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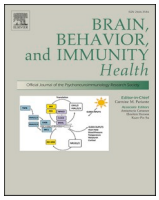

Estimating survival in data-driven phenotypes of mental health symptoms and peripheral biomarkers: A prospective study

Santiago Allende [a,b,*], Peter J. Bayley [a,b]

[a] War Related Illness and Injury Study Center, VA Palo Alto Health Care System, Palo Alto, CA, USA
[b] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA

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ABSTRACT

Background: Chronic psychological stress has widespread implications, including heightened mortality risk, mental and physical health conditions, and socioeconomic consequences. Stratified precision psychiatry shows promise in mitigating these effects by leveraging clinical heterogeneity to personalize interventions. However, little attention has been given to patient self-report.

Methods: We addressed this by combining stress-related self-report measures with peripheral biomarkers in a latent profile analysis and survival model. The latent profile models were estimated in a representative U.S. cohort ($n = 1255$; mean age = 57 years; 57% female) and cross-validated in Tokyo, Japan ($n = 377$; mean age = 55 years; 56% female).

Results: We identified three distinct groups: "Good Mental Health", "Poor Mental Health", and "High Inflammation". Compared to the "Good Mental Health" group, the "High Inflammation" and "Poor Mental Health" groups had an increased risk of mortality, but did not differ in mortality risk from each other.

Conclusions: This study emphasizes the role of patient self-report in stratified psychiatry.

1. Introduction

Chronic psychological distress adversely impacts social, occupational, physical, and mental functioning and has serious implications for the global economy (Counts et al., 2023) Indeed, it is well documented that chronic stress-related inflammatory processes have pernicious effects on aging, disease progression, and mortality (Epel et al., 2018). Prior research has primarily focused on isolated associations between biomarkers of chronic stress, morbidities, and mortality (Steptoe et al., 2013; Baune et al., 2011; Marsik et al., 2008; Kiecolt-Glaser et al., 2003; Hodes et al., 2016). While critical for advancing the field, isolated approaches are less sensitive in detecting distinct patterns across multiple biopsychosocial markers important for clinical decision making (Fernandes et al., 2017). Identifying person-level patterns of multiple psychological constructs and inflammatory biomarkers could help to exact diagnosis, prognosis, and treatments of chronic stress-related health conditions and reduce their negative socioeconomic consequences.

Implementing person-level approaches is consistent with the tenets of precision psychiatry, which seeks to refine diagnosis, prognosis, and treatment at the individual level through multimodal methods that simultaneously factor in biological, psychological, and environmental variables (Fernandes et al., 2017). This also coincides with efforts to move from a stepped-care approach, where interventions progress from less to more intensive, to a matched-care or stratified-care approach based on phenotypic biomarkers (Arns et al., 2023). To date, precision psychiatry has largely focused on identifying latent biosignatures to explain variation in mental health, with patient self-report regarded as secondary to putative biological underpinnings (Gómez-Carrillo et al., 2023). However, this may be an incomplete account because mental health is mediated by narrative meaning-making processes related to self-understanding, interpersonal dynamics, and broader sociocultural epistemologies (Gómez-Carrillo et al., 2023). To move beyond current limitations of the bio-centric model of precision psychiatry, some investigators have emphasized the development of models that give parallel consideration to self-report, phenomenological, and sociocultural aspects of illness experience (Gómez-Carrillo et al., 2023; Kirmayer and Gold, 2011; Borsboom et al., 2018; Ioannidis, 2019).

One particularly appealing approach in precision psychiatry is to utilize data-driven combinatorial methods, such as latent class and latent profile analyses, that partition large samples into latent subgroups of participants who share similar patterns of disease across observed indicator variables (Scrucca et al., 2016). By way of maximum

* Corresponding author. War Related Illness and Injury Study Center, VA Palo Alto Health Care System, Palo Alto, CA, USA.
E-mail address: sallende@stanford.edu (S. Allende).

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likelihood estimation, each participant is estimated a probability of membership to each group and is assigned membership to the group with the highest probability (Scrucca et al., 2016). In the psychological stress and disease literature, depression (Goodwin, 2006), anxiety (Stein and Sareen, 2015), poor sleep (Zeitzer and Gillette, 2013), interleukin-6 (IL-6) (Marsland et al., 2017), C-reactive Protein (CRP) (Pitharouli et al., 2021), dehydroepiandrosterone (DHEA) (Kamin and Kertes, 2017), and cortisol (Adam et al., 2017) have emerged as potent indicators of chronic stress robustly associated with mental and physical functioning. Examples of physical health conditions associated with these indicators, which are also linked to higher risk of mortality, include diabetes (Castro-Costa et al., 2019), heart disease (Halaris, 2013), stroke (Rallidis et al., 2006), and cancer occurrence (Meaney et al., 2017). Therefore, using these as indicator variables in a latent profile analysis may be especially telling in identifying heterogeneous clinical presentations that vary with regard to health conditions, prognostic factors, and risk of mortality.

In this study, our first hypothesis-generating aim was to use a latent variable mixture modeling approach (i.e., latent profile analysis; LPA) to derive distinct person-centered phenotypes of chronic stress-related self-report measures and peripheral biomarkers. We used data from a large representative population cohort of adults in the United States to estimate the models. The profiles were cross-validated with a representative sample from Tokyo, Japan. The second prospective aim was to examine whether risk of mortality differed among the three distinct groups derived from the United States sample only, as survival data was not collected in the Tokyo, Japan sample. Due to strong associations between mental health, physical health, and all-cause mortality (Epel et al., 2018), we expected to find a difference in survival curves between the three distinct person-centered phenotypes identified in our first aim ("Good Mental Health", "Poor Mental Health", and "High Inflammation"). Namely, we expected to find differences between the "Good Mental Health" and "High Inflammation" profiles as well as the "Good Mental Health" and the "Poor Mental Health" profiles, but not between the "High Inflammation" and the "Poor Mental Health" profiles.

