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MIDUS Biomarker Dataset

https://www.icpsr.umich.edu/web/ICPSR/studies/29282/summary

Research Idea:

Multisystem coordination of stress responses across biological systems (HPA axis, autonomic nervous system, catecholaminergic activity, immune system): Examining profiles, predictors, and health implications.

Research Question 1:

How do latent profiles of multisystem stress responses (cortisol, HRV, catecholamines) predict health outcomes such as cardiovascular disease risk, physical health problems, anger expression, depression, and anxiety?

cardiovascular disease 1, physical health 0, anger 0 , depression 0 , and anxiety0
cardiovascular disease 1, physical health 1, anger 0 , depression 0 , and anxiety 0

Conceptual Rationale:

- The body's response to stress involves multiple physiological systems — the HPA axis (cortisol), the autonomic nervous system (HRV), and catecholamine secretion (sympathetic activation).
- Traditional studies often examine one system at a time, but these systems are interconnected and dynamic, functioning together to maintain allostasis.
- Chronic dysregulation across systems (e.g., high cortisol + low HRV + elevated catecholamines) reflects multisystem allostatic load, which is linked to adverse physical and mental health outcomes.
- Identifying distinct physiological profiles allows us to see which patterns, not just single biomarkers, are the most predictive of maladaptive outcomes (e.g., heightened cardiovascular risk, emotion dysregulation, depression).

Potential Hypotheses:

- Participants showing a "high reactivity" or "sympathetic-dominant" profile (high catecholamines, low HRV, high cortisol) will show greater cardiovascular risk and anger expression.

- A “blunted” profile (low across systems) might be associated with depression or emotional numbing.
- A “balanced” or “adaptive” profile (moderate cortisol, high HRV, moderate catecholamines) may relate to lower psychological distress and better health outcomes.

Statistical Analysis Plan

Step 1. Identify latent profiles

- Conduct Latent Profile Analysis (LPA) on standardized biomarkers.
- Compare 1–6 class models using BIC, AIC, Entropy, Lo-Mendell-Rubin (LMR) test.
- Select best-fitting and theoretically interpretable model.

Step 2. Assign participants to latent profiles

- Use posterior probabilities to classify participants to their most likely class.
- Report classification accuracy (entropy ≥ 0.70 desirable).

Step 3. Predict health outcomes from profile membership

- Option 1: Instead of treating class membership as fixed, analyses can incorporate posterior probabilities (i.e., the likelihood that each individual belongs to each profile).
    - use probability-weighted regression or multiple imputation-style approaches to model outcomes while accounting for uncertainty in class assignment.
- Option 2: Assign each participant to their most likely profile based on maximum posterior probability. Then, test whether outcomes differ by profile using:
    - ANOVA/ANCOVA (for continuous outcomes),
    - χ^2 tests (for categorical outcomes),
    - or regression models (e.g., logistic or linear regression) with profile membership as a categorical predictor.

Research Question 2:

Do individuals from different ethnic groups (e.g., White vs. Black adults) exhibit distinct latent profiles of multisystem physiological regulation (cortisol, HRV, catecholamines)?

Conceptual Rationale:

- A growing body of work documents racial/ethnic disparities in physiological stress systems, often linked to structural and sociocultural stressors (e.g., discrimination, socioeconomic inequities, vigilance).
- Rather than testing mean differences in single biomarkers, a latent profile approach captures patterns of multisystem coordination, offering a more holistic view of how stress systems operate in different groups.

- Ethnic differences in stress response profiles could reflect contextual adaptation rather than biological deficiency, suggesting distinct physiological strategies for maintaining homeostasis under varying chronic stress conditions.
- Understanding these profiles can help explain health disparities, as certain multisystem configurations may confer greater vulnerability or resilience to stress-related disease.

