress Disorder.

Role of the sponsor: The funding agency had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Supplementary material: Available at Psychiatrist.com.

REFERENCES

1. Yang R, Wu GWY, Verhoeven JE, et al; PTSD Systems Biology Consortium. A DNA methylation clock associated with age-related illnesses and mortality is accelerated in men with combat PTSD. *Mol Psychiatry*. 2021;26(9):4999–5009.
2. Okulski P, Jay TM, Jaworski J, et al. TIMP-1 abolishes MMP-9-dependent long-lasting long-term potentiation in the prefrontal cortex. *Biol Psychiatry*. 2007;62(4):359–362.
3. Le-Niculescu H, Roseberry K, Levey DF, et al. Towards precision medicine for stress disorders: diagnostic biomarkers and targeted drugs. *Mol Psychiatry*. 2020;25(5):918–938.
4. Tavenier J, Rasmussen LJH, Andersen AL, et al. Association of GDF15 with inflammation and physical function during aging and recovery after acute hospitalization: a longitudinal study of older patients and age-matched controls. *J Gerontol A Biol Sci Med Sci*. 2021;76(6):964–974.
5. Michopoulos V, Powers A, Gillespie CF, et al. Inflammation in fear- and anxiety-based disorders: PTSD, GAD, and beyond. *Neuropsychopharmacology*. 2017;42(1):254–270.
6. McQuaid RJ. Transdiagnostic biomarker approaches to mental health disorders: consideration of symptom complexity, comorbidity and context. *Brain Behav Immun Health*. 2021;16:100303.

See supplementary material for this brief report at PSYCHIATRIST.COM.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Brief Report Title: Association of Symptoms of Posttraumatic Stress Disorder and GrimAge, an Epigenetic Marker of Mortality Risk, in US Military Veterans

Authors: Peter J. Na, MD, MPH; Janitza L. Montalvo-Ortiz, PhD; Sheila T. Nagamatsu, PhD; Steven M. Southwick, MD; John H. Krystal, MD; Joel Gelernter, MD; and Robert H. Pietrzak, PhD, MPH

DOI Number: 10.4088/JCP.21br14309

List of Supplementary Material for the brief report

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published report. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Methods

Participants

The National Health and Resilience in Veterans Study (NHRVS) is a nationally representative survey of U.S. military veterans. The NHRVS sample was drawn from KnowledgePanel, a research panel of more than 50,000 households that is maintained by Ipsos, a survey research firm. KnowledgePanel® is a probability-based, online non-volunteer access survey panel of a nationally representative sample of U.S. adults that covers approximately 98% of U.S. households. Panel members are recruited through national random samples, originally by telephone and now almost entirely by postal mail. Households are provided with access to the Internet and computer hardware if needed. KnowledgePanel® recruitment uses dual sampling frames that include both listed and unlisted telephone numbers, telephone and non-telephone households, and cell-phone-only households, as well as households with and without Internet access.

Of the 4,750 veterans who were in KnowledgePanel® when the NHRVS was fielded (veteran status was assessed using a general demographic questionnaire), 3,408 (71.7%) responded to an invitation to participate and completed a screening question to confirm their study eligibility (current or past active military service). Of these respondents, 3,199 (93.5%) confirmed their current or past active military service, 3,157 (92.6%) complete a confidential, 60-minute online survey, and 2,397 (70.3%) consented to and provided a saliva sample for genotyping. Given that the vast majority of U.S. veterans are male and European-American and to increase statistical power and avoid confounding analyses with low numbers of female and ethnically diverse veterans, epigenetic analyses were limited to male European-American veterans in the genotyped cohort (n=1,132).

Demographic data of survey panel members are assessed regularly by Ipsos using the same set of questions used by the U.S. Census Bureau. To permit generalizability of study results to the entire population of U.S. veterans, the Ipsos statistical team computed post-stratification weights using the following benchmark distributions of U.S. military veterans from the 2011 Current Veteran Population Supplemental Survey of the U.S. Census Bureau's American Community Survey: age, gender, race/ethnicity, Census Region, metropolitan status, education, household income, branch of service, and years in service. An iterative proportional fitting (raking) procedure was used to produce the final post-stratification weights. All participants provided informed consent and the study was approved by the Human Subjects Committee of the VA Connecticut Healthcare System.

Assessments

Cumulative trauma burden. The Trauma History Screen (THS)[1] was used to assess exposure to the lifetime occurrence of 14 potentially traumatic events; the NHRVS additionally assessed exposure to life-threatening illness or injury. The sum of potentially traumatic events endorsed, ranging from 0–15, was used as an index of lifetime trauma burden.