2. Methods

2.1. Data source and participants

We obtained data from two population-based longitudinal studies (Midlife in the United States II [MIDUS II; 2004–2009] and Midlife in Japan [MIDJA; 2009–2010]) of age-related individual differences in physical and psychosocial health in representative adults from the United States ($n = 1255$; age $= 57.32 \pm 11.55$ years; 57% female) and from Tokyo, Japan ($n = 377$; age $= 55.27 \pm 14.03$ years; 56% female) (Dienberg et al., 2010; Kitayama et al., 2010; Ryff et al., 2015). The MIDUS series is supported by the National Institute on Aging and currently includes three waves of data collection: MIDUS, MIDUS II, and MIDUS III (Radler, 2014). Participants were recruited for the initial MIDUS study via random digit dialing of telephone numbers. During MIDUS II, in addition to completing self-report measures, a subset of participants provided biomarker data during a laboratory visit and saliva samples during a daily diary study. We used data from MIDUS II sources in the present study. To provide researchers with data for cross-cultural comparisons, the methods used in MIDJA paralleled those of the MIDUS study (Kitayama et al., 2010). Mortality data have been collected through 2022 for the MIDUS study. Mortality data have not been collected for the MIDJA study. Further details on recruitment and data collection methods can be found elsewhere (Radler, 2014). Data are publicly available and can be requested from https://www.icpsr.umich.edu/web/ICPSR/series/203.

2.2. Latent profile analysis indicator variables

2.2.1. Fasting blood draw biomarkers

Three inflammatory and neuroendocrine biomarkers, IL-6, CRP, and DHEA, were obtained from participants in both cohorts. In the United States, serum samples were collected from a 12-h fasting blood draw on the morning of the second day of a 2-day clinic visit, while in Japan, samples were collected from a 1-h fasting blood draw at any time during the day of the clinic visit. (Midlife in the United States) Blood specimens were collected by clinic staff using a standardized set of study procedures. Samples from both cohorts were stored in a −60 °C to −80 °C freezer and were delivered on dry ice to the MIDUS Biocore at the University of Wisconsin, where they were stored at −65 °C prior to analysis by various laboratories in the United States.

An enzyme-linked immunosorbent assay (ELISA; Quantikine® High-sensitivity ELISA kit #HS600B; R&D Systems, Minneapolis, MN) was used to derive IL-6 ligand concentrations in both cohorts (minimum detectable level: 0.156 pg/mL, inter-assay CV: 12.31%; intra-assay CV: 3.25%, assay range: 0.156–10 pg/mL; reference range: 0.45–9.96 pg/mL). Immunonephelometry (Siemens Dade Behring BN II Nephelometer) was used to derive C-reactive protein concentrations in both cohorts (minimum detectable level: 10^{-6} μg/mL; assay range: 0.014–216 μg/mL; inter-assay CV: 4.72–5.16%; intra-assay CV: 2.2–4.1; sensitivity: <3 μg/mL). Radioimmunoassay (Diagnostic Systems Laboratories, #DSL8900, Webster, TX) was used to derive DHEA concentrations in the United States (assay range: 0.2–2.26 ng/mL; inter-assay CV: 5.47%; intra-assay CV: 2.7–3.8%; reference range: 1.9–7.6 ng/mL [21–49 y/o], 1.0–4.5 ng/mL [≥50 y/o] and Tokyo, Japan (assay range: 0.05–9 ng/mL; inter-assay CV: <7.4%; intra-assay CV: <7.4%; reference range: 1.33–7.78 [18–40 y/o], 0.63–4.70 [≥41 y/o]. Additional details on the laboratory assay procedures are described in the MIDUS documentation. (Midlife in the United States).

2.2.2. Nighttime cortisol

Due to differences in self-report and biomarker collection procedures, we used 12-h urinary-free cortisol as a measure of HPA axis function in the United States sample and the average of three evening salivary cortisol samples in the Tokyo, Japan sample. The urine samples in the United States group were collected overnight, from 1900h to 0700 h, on the second day of a 2-day clinic visit. Samples were stored between −60 °C and −80 °C and then mailed to the MIDUS Biocore lab for analysis. High-Pressure Liquid Chromatography was used to assay urinary-free cortisol (minimum detectable level: 0.08 μg/dL; inter-assay CV: 6.1%; reference range: 3.5–45 μg/day). Evening saliva samples were collected using cotton swab Salivette devices (Sarstedt, Nümbrecht, Germany) on three consecutive days immediately following the clinic visit. Participants kept a written log of collection times. Samples were frozen at −60 °C and then shipped to and stored at the MIDUS Biocore lab. A luminescence immunoassay assay procedure (IBL, Hamburg, Germany) was used in the Kirschbaum laboratory at the Technical University of Dresden, Germany to quantitate salivary cortisol (minimum detectable level: 0.43 nM, inter-assay CV: 15%, intra-assay CV: 3%, reference range: 3–25 nM).

2.2.3. Depressive symptoms

The Center for Epidemiologic Studies—Depression Scale (Radloff, 1977; Wada et al., 2007; Fushimi et al., 2013; Cosco et al., 2017) (CES-D; English and Japanese versions) was used to measure depressive symptoms. This is a 20-item measure with four subscales: depressed affect, positive affect, somatic complaints, and interpersonal problems. Participants used a 4- point Likert-type scale ranging from 0 (rarely or none of the time) to 3 (most or all of the time) to indicate how often they felt a particular way or behaved a certain way during the past week (e.g., "I felt sad" and "I had crying spells"). Items were summed to derive a total score that ranges from 0 to 60, with higher scores indicative of greater symptomatology.