Potential Hypotheses:

- Black participants may show higher prevalence of high-cortisol/low-HRV/low catecholamine profiles (consistent with chronic vigilance or "weathering" effects).
- White participants may show a higher prevalence of balanced or moderate-reactivity profiles.
- The structure (in terms of number and nature) of latent profiles may be similar across groups, but the membership proportions may differ.

Statistical Analysis Plan

Option 1: Ethnicity as a covariate (predictor of class membership)

- Conduct LPA on full sample.
- Add ethnicity as a covariate to predict latent class membership.
- This tests whether ethnicity predicts likelihood of belonging to each class. Odds ratios showing how ethnicity predicts profile membership. e.g., Black participants 2.5× more likely to belong to the "high cortisol / low HRV" profile.

Option 2: Multigroup LPA (to test structural differences)

- Fit separate LPA models for each ethnic group.
- Compare:
    - Number of profiles (same or different).
    - Profile shapes (means, variances).
    - Use log-likelihood and BIC difference tests to evaluate invariance.

Research Question 3:

Do experiences of childhood trauma (physical abuse, emotional abuse, sexual abuse, physical neglect, emotional neglect before age 18) predict membership in distinct latent profiles of multisystem stress responses (cortisol, HRV, catecholamines)?

Conceptual Rationale:

- Early life adversity can "program" physiological stress systems, leading to lasting biological embedding of stress.

- Childhood trauma is linked to both hyper-reactivity (overactive stress responses) and hypo-reactivity (blunted stress responses), depending on the nature, timing, and chronicity of adversity.
- A latent profile framework allows detection of multiple trauma-related adaptations. For example, some individuals may exhibit hyperarousal profiles, others hypoarousal, and others resilient regulation.
- Identifying how childhood trauma shapes multisystem coordination provides insight into pathways from early adversity to adult health and psychopathology.

Potential Hypotheses:

- Greater childhood trauma exposure will predict a higher likelihood of membership in dysregulated profiles (e.g., high cortisol and catecholamines with low HRV, or blunted across systems).
- Specific trauma types (e.g., emotional neglect) may relate to blunted responses, whereas physical/sexual abuse may predict hyperarousal profiles.

Statistical Analysis Plan

Step 1. Conduct LPA as above

- Identify best-fitting model for stress biomarkers.

Step 2. Test trauma as predictor of profile membership

- multinomial logistic regression
    - Profiles as outcome (categorical latent variable).
    - Childhood trauma scores as predictors.
    - Odds ratios showing how trauma exposure predicts membership in each stress profile.
    - Distinct trauma types may differentially predict hyper- vs. hypo-reactive profiles.

Exploratory analyses: Mediation models

- Test whether stress profiles mediate the association between trauma and outcomes (depression, anxiety, health, etc.)

Research Question 4:

What are the latent profiles of immune biomarkers (CRP, IL-6, TNF-α, fibrinogen, IL-8, IL-10), and how do these immune profiles relate to multisystem stress profiles derived from cortisol, heart rate variability (HRV), and catecholamines?

Conceptual Rationale:

- The immune system plays a central role in the physiological embodiment of stress, translating neural and endocrine activity into downstream biological responses that influence inflammation, tissue repair, and disease risk.
- Chronic stress exposure alters immune functioning through sustained activation of the hypothalamic–pituitary–adrenal (HPA) and sympathetic–adrenal–medullary (SAM) systems. Over time, these changes can lead to proinflammatory states that contribute to cardiovascular disease, depression, and other stress-related illnesses.
- However, individuals vary substantially in how their immune systems respond to stress. Some exhibit heightened inflammation, others show suppressed immune activity, and others maintain a balanced inflammatory tone.
- These patterns reflect the coordination—or dysregulation—across multiple immune pathways, including proinflammatory cytokines (e.g., IL-6, TNF-α), acute-phase proteins (e.g., CRP, fibrinogen), and anti-inflammatory mediators (e.g., IL-10).
- A latent profile approach allows identification of naturally occurring immune phenotypes that capture this heterogeneity. Once identified, these immune profiles can be examined in relation to previously derived multisystem stress profiles (based on cortisol, HRV, and catecholamines) to test whether dysregulated stress physiology co-occurs with specific immune configurations.
- If certain stress response patterns are systematically linked to proinflammatory immune profiles, it would support models of allostatic load and biological embedding, in which chronic activation of stress systems promotes immune dysregulation and disease vulnerability.