PTSD symptoms. PTSD symptoms were assessed using the PTSD Checklist-Specific Stressor Version (PCL-S); score $\geq$ 35, which have been recommended for general population samples,[2] were indicative of a positive screen (Cronbach's α in the current sample=0.94). Participants were asked to respond to PCL-S in relation to their 'worst' trauma endorsed on the THS.

Combat veteran. Combat veteran status was assessed with the following question: "Did you ever serve in a combat or war zone?" and the Combat Exposure Scale,[3] a 7-item self-report measure that assesses wartime stressors experienced by combatants.

Childhood physical or sexual abuse. Childhood physical or sexual abuse was assessed using two items from the THS: "Hit or kicked hard enough to injure – as a child" and/or "Forced or made to have sexual contact – as a child." A three-level variable was created based on responses to these items: No physical or sexual childhood abuse; physical abuse; and physical and sexual abuse.

Years since index trauma. Years since index trauma was assessed by subtracting current age from age of index trauma.

Number of medical conditions. Sum of number of medical conditions endorsed in response to question: "Has a doctor or healthcare professional ever told you that you have any of the following medical conditions?" (e.g., arthritis, cancer, diabetes, heart disease, asthma, kidney disease). Range: 0-24 conditions.

Body mass index (BMI). BMI was calculated based on self-reported height and weight using the standard formula weight (kg)/height (m^2). Obesity was defined as BMI $\geq$30.00, consistent with CDC guidelines.[4]

Current major depressive disorder. Major depressive disorder symptoms were assessed using the two depressive symptoms items of the PHQ-4,[5] which assessed symptoms occurring in the past two weeks; score $\geq$ 3 was indicative of a positive screen for major depressive disorder (Cronbach's α in the current sample=0.90).[5]

Current alcohol use disorder. Alcohol use disorder was assessed using the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C), a validated measure used to screen for alcohol use disorder.[6] The AUDIT-C consists of 3 questions that assess severity of alcohol consumption and yield a total score ranging from 0 to 12. A score of 5 or higher was considered as indicative of probable alcohol use disorder.[7,8]

Current smoker. Current smoking status was assessed using a question that asked whether veterans had ever smoked cigarettes; response options were "Yes, in the past;" "Yes, currently;" and "Never."

GrimAge calculation

GrimAge is a composite epigenetic biomarker based on the DNAm surrogates of plasma proteins that are known to be associated with mortality or morbidity, and a DNAm-based estimator of smoking pack-years. A two-stage procedure was performed to develop GrimAge. First, DNAm-based surrogate biomarkers of smoking pack-years and 88 plasma proteins previously identified to be linked to mortality were identified. Second, time-to-death was regressed on chronological age, sex, and DNAm-based biomarkers of smoking pack-years and the 12 plasma proteins that exhibited a correlation $r>0.35$ with their respective DNAm-based surrogate marker in step 1. The plasma protein surrogates that were selected by an elastic net regression model were leptin, cystatin C, tissue inhibitor metalloproteinases 1 (TIMP1), adrenomedullin (ADM), beta-2-microglobulin (B2M), growth differentiation factor-15 (GDF-15), and plasminogen activation inhibitor 1 (PAI-1). The resultant mortality risk estimate of the regression model was then transformed linearly into units of years. The rationale for selecting these proteins and details of analytical procedures that generate GrimAge have been described in detail previously.[9]

In the current study, we operationalized accelerated GrimAge as a residual GrimAge acceleration of 5 or more years relative to chronologic age (mean in full sample=8.3 years, SD=2.2, range=5-16). This magnitude difference is clinically meaningful (i.e., approximates an average 5-10 year greater acceleration of epigenetic relative to chronological aging) and permits comparability to prior studies.[10-12] We calculated DNAm age for each individual based on salivary DNA samples profiled with the Illumina Infinium EPIC array and Horvath age estimation algorithm.[13] In the present sample, chronological age correlated strongly with GrimAge ($r=0.91$; $p<0.001$).

Cell proportion estimation analysis was conducted using a modified version of the Houseman method,[14] which yielded estimates of each cell type proportion (e.g., CD14, CD34, and buccal cells) in the peripheral saliva samples. Principal component analysis was conducted to adjust for population stratification using the Barfield method;[15] the first 10 principal components were included in analyses.