2.2.4. Anxiety symptoms

The Spielberger Trait Anxiety Inventory (Spielberger, 1983) was used to assess symptoms of anxiety. Participants rated 20 descriptive items about how they generally feel (e.g., "some unimportant thought runs through my mind and bothers me" and "I worry too much over something that really doesn't matter") on a 4-point Likert-type scale ranging from 1 (not at all) to 4 (very well). A total score was computed as the sum of all items, with higher scores reflecting worse anxiety.

2.2.5. Subjective sleep quality

Subjective sleep quality was measured using a single-item subscale from the 19-item Pittsburgh Sleep Quality Index (Buysse et al., 1989): "During the past month, how would you rate your sleep quality overall?" Participants rated this item on a 4-point Likert-type scale ranging from 1 (very good) to 4 (very bad), with higher ratings reflecting worse sleep quality.

2.3. Survival analysis outcome

2.3.1. Mortality

The University of Wisconsin Survey Center obtained mortality information through December 2022 from the National Death Index and longitudinal sample maintenance. We calculated survival time by subtracting the biomarker MIDUS II laboratory visit month and year from the month and year of death. Of the 1255 MIDUS II participants in this study, 267 (21.27%) were recorded as deceased.

2.4. Statistical analysis

2.4.1. Latent profile analysis

We performed a latent profile analysis (LPA; *tidyLPA* R package (Rosenberg et al., 2018) based on the *mclust* package (Scrucca et al., 2016) to examine our hypothesis-generating aim of identifying distinct person-centered phenotypes of chronic stress-related biomarkers and self-report measures. We performed the analysis in the United States sample and cross-validated the profiles with the Tokyo, Japan sample. The LPA is a latent variable mixture modeling approach that identifies distinct subgroups of participants who share similar levels of continuous indicator variables (Scrucca et al., 2016). We entered IL-6, CRP, DHEA, nighttime cortisol, depressive symptoms, anxiety symptoms, and subjective sleep quality into the LPA. An analytic hierarchy methodology based on Akaike's Information Criterion (*AIC*), Approximate Weight of Evidence (AWE), Bayesian Information Criterion (*BIC*), Classification Likelihood Criterion (*CLC*), and Kullback Information Criterion (*KIC*) was used to determine the best-fitting model (Akogul and Erisoglu, 2017). Single imputation was performed under the general location model and, to aid the interpretation of results, all indicator variables were standardized prior to running the LPA.

Class assignment for each participant was determined by posterior probabilities of the most likely class membership (i.e., participants were assigned to the class that they had the highest probability of belonging to). We reported minimum and maximum average latent class probabilities and entropy values as measures of classification certainty. Higher minimum and maximum average latent class probabilities are indicative of greater model classification certainty. Entropy values range from 0 to 1, with 0 indicating complete classification uncertainty and 1 indicating complete certainty. Simulation studies suggest that an entropy value of 0.4 reflects low classification certainty, an entropy value of 0.6 reflects medium classification certainty, and an entropy value of 0.8 reflects high classification certainty (Clark and Muthén, 2009). We also used the *get_estimates()* function from the *tidyLPA* R package to examine whether the mean of each standardized indicator variable for each profile was significantly different from zero ($p < 0.05$).

2.5. Survival analysis

In the United States cohort, we used a Cox proportional hazards model to test whether survival time differed among the three latent profile groups. The *survival* R package was used to estimate the Cox regression, while the *adjustedCurves* R package was used to derive covariate-adjusted curves with confidence intervals and to calculate differences in survival curves. We expected to find a difference in survival curves between the "Good Mental Health" and "High Inflammation" profiles as well as the "Good Mental Health" and the "Poor Mental Health" profiles but not between the "High Inflammation" and the "Poor Mental Health" profiles. Age- and gender-adjusted survival curves and point-wise confidence intervals for each group were derived using G-Computation (AKA Direct Standardization or Corrected Group Prognosis Method) (Denz et al., 2023). All possible pairwise comparisons were estimated using the *adjusted_curve_test()* function from the *adjustedCurves* package, which used bootstrapped adjusted curves to test whether the integral of the difference between each pair of latent profile survival curves from years 0–15 was equal to 0 (Denz et al., 2023; Pepe and Fleming, 1989). To aid interpretation of results, age was grand-mean centered and gender was coded −0.5 (male) and 0.5 (female). The proportional hazards assumption was adequately met per examination of the Schoenfeld residuals plot. Refer to the Supplementary Material for the R code related to all study analyses.

3. Results

3.1. Latent profile analysis

Table 1 indicates that the best-fitting model in both cohorts was a 3-profile class-varying diagonal solution, where variances are allowed to freely vary across profiles and covariances are fixed to 0. In the United States cohort, the minimum and maximum average latent class probabilities were 0.90 and 0.95, respectively. In the Tokyo, Japan cohort, the minimum and maximum average latent class probabilities were 0.87 and 0.97, respectively, indicating high classification certainty. The entropy value in the United States LPA model was 0.82 and the entropy value in the Tokyo, Japan model was 0.89, both indicating high classification certainty. As shown in Figs. 1 and 2, the 3-profile class-varying diagonal solutions were similar in the United States and Tokyo, Japan cohorts, with both cohorts showing evidence of three distinct profiles marked by similar patterns of IL-6, CRP, DHEA, nighttime cortisol, depressive symptoms, anxiety symptoms, and subjective sleep quality. Table 2 shows descriptive characteristics of each of the 3 profiles by cohort. Supplementary Fig. 1 displays prevalence rates of 20 physical health conditions in the United States cohort, while Supplementary Fig. 2 presents the rates in the Tokyo, Japan cohort.

