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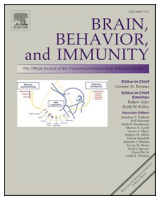

Using social risk factors to predict allostatic biotypes of depression: A latent profile and multinomial regression analysis

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A B S T R A C T

Objective: Major depression is often difficult to treat, particularly among individuals exposed to psychosocial risks like childhood maltreatment, loneliness, and recent stress. These experiences may lead to biological dysregulation consistent with allostatic load theory. This study explored whether distinct biological profiles among adults with depression are associated with specific psychosocial and health-related factors.
Method: Data were drawn from the Midlife in the United States study (MIDUS), including 367 participants with clinically significant depressive symptoms (CES-D ≥ 16). Latent profile analysis identified biological profiles based on 23 biomarkers across seven systems: inflammation, glucose, sympathetic and parasympathetic nervous systems, HPA-axis, cardiovascular, and lipids. Multinomial regression models examined associations between profile membership and psychosocial (childhood maltreatment, loneliness, recent stress), health (alcohol use, smoking, exercise), and demographic variables (sex, race/ethnicity, age, education).
Results: A five-profile solution best fit the data: High Inflammation & Glucose ($n = 74$), Low PNS ($n = 83$), High PNS ($n = 73$), Healthy Depression ($n = 67$), and High HPA-Axis ($n = 70$). Childhood maltreatment significantly predicted membership in the High Inflammation & Glucose and Low PNS profiles compared to the Healthy Depression group, even after controlling for health behaviors and demographics. Loneliness and recent stress were not significant predictors.
Conclusion: Childhood maltreatment is a predictor of biological dysregulation in depression, differentially predicting profiles characterized by inflammatory and metabolic vs parasympathetic functioning. These may represent different vulnerability pathways from social experiences to depressive illness. Incorporating measurement strategies specific to these pathways may aide in selecting treatment options for people who have depression and a history of childhood maltreatment.

1. Introduction

Major depressive disorder (MDD) affects between 10 % and 30 % of individuals at some point in their life and is one of the leading causes of burden of disease across the globe (Otte et al., 2016; Marx et al., 2023). Despite the pressing need for effective treatment options, many individuals do not experience symptom relief with the available front-line treatments (Gaynes et al., 2009; Pigott et al., 2023). Further, among those who initiate treatment, at least a quarter do not receive services (Wang et al., 2007). Thus, the identification of targeted, effective treatments for MDD is of critical importance.

One barrier to the effective treatment of MDD is its numerous presentations (Fried, 2017a). Under the Diagnostic and Statistics Manual (DSM) system alone, there are 227 different possible presentations, 170 of which were confirmed in a sample of over 1,500 MDD patients (Zimmerman et al., 2015). Further, results from the Sequenced Treatment Alternatives to Relieve Depression and the International Study to Predict Optimized Treatment in Depression showed that participants had similar remission rates after treatment with an antidepressant, regardless of symptom clustering (Arnow et al., 2015). Expanding symptom measurement to the 52 different symptoms covered by the 7 most common depressive symptom scales may be one avenue for improving diagnostic subtyping (Fried, 2017b). However, a review of 20 data-driven subtyping studies that used many of these same scales revealed significant heterogeneity across studies (van Loo et al., 2012). Thus, subtyping efforts using depressive symptoms alone has produced significant heterogeneity without aiding in treatment selection. An alternative to symptom-based subtyping would be to use biological markers. Although, data-driven biomarker studies of MDD have yielded similarly heterogeneous results (Beijers et al., 2019). Furthermore, recent trends towards the increasing use of imaging and genomic data in biological subtyping present translational barriers, given the cost and equipment necessary to implement findings into treatment selection (Beijers et al., 2019; Najafpour et al., 2021; Karamperis et al., 2021).

1.1. Allostatic load and MDD

The allostatic load (AL) framework may offer a unique solution to

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many of these issues. AL is commonly used as a measure of 'wear and tear' on several interdependent biological systems implicated in the body's stress response. Systems accounted for in AL studies have varied since the inception of the field, but recent efforts have attempted to crystallize measurement via a total of 23 markers across the sympathetic nervous, parasympathetic nervous, hypothalamic pituitary adrenal axis, inflammation, cardiovascular, glucose, and lipid systems (Wiley et al., 2016). AL theory proposes that as these systems are activated and attempt to regulate each other during the stress response, some systems weaken, leading to stress response dysregulation. This dysregulation in the stress response is thought to explain the association between stressful experiences and several stress-related pathologies, including MDD. Indeed, a body of work has started to emerge that indicates several common risk factors for MDD are associated with greater dysregulation as measured by AL, including childhood maltreatment (Scheuer et al., 2018; O'Shields and Gibbs, 2021; O'Shields et al., 2022), loneliness (Wiley et al., 2017), and recent stress (Goldman et al., 2005; Hellhammer et al., 2004 Mauss and Jarczok, 2021).