Potential Hypotheses:

- Distinct latent immune profiles will emerge, reflecting patterns of inflammatory balance:
    - Proinflammatory profile: elevated CRP, IL-6, TNF-α, IL-8, fibrinogen; low IL-10.
    - Anti-inflammatory profile: elevated IL-10; low proinflammatory markers.
    - Balanced/moderate profile: moderate levels across both pro- and anti-inflammatory indicators.
- Individuals characterized by high-stress dysregulation profiles (e.g., high cortisol, low HRV, elevated catecholamines) will be more likely to belong to the proinflammatory immune profile, indicating cross-system dysregulation consistent with allostatic load.
- Balanced stress profiles (moderate activation across systems) will be associated with balanced immune profiles, reflecting resilient multisystem regulation.
- (Exploratory) Immune profiles showing higher proinflammatory activity will be associated with greater physical health risk (e.g., higher blood pressure, cardiovascular symptoms) and poorer psychological outcomes (e.g., depression, anxiety)

Statistical Analysis Plan

Step 1. Identify Immune Profiles LPA

- Conduct a Latent Profile Analysis (LPA) using standardized (z-scored) immune biomarkers: CRP, IL-6, TNF-α, IL-8, fibrinogen, and IL-10.
- Evaluate models with 1–6 classes, comparing AIC, BIC, sample-size adjusted BIC, entropy, and likelihood ratio tests to determine the optimal number of profiles.
- Interpret profiles based on mean levels of each biomarker, labeling them as proinflammatory, anti-inflammatory, or balanced, depending on the pattern of cytokine and acute-phase activity.
- Examine profile separation and classification accuracy (entropy ≥ 0.70 preferred).

Step 2. Relate Immune Profiles to Stress Profiles

- Use cross-tabulations or multinomial logistic regression to test associations between immune profile membership (dependent variable) and stress profile membership (predictor).
- Stress profiles will be derived from a separate LPA using cortisol, HRV, and catecholamines as indicators.
- Include posterior probabilities of profile membership as weights or predictors to account for classification uncertainty.
- Assess whether certain stress profiles predict greater odds of belonging to proinflammatory versus balanced immune profiles.

Exploratory Analyses: Predicting Health Outcomes

- Explore whether immune profiles are associated with physical health markers (e.g., blood pressure, cardiovascular risk scores) and psychological outcomes (e.g., anger, depression, anxiety).
- Use general linear models or logistic regression depending on outcome type, controlling for covariates.
- Optionally, test a pathway model in which stress profiles predict immune profiles, which in turn predict health outcomes (i.e., stress → immune → health mediation).

Variables from MIDUS 2 Biomarker Dataset:

Demographic variables

- Race (White vs. Black) B1PF7A (from MIDUS 2), 2004-2006
- Sex (Female vs. Male) B1PRSEX

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# Cortisol
# Urinary epinephrine
# Urinary norepinephrine
# Heart rate (HR)
# rMSSD
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Baseline HRV

- LF-HRV B1 B4VB1LF
- LF-HRV B2 B4VB2LF
- HF-HRV B1 B4VB1HF
- HF-HRV B2 B4VB2HF
- rMSSD HRV B1 B4VB1RM
- rMSSD HRV B2 B4VB2RM
- HR B1 B4VB1HR
- HR B2 B4VB2HR

Either combine B1 and B2 (mean of B1 and B2), or just do B1

Baseline Cortisol

- Urine Cortisol B4BCORTL
- Urine Cortisol adjusted for Urine Creatinine (ug/g) B4BCLCRE
- Saliva Cortisol B4BSCL1A