3.1.1. Good Mental Health

The "Good Mental Health" profiles (United States: $n = 618$; 49% of the cohort) in the United States was primarily driven by low levels of anxiety (mean = −0.65, $se = 0.06$, $p < 0.001$), low levels of depression (mean = −0.62, $se = 0.04$, $p < 0.001$), and the absence of poor sleep quality (mean = −0.36, $se = 0.05$, $p < 0.001$); secondarily by low levels of IL-6 (mean = −0.28, $se = 0.06$, $p < 0.001$) and low CRP (mean = −0.23, $se = 0.06$, $p < 0.001$); and lastly by somewhat lower levels of DHEA (mean = −0.20, $se = 0.08$, $p = 0.010$) relative to cortisol (mean = −0.04, $se = 0.05$, $p = 0.401$; Fig. 1; Supplementary Table S1). Similarly, in Tokyo, Japan (Tokyo: $n = 260$; 68% of the cohort), the "Good Mental Health" group was driven primarily by low levels of depression (mean = −0.39, $se = 0.08$, $p < 0.001$), low anxiety (mean = −0.38, $se = 0.09$, $p < 0.001$), and good sleep quality (mean = −0.26, $se = 0.07$, $p = 0.001$); secondarily by low levels of IL-6 (mean = −0.22, $se = 0.06$, $p < 0.001$) and low CRP (mean = −0.20, $se = 0.03$, $p < 0.001$); and lastly by somewhat higher levels of DHEA (mean = −0.05, $se = 0.09$, $p = 0.555$) relative to PM cortisol (mean = −0.17, $se = 0.04$, $p < 0.001$; Fig. 2;

Table 1
Fit statistics for latent profile modeling solutions in the United States and Tokyo, Japan cohorts.

Cohort	Model	Classes	*AIC*	*AWE*	*BIC*	*CLC*	*KIC*
United States	1	1	24951.75	25163.52	25023.64	24925.75	24968.75
(n = 1255)	1	2	23780.21	24114.38	23893.18	23737.97	23805.21
	1	3	23275.24	23731.60	23429.29	23216.97	23308.24
	2	1	24951.75	25163.52	25023.64	24925.75	24968.75
	2	2	21393.10	21834.22	21542.01	21336.80	21425.10
	2	**3**	**20352.98**	**21023.21**	**20578.91**	**20266.62**	**20399.98**
	3	1	23228.03	23760.48	23407.75	23160.03	23266.03
	3	2	22874.73	23529.50	23095.53	22790.55	22920.73
	3	3	22052.71	22829.58	22314.59	21952.60	22106.71
Tokyo, Japan	1	1	7609.47	7787.95	7664.71	7583.47	7626.47
(n = 377)	1	2	7318.27	7600.06	7405.07	7276.08	7343.27
	1	3	7160.35	7545.31	7278.71	7102.11	7193.35
	2	1	7609.47	7787.95	7664.71	7583.47	7626.47
	2	2	5795.84	6167.81	5910.26	5739.71	5827.84
	2	**3**	**5440.02**	**6005.46**	**5613.62**	**5353.77**	**5487.02**
	3	1	7064.72	7513.90	7202.81	6996.72	7102.72
	3	2	6819.70	7372.01	6989.35	6735.68	6865.70
	3	3	6795.32	7450.87	6996.54	6695.21	6849.32

AIC = Aikake Information Criterion is derived from −2 log-likelihood, penalized by number of parameters; AWE = Approximate Weight of Evidence integrates model fit and classification accuracy information; Bayesian Information Criterion uses −2 log-likelihood, adjusted for the number of parameters and sample size; CLC = Classification Likelihood Criterion is derived from −2 log-likelihood, adjusted with entropy penalty.; Kullback Information Criterion id derived from −2 log-likelihood, penalized by triple the number of parameters minus one. The best fitting models are highlighted in bold font.

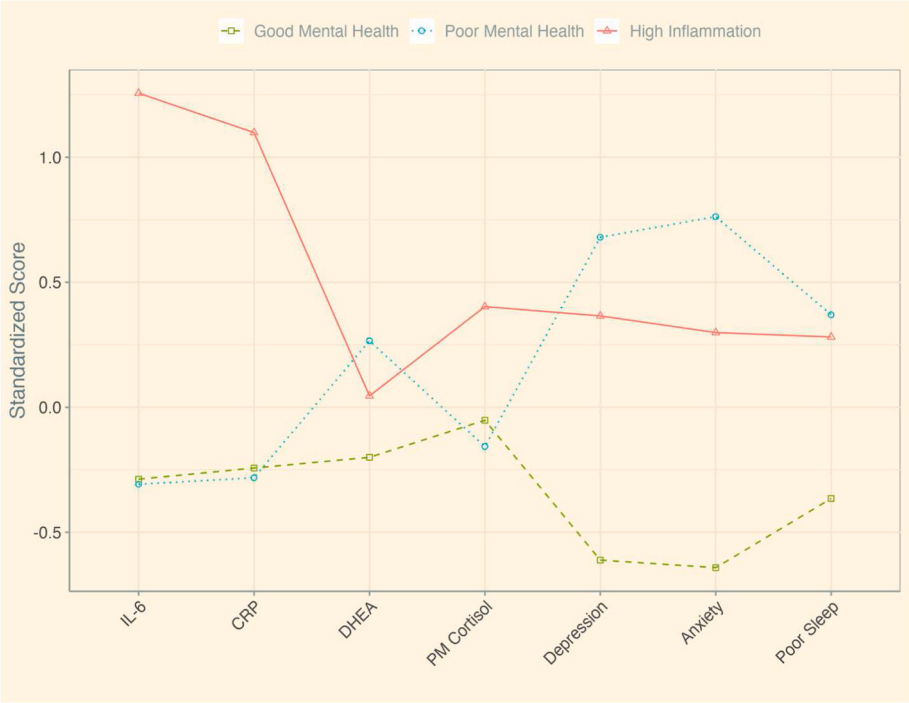

Fig. 1. Model-derived latent subgroups in the United States cohort. The 3 United States profiles estimated by the latent profile modeling procedure are shown. IL-6 = Interleukin-6, CRP=C-reactive Protein; DHEA = Dehydroepiandrosterone; PM Cortisol = 12-h Urinary-Free Cortisol; Depression = Center for Epidemiologic Studies—Depression Scale; Anxiety = Spielberger Trait Anxiety Inventory; Poor Sleep = Pittsburgh Sleep Quality Index Subject Sleep Quality Subscale; y-axis does not start at 0.