Data Analysis

First, we compared baseline characteristics of veterans with or without PTSD using chi-square and independent-samples t-tests. Second, we conducted a multivariable relative risk regression analysis to identify variables associated with accelerated GrimAge variables associated with accelerated GrimAge at the $p<0.05$ level in bivariate analyses were entered into this analysis; PTSD screening status and variables shown in Table 1, as well as cell type proportions (CD34, CD14, and buccal) and 10 ancestry principal components, were entered into this analysis. Given that GrimAge includes a measure of smoking pack-years, analyses were first conducted without adjusting for smoking status; we then conducted a sensitivity analysis to determine whether any significant associations were robust to smoking status. Third, we conducted a second regression analysis with individual PTSD symptoms entered as independent variables to identify symptom(s) that were independently associated with accelerated GrimAge; alpha for this analysis was Bonferroni-corrected to 0.0029 (0.05/17 symptoms). Fourth, we conducted a multivariate analysis of covariance to evaluate how PTSD related to component aspects of GrimAge; this analysis adjusted for variables identified as significant correlates of accelerated GrimAge in the regression model.

Supplement References

1. Carlson EB, Smith SR, Palmieri PA, et al. Development and validation of a brief self-report measure of trauma exposure: the Trauma History Screen. *Psychol Assess* 2011;23(2):463-477.
2. VA National Center for PTSD. Using the PTSD checklist for DSM-IV (PCL). Accessed Sep 9, 2021. https://www.ptsd.va.gov/professional/assessment/documents/PCL_handoutDSM4.pdf
3. Keane TM, Fairbank JA, Caddell JM, et al. Clinical evaluation of a measure to assess combat exposure. *Psychol Assess* 1989;1:53-55.
4. Defining adult overweight and obesity. Centers for Disease Control and Prevention. 2011; Accessed Sep 9, 2021. https://www.cdc.gov/obesity/adult/defining.html
5. Kroenke K, Spitzer RL, Williams JB, Lo¨we B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. *Psychosomatics* 2009;50:613-621.
6. Bush K, Kivlahan DR, McDonell MB. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). *Arch Intern Med* 1998;158:1789-1795.
7. Rumpf H, Hapke U, Meyer C, John U. Screening for alcohol use disorders and at-risk drinking in the general population: psychometric performance of three questionnaires. *Alcohol Alcohol* 2002;37:261–8.
8. Dawson DA, Grant BF, Stinson FS. The AUDIT-C: screening for alcohol use disorders and risk drinking in the presence of other psychiatric disorders. *Compr Psychiatry* 2005;46:405–16.
9. Lu AT, Quach A, Wilson JG, et al. DNA methylation GrimAge strongly predicts lifespan and healthspan. *Aging* (Albany NY) 2019;11(2):303-327.
10. Marioni RE, Shah S, McRae AF, et al. DNA methylation age of blood predicts all-cause mortality in later life. *Genom Biol* 2015;16:25.
11. Christiansen L, Lenart, A, Tan Q, et al. DNA methylation age is associated with mortality in a longitudinal Danish twin study. *Aging Cell* 2016; 15(1):149-154.
12. Tamman AJF, Montalvo-Ortiz JL, Southwick SM, et al. Accelerated DNA methylation age in U.S. military veterans: Results from the National Health and Resilience in Veterans Study. *Am J Geriatr Psychiatry* 2019; 27(5):528-532.
13. Horvath S. DNA methylation age of human tissues and cell types. *Genom Biol* 2013;14: 3156.
14. Houseman EA, Kile ML, Christiani DC, et al. Reference-free deconvolution of DNA methylation data and mediation by cell composition effects. *BMC Bioinformatics* 2016; 17:259.
15. Barfield RT, Almli LM, Kilaru V, et al. Accounting for population stratification in DNA methylation studies. *Genet Epidemiol* 2014;38:231-241.