Catecholamine

- Urine Epinephrine B4BEPIN
- Urine Epinephrine 12 hour B4BEPI12
- Urine Epinephrine adjusted for Urine Creatinine B4BEPCRE
- Urine Norepinephrine B4BNOREP
- Urine Norepinephrine 12 hour B4BNE12
- Urine Norepinephrine adjusted for Urine Creatinine B4BNOCRE

Inflammatory markers

CRP B4BCRP
TNF alpha B4BMSDTNFA
IL-6 B4BMSDIL6
IL-8 B4BMSDIL8
IL-10 B4BMSDIL10
Fibrinogen B4BFGN

Depression

- CESD Interpersonal Subscale B4QCESDI
- CESD Positive Affect Subscale B4QCESDPA
- CESD Depressive Affect Subscale B4QCESDDA
- CESD Somatic Complaints Subscale B4QCESDSC
- CESD Total w
- MASQ: General Distress-Depressive Symptoms B4QMA_D
    - Stress+Depression

Anxiety
- Spielberger Trait Anxiety Inventory B4QTA_AX
  - Latent, trait, in general (more stable)
- MASQ: General Distress-Anxious Symptoms B4QMA_A
  - Current (state, acute)

Anger
- Spielberger Trait Anger Inventory B4QTA_AG
- Spielberger Anger Expression: Anger/Control B4QAE_AC
- Spielberger Anger Expression: Anger/Out B4QAE_AO
- Spielberger Anger Expression: Anger/In B4QAE_AI

Cardiovascular Health Problems
- heart disease B4H1A
- Stroke B4H1F
- high blood pressure B4H1B
- Diabetes B4H1I

Physical Health Complaints
- Total number of other major health events reported B4HOHLTH

Childhood Trauma Questionnaire
- physical abuse B4QCT_PA
- emotional abuse B4QCT_EA
- sexual abuse B4QCT_SA
- physical neglect B4QCT_PN
- emotional neglect B4QCT_EN

Covariates
- Age B4ZAGE
- Income
  - Mean respondent's wages last calendar year B1SG8A (from MIDUS 2), 2004-2006
- Education Level B1PB1 (from MIDUS 2), 2004-2006
- BMI
  - Height in centimeters B4P1A
  - Weight in kilograms B4P1B
- Smoking
  - “Do you currently smoke cigarettes regularly?” B4H26A
  - “Have you ever smoked cigarettes regularly. That is, at least a few cigarettes every day?” B4H26
- Physical Activity Habits
  - “Do you engage in regular exercise, or activity, of any type for 20 minutes or more at least 3 times/week?” B4H25

- Urinary norepinephrine corrected for creatinine levels B4BNOCRE
- Medication
    - Statins B4XTC1S1_1 value 173
    - anti-inflammatory drugs B4XTC1S1_1 value 61
    - beta-blockers B4XPC_1291
    - anti-cholinergic agent B4XTC1S1_1 value 89
    - Antidepressants B4XPC_1050
    - Sedatives B4XTC1S1_1 value 70
    - Anti-psychotics B4XTC1S1_1 value 77
- race

Included measure for LPA and rationale

Measure	Physiological System	What It Indexes at Baseline	Why It's Included
Cortisol	HPA axis	Basal neuroendocrine stress activity	Captures chronic stress burden and HPA regulation
Urinary Epinephrine	Sympathetic–adrenal medullary system	Adrenal sympathetic activation	Reflects acute/chronic arousal and stress reactivity
Urinary Norepinephrine	Sympathetic nervous system	Peripheral sympathetic tone	Linked to vascular resistance and CV risk
Heart Rate (HR)	Integrated autonomic output	Net cardiac workload and autonomic balance	Simple, robust index of physiological strain
rMSSD	Parasympathetic (vagal) system	Beat-to-beat vagal regulation	Clean parasympathetic marker; emotion regulation