Supplementary Table S1).

3.1.2. *Poor Mental Health*

The "Poor Mental Health" profile in the United States sample (United States: n = 407; 32% of the cohort) was driven primarily by relatively higher levels of anxiety (mean = 0.75, *se* = 0.18, $p < 0.001$), high depression (mean = 0.66, *se* = 0.19, $p = 0.001$), and poor sleep quality (mean = 0.35, *se* = 0.10, $p = 0.001$); secondarily by low levels of IL-6 (mean = 0.66, *se* = 0.19, $p = 0.001$) and CRP (mean = −0.28, *se* = 0.08, $p = 0.001$); and lastly by high levels of DHEA (mean = 0.27, *se* = 0.13, $p = 0.038$) relative to PM Cortisol (mean = −0.16, *se* = 0.05, $p = 0.002$; Fig. 1; Supplementary Table S1). similarly, in Tokyo, Japan, the "Poor Mental Health" profile (Tokyo: n = 70; 18% of the cohort) was driven primarily by high levels of depression (mean = 1.36, *se* = 0.41, $p = 0.001$), high anxiety (mean = 1.35, *se* = 0.38, $p = < 0.001$), and poor sleep quality (mean = 0.79, *se* = 0.28, $p = 0.005$); secondarily by high DHEA (mean = 0.50, *se* = 0.19, $p = 0.010$) relative to PM Cortisol (mean = −0.09, *se* = 0.09, $p = 0.279$), and lastly by low IL-6 (mean = −0.28, *se* = 0.10, $p = 0.006$) and CRP (mean = −0.18, *se* = 0.05, $p = 0.001$; Fig. 2; Supplementary Table S1).

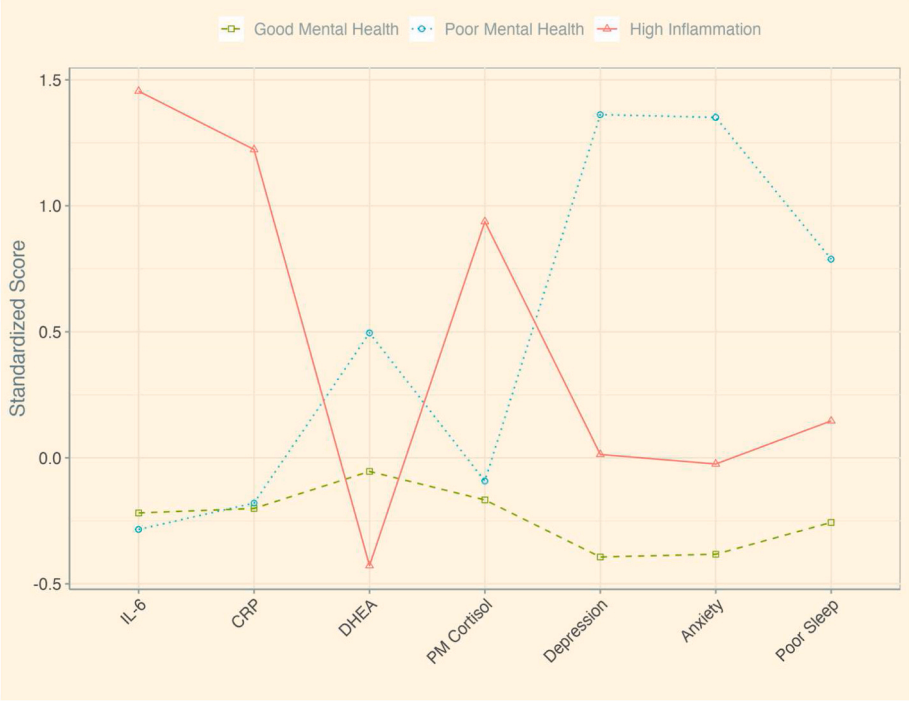

Fig. 2. Model-derived latent subgroups in the Tokyo, Japan cohort. The 3 Tokyo, Japan profiles estimated by the latent profile modeling procedure are shown. IL-6 = Interleukin-6, CRP=C-reactive Protein; DHEA = Dehydroepiandrosterone; PM Cortisol = average of three evening salivary cortisol samples; Depression = Center for Epidemiologic Studies—Depression Scale; Anxiety = Spielberger Trait Anxiety Inventory; Poor Sleep = Pittsburgh Sleep Quality Index Subject Sleep Quality Subscale; y-axis does not start at 0.

3.2. High Inflammation

The "High Inflammation" profile in the United States (United States: $n = 230$; 18% of the cohort) was driven primarily by high levels of IL-6 (mean = 1.27, $se = 0.17$, $p = < 0.001$) and CRP (mean = 1.11, $se = 0.16$, $p = < 0.001$); secondarily by low levels of DHEA (mean = 0.04, $se = 0.13$, $p = 0.755$) relative to PM cortisol (mean = 0.39, $se = 0.19$, $p = 0.039$); and lastly by somewhat higher levels of depression (mean = 0.41, $se = 0.17$, $p = 0.018$), anxiety (mean = 0.33, $se = 0.16$, $p = 0.040$), and sleep quality (mean = 0.30, $se = 0.12$, $p = 0.015$; Fig. 1; Supplementary Table S1). Similarly, in Tokyo, Japan, the "High Inflammation" profile (Tokyo: $n = 52$; 14% of the cohort) was driven primarily by high levels of IL-6 (mean = 1.45, $se = 0.31$, $p = < 0.001$) and CRP (mean = 1.22, $se = 0.41$, $p = 0.003$); secondarily by low levels of DHEA (mean = −0.43, $se = 0.10$, $p = < 0.001$) relative to PM cortisol (mean = 0.94, $se = 0.30$, $p = 0.002$), and lastly by average levels of depression (mean = −0.02, $se = 0.10$, $p = 0.807$) and anxiety (mean = 0.01, $se = 0.10$, $p = 0.897$) and somewhat higher levels of sleep quality (mean = 0.15, $se = 0.18$, $p = 0.422$; Fig. 2; Supplementary Table S1).