Supplementary Table 1. DNAm surrogate markers by PTSD screening status

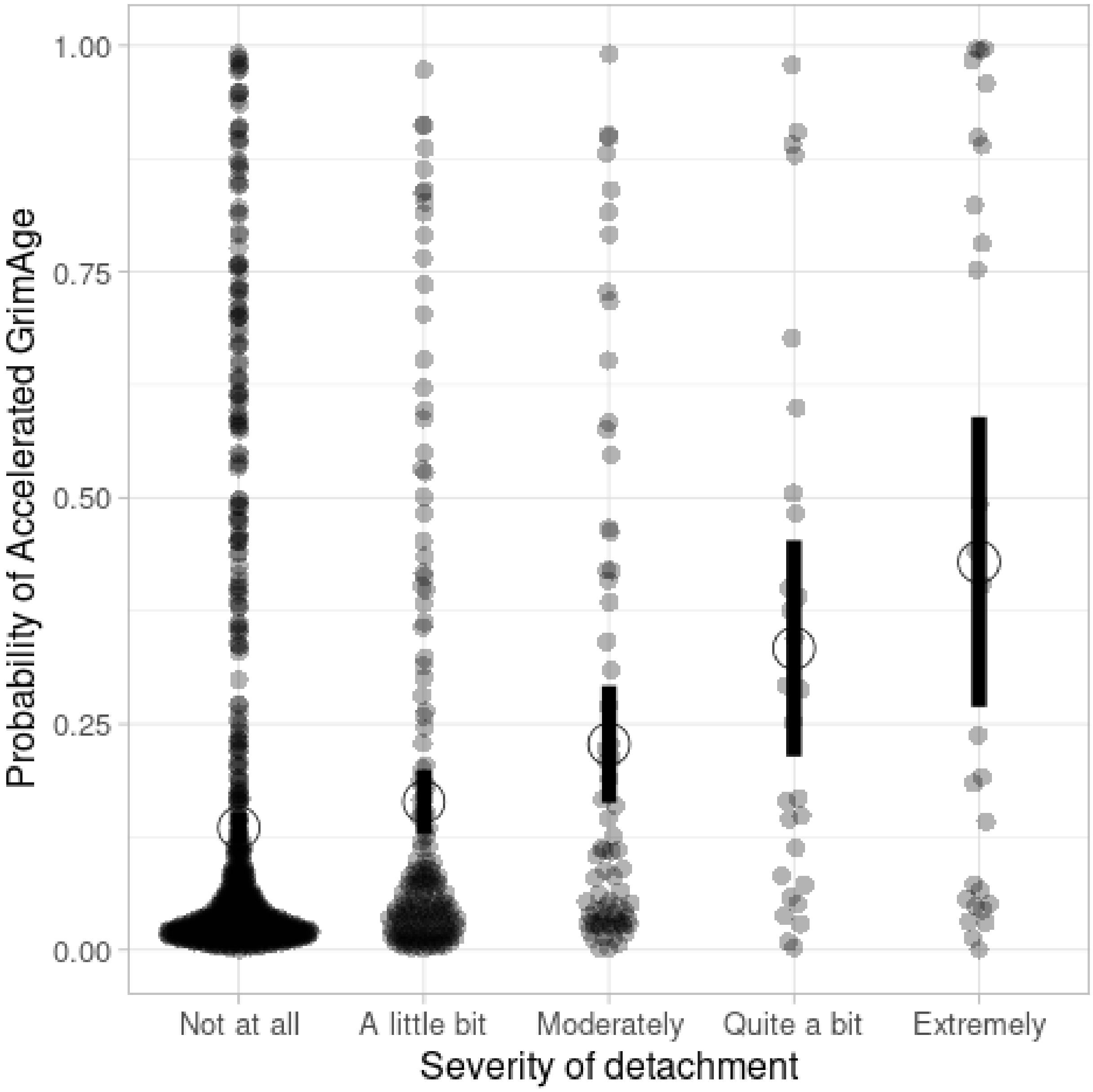
	No Positive Screen for PTSD N=1,019 (weighted 88.5%)	Positive Screen for PTSD N=113 (weighted 11.5%)	Bivariate test of difference
	Weighted mean (SE)	Weighted mean (SE)	F
DNAm PACKYRS	6.45 (0.46)	7.20 (0.93)	0.61
DNAm Cystatin C	2718.12 (1036.58)	2698.06 (2100.63)	0.00
DNAm Leptin	597.09 (251.26)	114.67 (509.18)	0.85
DNAm TIMP-1	101.37 (26.10)	219.29 (52.89)	4.71*
DNAm ADM	2.19 (0.70)	3.31 (1.42)	0.59
DNAm B2M	1886.92 (3892.29)	21033.80 (7887.71)	8.01**
DNAm GDF-15	17.71 (6.77)	53.80 (13.72)	6.56*
DNAm PAI-1	284.29 (131.89)	160.71 (267.28)	0.20

Note. SE=standard error of the mean; PTSD=posttraumatic stress disorder; DNAm=DNA methylation; PACKYRS= smoking pack-years; TIMP-1=tissue inhibitor metalloproteinase 1; ADM=adrenomedullin; B2M=beta-2 microglobulin; GDF-15=growth differentiation factor-15; PAI-1=plasminogen activation inhibitor 1.

Analysis is adjusted for education, current smoking status, cell type proportions (CD34, CD14, and buccal), and top 10 ancestry principal components.

Significant difference: *=p<0.05; **p<0.01.

Supplementary Figure 1. Probability of accelerated GrimAge as a function of severity of detachment symptoms of PTSD



Note. Circles represent mean probabilities; error bars represent 95% confidence intervals. Mean probability of accelerated GrimAge in the sample was 0.18.