Quick-Reference Interpretation Table

Measure	High	Moderate	Low
Cortisol	Chronic stress, anxiety, CV/metabolic risk	Adaptive HPA regulation	Depression, burnout, fatigue
Urinary Epinephrine	Hyperarousal, anger, stress reactivity	Adaptive arousal	Hypoarousal, disengagement
Urinary Norepinephrine	Sympathetic dominance, hypertension risk	Adaptive tone	Reduced alertness, low drive
Heart Rate (HR)	CV strain, stress, low vagal control	Normative	Efficient cardiac function

rMSSD	Protective parasympathetic regulation	–	Poor emotion regulation, CV risk

Details

Cortisol (HPA Axis)

- What it reflects
  - Baseline cortisol reflects tonic HPA axis activity
  - Integrates cumulative stress exposure rather than momentary reactivity
- Interpretation nuance
  - High baseline cortisol
    - Chronic stress exposure
    - Linked to inflammation, metabolic syndrome, CV disease
    - Common in anxiety, anger, hypervigilance
  - Low baseline cortisol
    - HPA axis hypoactivity
    - Seen in depression, PTSD, chronic fatigue
    - Interpreted as burnout or allostatic exhaustion
- Important note
  - Cortisol follows a U-shaped risk pattern: both high and low levels can indicate dysregulation, but with different clinical correlates.

Urinary Epinephrine

- What it reflects
  - Adrenal medulla output
  - “Fight-or-flight” mobilization
  - Strongly linked to emotional arousal and stress intensity
- Interpretation nuance
  - High epinephrine
    - Heightened emotional reactivity
    - Anger expression
    - Acute and chronic stress load
  - Low epinephrine
    - Reduced physiological engagement
    - May reflect emotional blunting or fatigue
- Why epinephrine matters
  - Epinephrine captures arousal intensity, complementing norepinephrine’s role in vascular tone.

Urinary Norepinephrine

- What it reflects
  - Peripheral sympathetic nervous system activity

    - Vascular resistance and blood pressure regulation
- Interpretation nuance
    - High norepinephrine
        - Sympathetic dominance
        - Hypertension and cardiovascular risk
        - Often co-occurs with low HRV
    - Low norepinephrine
        - Reduced sympathetic tone
        - May accompany depression or low motivation
- Why both catecholamines are useful
    - Epinephrine and norepinephrine reflect related but non-identical sympathetic processes; together they strengthen inference about sympathetic dominance vs. disengagement.

Heart Rate (HR)

- What it reflects
    - Net output of sympathetic and parasympathetic influences
    - Cardiac workload at rest
- Interpretation nuance
    - High resting HR
        - Elevated physiological strain
        - Predictor of CV morbidity and mortality
        - Often reflects low vagal tone and/or high sympathetic drive
    - Lower resting HR
        - More efficient cardiovascular functioning
        - Greater parasympathetic influence
- Why HR adds value beyond HRV
    - HR captures overall physiological cost, whereas HRV captures regulatory capacity.

rMSSD-HRV

- What it reflects
    - Short-term variability in heart periods
    - Purest time-domain index of cardiac vagal tone
- Interpretation nuance
    - High rMSSD
        - Strong parasympathetic control
        - Better emotion regulation
        - Faster stress recovery
    - Low rMSSD
        - Autonomic rigidity
        - Poor emotion regulation
        - Increased CV and mental health risk
- Why rMSSD is ideal for baseline LPA

    - Strongly correlated with HF-HRV
    - Less sensitive to respiration
    - Recommended in psychophysiology and health research

Potential Synthesis of Profiles Across These Measures

- Adaptive / Balanced
    - Moderate cortisol
    - Moderate epinephrine & norepinephrine
    - Lower HR
    - High rMSSD
- Sympathetic-Dominant / High Reactivity
    - High cortisol
    - High catecholamines
    - High HR
    - Low rMSSD
- Blunted / Exhausted
    - Low cortisol
    - Low catecholamines
    - Normal–low HR
    - Low rMSSD