3.3. Survival analysis

Results from the Cox proportional hazards model are shown in Fig. 3. After correcting for multiple comparisons using the Bonferroni adjustment (individual $\alpha = 0.017$ for 3 tests), the area between the curves (*ABC*) of the "Good Mental Health" profile and the "High Inflammation" profile was significant ($ABC = 0.734$, $se = 0.19$, $p < 0.001$) as was the ABC of the "Good Mental Health" profile and the "Poor Mental Health" profile ($ABC = 0.488$, $se = 0.129$, $p < 0.001$). However, the *ABC* of the "Poor Mental Health" profile and the "High Inflammation" profile was not significant ($ABC = 0.246$, $se = 0.201$, $p = 0.206$). Holding age and gender constant, there was a 115% increase in the risk of mortality in the "High Inflammation" profile compared to the "Good Mental Health" profile [(2.153–1) x 100 = 115.3]. That is, the expected hazard was 2.153 times higher in the "High Inflammation" profile compared to the "Good Mental Health" profile. Relative to the "Good Mental Health" profile, there was a 74% increase in the risk of mortality in the "Poor Mental Health" profile [(1.738–1) x 100 = 73.8], holding age and gender constant. That is, the expected hazard was 1.738 times higher in the "High Inflammation" profile compared to the "Good Mental Health" profile.

4. Discussion

The hypothesis-generating aim of this study was to use a data-driven approach to partition a large epidemiologic sample of representative adults from the United States into distinct subgroups of participants who shared similar patterns across 7 stress-related indicator variables: (a) depression, (b) anxiety, (c) poor sleep, (d) IL-6, (e) CRP, (f) DHEA, and (g) cortisol. Our results revealed 3 distinct groups in the United States sample that were cross-validated in a large representative sample of adults from Tokyo, Japan: (a) "Good Mental Health", (b) "Poor Mental Health", and (c) "High Inflammation". Our second prospective aim was to examine whether the risk of mortality differed among the three groups. In support of our second hypothesis, relative to the "Good Mental Health" group, both the "High Inflammation" and "Poor Mental Health" groups had an increased risk of mortality, with the "High Inflammation" versus "Good Mental Health" difference being greater than the "Poor Mental Health" versus "Good Mental Health" difference. The difference in risk of mortality between the "High Inflammation" and "Poor Mental Health" groups was not statistically significant.

The most prevalent group in both cohorts was the "Good Mental Health" group (US = 49%; Tokyo = 68%), followed by the "Poor Mental Health" group (US = 32%; Tokyo = 18%), and the "High Inflammation" group (US = 18%; Tokyo = 14%). Not surprisingly in both cohorts, low levels of mental health indicator variables (i.e., anxiety, depression, and poor sleep) were the most distinguishing features of the "Good Mental Health" group, while high levels of mental health indicator variables were the most distinguishing features of the "Poor Mental Health" group. High levels of inflammatory biomarkers (i.e., IL-6 and CRP) were

Table 2
Descriptive statistics for characteristic variables in latent profile subgroups in the United States and Tokyo, Japan.

Characteristic	United Sates			Tokyo, Japan		
	Good Mental Health *n* = 618[a]	Poor Mental Health *n* = 407[a]	High Inflammation *n* = 230[a]	Good Mental Health *n* = 260[a]	Poor Mental Health *n* = 70[a]	High Inflammation *n* = 52[a]
Age	56 (11)	52 (11)	54 (13)	56 (14)	49 (13)	62 (14)
Gender						
Male	302 (49%)	163 (40%)	77 (33%)	113 (43%)	22 (31%)	33 (63%)
Female	316 (51%)	244 (60%)	153 (67%)	147 (57%)	48 (69%)	19 (37%)
Body Mass Index	29 (6)	32 (48)	34 (8)	22.48 (2.80)	22.31 (3.37)	23.46 (3.03)
Smoker						
Yes	56 (9.1%)	83 (20%)	48 (21%)	44 (17%)	23 (33%)	15 (29%)
No	562 (91%)	323 (79%)	182 (79%)	197 (76%)	44 (63%)	33 (63%)
Don't Know	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	0 (0%)	1 (0.2%)	0 (0%)	19 (7.3%)	3 (4.3%)	4 (7.7%)
Ethnicity						
White	526 (94%)	306 (91%)	146 (93%)	–	–	–
Black	12 (2.1%)	11 (3.3%)	4 (2.5%)	–	–	–
Native American	7 (1.2%)	4 (1.2%)	3 (1.9%)	–	–	–
Asian	2 (0.4%)	1 (0.3%)	0 (0%)	–	–	–
Other	14 (2.5%)	11 (3.3%)	4 (2.5%)	–	–	–
Don't Know	1 (0.2%)	1 (0.3%)	0 (0%)	–	–	–
Refused	0 (0%)	1 (0.3%)	0 (0%)	–	–	–
Missing	56	72	73	–	–	–
Marital Status						
Married	436 (71%)	232 (57%)	121 (53%)	201 (77%)	36 (51%)	37 (71%)
Separated	11 (1.8%)	11 (2.7%)	9 (3.9%)	3 (1.2%)	1 (1.4%)	0 (0%)
Divorced	81 (13%)	67 (16%)	38 (17%)	11 (4.2%)	6 (8.6%)	4 (7.7%)
Widowed	36 (5.8%)	27 (6.6%)	25 (11%)	17 (6.5%)	4 (5.7%)	6 (12%)
Never Married	42 (6.8%)	62 (15%)	34 (15%)	27 (10%)	23 (33%)	5 (9.6%)
Living With Someone	12 (1.9%)	8 (2.0%)	3 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Missing	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)
Education						
High School or Less	123 (20%)	89 (22%)	42 (18%)	130 (50%)	37 (53%)	30 (58%)
Some College	113 (18%)	73 (18%)	38 (17%)	5 (1.9%)	1 (1.4%)	3 (5.8%)
College or More	325 (53%)	173 (43%)	75 (33%)	123 (47%)	31 (44%)	18 (35%)
Don't Know	1 (0.001%)	0 (0%)	2 (0.009%)	0 (0%)	0 (0%)	0 (0%)
Missing	56 (9%)	72 (18%)	73 (32%)	2 (0.8%)	1 (1.4%)	1 (1.9%)

[a] Mean (SD); n (%).

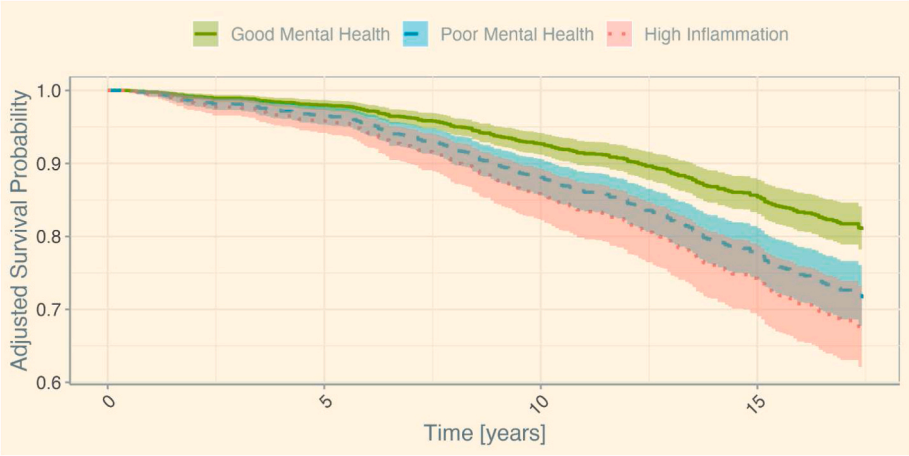

Fig. 3. Age- and gender-adjusted survival curves for each latent profile identified in the United States cohort. Participants in the Poor Mental Health and High Inflammation profiles were at greater risk of mortality than participants in the Good Mental Health profile. The difference in survival time was not statistically significant between the Poor Mental Health and High Inflammation groups. y-axis does not start at 0.

the most distinguishing features of the "High Inflammation" group in both cohorts. DHEA, an anti-glucocorticoid hormone with immuno-regulatory and neuroprotective properties (Kamin and Kertes, 2017), was highest in the "Poor Mental Health" group and lowest in the "High Inflammation" group. Its inverse relationship to cortisol, IL-6, and CRP across groups was consistent with the anabolic/catabolic pattern found in existing literature (Wolkowitz et al., 1997; Straub et al., 1998); specifically, high levels of DHEA in the "Poor Mental Health" group were associated with low levels of cortisol, IL-6, and CRP, while low levels of DHEA in the "High Inflammation Group" were associated with high levels of cortisol, IL-6, and CRP.

Apropos our survival findings that demonstrate a greater risk of mortality with increasing mental and physical health conditions, the three profiles could be considered along a continuum from "Good

Mental Health" to "High Inflammation", with DHEA at the crux of modulating biological responses to experiences of poor mental health. As there were no statistical differences in survival time between the "Poor Mental Health" and "High Inflammation" groups, their underlying physiology may converge over time, leading to nonsignificant differences in survival. That is, prolonged stress among participants in the "Poor Mental Health" group may catalyze a transition from the "Poor Mental Health" group to the "High Inflammation" group.

As shown in Figs. 1 and 2, DHEA/cortisol, DHEA/IL-6, DHEA/CRP exhibited an inverted pattern between the "Poor Mental Health" and "High Inflammation" groups. In the "Poor Mental Health" group, it is plausible that a relatively higher DHEA level, compared to other biomarkers, may function as an inhibitory factor against the proinflammatory environment associated with chronic psychological stress. Conversely, the inverse DHEA-biomarker relationships observed in the "High Inflammation" group suggest that DHEA may ultimately not be effectively mitigating proinflammatory processes. With sustained exposure to chronic stress, some individuals in the "Poor Mental Health" group may eventually display the inverse, low DHEA relationships characteristic of the "High Inflammation" group. This phenomenon could offer a partial explanation for the lack of a statistically significant difference in survival time and is corroborated by empirically-derived models of prolonged stress that have delineated robust mechanistic pathways between chronic psychological stress and morbidity and mortality (Epel et al., 2018).

These patterns align with prior research demonstrating the central role of DHEA in maintaining homeostasis and improving survival outcomes. For example, both in vivo and in vitro studies have found that DHEA inhibits the production of IL-6 (Straub et al., 1998; Kipper-Galperin et al., 1999), which reduces its stimulatory effects in the liver and results in decreased CRP synthesis (Yap et al., 1991). Independent from the examination of DHEA, elevated levels of both IL-6 and CRP have been associated with increased risk of all-cause, cancer, and cardiovascular mortality (Ni et al., 2020; Singh-Manoux et al., 2017). Similarly, DHEA has been shown to dampen the adverse effects of elevated cortisol levels on hippocampal long-term potentiation (Kaminska et al., 2000), mood (Alhaj et al., 2006), and episodic memory (Alhaj et al., 2006). In addition, higher evening cortisol/DHEA ratios, but not either hormone alone, have been shown to accurately differentiate between participants with and without depression, and have predicted the duration of depressive episodes in participants with depression (Young et al., 2002). The cortisol/DHEA ratio has also predicted increased risk of cancer mortality, mortality due to other medical conditions, and all-cause mortality in older adults (Phillips et al., 2010). Taken together with the present findings, these data underscore the significance of DHEA in maintaining homeostasis and promoting longevity by attenuating the adverse effects of chronic stress.

Despite the potential centrality of DHEA in regulating biological responses to chronic stress, some prevention and intervention efforts may benefit by focusing on the psychosocial end of the biopsychosocial spectrum. Psychosocial interventions for common mental health conditions have been shown to offer greater accessibility (Lenze et al., 2024), affordability (Vos et al., 2005), and safety (Farah et al., 2016; Qaseem et al., 2016) compared to biological interventions. In the present study, the "good" and "poor" mental health groups comprised the largest number of participants and were driven primarily by mental health factors, rather than peripheral biomarkers. This finding suggests that these participants may respond more favorably to psychosocial interventions than to biological interventions, such as selective serotonin reuptake inhibitors and neuromodulation therapies, that may partially exert their effects by regulating stress-related biomarkers (Guo et al., 2023; Wang et al., 2019; Hou et al., 2019). However, additional research is required to ascertain whether these identified subgroups do indeed respond differently to specific intervention types, be they biological, psychosocial, or a combination of both. Through this research, the field has the potential to shift away from a stepped-care approach, which can be plagued by inefficiencies and suboptimal outcomes, toward a matched-care or stratified precision medicine approach that is based on harnessing the richness of clinical heterogeneity, rather than controlling for it (Arns et al., 2023). Our results also support an expanded view of stratified psychiatry, whereby psychological indicators of stress are simultaneously considered alongside stress-related biomarkers in distinguishing person-level subtypes of mental health and inflammation.

While helpful in justifying a more encompassing biopsychosocial approach in the development of precision psychiatry, the present results are limited by the exclusion of social determinants of health and contextual factors, such as familial, social, financial, and workplace indicators of stress. To the extent that contextual factors are robust predictors of mental health (Kirmayer and Gold, 2011), future studies would benefit from including them in the mixture modeling procedure. Their inclusion may lead to the development of interventions that address specific sources of distress and domains of functioning in distinct populations. Detaching individuals from their social context and reducing mental health to biological or psychological factors may lead to treatments that only marginally and indirectly address the biopsychosocial model of health and wellness. For example, if a toxic workplace is the most salient stressor for an individual in the "Poor Mental Health" group, the most effective first-line approach, while perhaps challenging to implement, may be to target the workplace environment as opposed to focusing on individual factors.

Examining social determinants of health as potential drivers of the associations between the subgroups of the present study and survival would help to better understand potential cross-cultural differences and to develop culturally sensitive personalized treatments. Although our cross-cultural findings suggest a shared, underlying phenotypic marker of psychobiological health, it is essential to acknowledge that the sociocultural context may play an important role in shaping the development of culturally adapted, personalized interventions. Further research is necessary as prior studies have yielded inconclusive results regarding the extent to which factors such as independence/interdependence and perceived social relationships account for variations in depressive symptoms and peripheral biomarkers between the United States and Japan (Miyamoto et al., 2013; Kaveladze et al., 2022).

The possibility of reverse causality is important to note in latent profile analyses. In the present analysis, elevated levels of inflammation in the "High Inflammation" group may have been due to an underlying physical illness that caused subsequent chronic psychological stress, rather than the inverse. Similarly, the increased risk of mortality in the "High Inflammation" group may have been due to pre-existing physical health conditions. Although the latent profile results point to a continuum of psychobiological health, a latent transition analysis would be required to more accurately assess whether some participants in the "Poor Mental Health" group do indeed transition to the "High Inflammation" group.

Several other limitations are worth mentioning. First, using self-report inventories as proxies for clinical diagnoses limits the direct applicability of our findings from a general population to clinical settings. Future research should address this to enhance ecological validity and practical relevance. Second, our model's reliance on single-time-point data limits the prediction of long-term survival outcomes. Longitudinal data should be included in future research to better understand how these traits evolve and influence long-term survival. Third, while it is plausible that some individuals with poor mental health transition to a state of high inflammation due to chronic stress and insufficient DHEA, thereby explaining differences in inflammatory biomarkers, this hypothesis does not adequately explain the observed improvements in depression and anxiety. Other underlying mechanisms, perhaps better captured by longitudinal assessment procedures, may influence the relationship between mental health, inflammation, and psychological well-being over time. Fourth, it is notable that the American "High Inflammation" group exhibits higher DHEA levels compared to its "Good

Mental Health" group, while the Japanese "High Inflammation" group shows lower DHEA levels relative to its "Good Mental Health" group. Since increasing age is associated with lower DHEA, age differences between the American and Japanese cohorts may be contributing to this observation. Fifth, future studies would benefit from including medications as a covariate in the modeling procedure, as various medications alter biomarker concentrations. Finally, our study lacks ethnic and racial diversity in the United States cohort, which limits the generalizability of our results.

The findings of this study contribute to advancing a stratified or matched approach to precision psychiatry, reaffirming the importance of patient self-reported experience. Our results enhance our understanding of the nuanced interplay between self-reported mental health, stress-related biomarkers, and mortality. They also underscore the pivotal role of DHEA in modulating responses to chronic psychological stress. Moving forward, it will be crucial to investigate the roles that social determinants of health play in delineating these subtypes and matching patients to specific treatments.

CRediT authorship contribution statement

Santiago Allende: Conceptualization, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Peter J. Bayley:** Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

None.

Data availability

MIDUS is a publicly available dataset.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100815.

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