Thus far, only a handful of studies have explored biological subtypes of depression through an allostatic load framework. Three studies have explored allostatic profiles of community samples with both depressed and non-depressed participants (Carbone, 2021; Twait et al, 2023; Carbone and Casement, 2024). Each study identified a "baseline" or "average" group that reflected healthier overall functioning while also identifying profiles characterized by higher metabolic and inflammatory levels as well (Carbone, 2021; Twait et al., 2023; Carbone and Casement, 2024). Further, each study pointed towards an increase in depressive symptoms in the profile characterized by metabolic and inflammatory levels. However, only one of the studies included measures of parasympathetic nervous system functioning, which was also positively associated with depressive symptoms (Carbone, 2021). Only one study thus far by Spiegler et al. (2024) has explored AL subtypes in people with MDD, confirming a subgroup of MDD characterized by elevated inflammation and metabolic dysregulation while also still identifying a relatively healthy group that did not show any decrease or elevation in AL markers. Notably, Spiegler et al.'s work supported that data-driven subgroups of AL in people with current MDD could be used to predict symptom clusters consistent with those defined by the DSM-5 (e.g. melancholic, atypical) (APA, 2022) while also controlling for the experience of adverse childhood experiences.

1.2. Present study

Significant advancements have been made in exploring subtypes of MDD using an AL framework. While studies have been able to replicate AL subtypes across several studies, only one thus far has focused on individuals currently experiencing MDD. While informative, established work has not yet explored if risk factors for MDD such as childhood maltreatment, loneliness, and recent stress can be used to predict AL profiles in people currently experiencing a major depressive episode. Additionally, while several studies use an AL framework to guide analyses, studies vary in the markers included, with only one study including markers of the parasympathetic nervous system which were positively associated with depressive symptoms. Thus, the present study had two research goals:

1) identify allostatic profiles of people currently experiencing MDD using AL markers that can also replicate prior work.
2) identify if common risk-factors for MDD differentially predict data-driven AL profiles in people currently experiencing MDD.

2. Methods

2.1. Data

Data are from the Midlife Development in the United States (MIDUS) study, a national multi-wave, multidisciplinary survey of non-institutionalized English-speaking adults in the United States, ages 25 to 74 at initiation. The present study pooled data from Wave 2 (2004–2005) of the main survey (n = 5,555) as well as the expanded Refresher survey (n = 4,085, years: 2011–2014) (Ryff et al., 2017; Ryff et al., 2021). Of these 9,640 participants, 2,118 (main n = 1,255, refresher n = 863) participants agreed to participate in the biomarker subproject. This involved an overnight stay at one of three universities: University of California − Los Angeles, University of Wisconsin – Madison, and Georgetown University. While on site, participants were asked to participate in additional psychological screening as biomarker data collection. Biomarker data included a fasting blood draw, 12-hour urine and saliva collection, and electrocardiogram (ECG). From the total 2,118 participants in the biomarker project, we selected 367 participants (17.32 %) likely to have a current depressive episode as evidence by a score of 16 or greater on the Center for Epidemiological Studies-Depression (CES-D) scale (Lewinsohn et al., 1997). Mean, frequency, and proportion comparisons for all participants included vs excluded can be reviewed in Supplementary Tables 1 and 2.

2.2. Variables

2.2.1. Depression and depressive symptom severity

Was measured using the 20-item CES-D scale, a common measure of depressive symptoms (Radloff, 1977). The CES-D measures depressive symptoms across aspects of depressed affect, positive affect, somatic complaints, and interpersonal difficulties. Each item of the CES-D measures the occurrence of a symptom of depression during the past week via Likert scale (0 – Rarely or none of the time to 4 – Most or all of the time). Summing CES-D items results in a potential score range of 0 to 60, with greater scores indicating greater past week depressive symptom severity. Cronbach's α for the sample was 0.71, acceptable indicating internal consistency

2.2.2. Allostatic markers

We selected allostatic markers based on prior work by Wiley et al. (2016) which operationalized allostatic load using the MIDUS data set. This included 23 biomarkers across 7 different biological systems. Two markers of the sympathetic nervous systems (SNS) were included: Epinephrine and norepinephrine. Five markers of the parasympathetic nervous system (PNS) were included: Resting pulse rate, standard deviation of beat-to-beat intervals (SDRR), root mean square of successive differences (RMSSD), low frequency spectral power heart rate variability (LFHRV), and high frequency spectral power heart rate variability (HFHRV). Two measures of the hypothalamic–pituitary–adrenal (HPA)-axis were included: Cortisol and dehydroepiandrosterone sulfate (DHEA-s) five measures of inflammation were included: C-reactive protein (CRP), interleukin-6 (IL6), fibrinogen, soluble intercellular adhesion molecule-1 (sICAM1), and soluble E-selectin (sE-selectin). Two measures of cardiovascular system were included: Systolic blood pressure (SBP) and pulse pressure, calculated via subtracting diastolic blood pressure from SBP. Three measures of glucose were included: Insulin resistance, fasting glucose, and glycosylated hemoglobin (HbA1C). Last, four measures of lipids were included: Waist-to-hip ratio (WHR), high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, and triglycerides

To obtain this data, participants consented to direct measurement by a nurse, urine collection, blood draws, and ECG readings. Upon arrival to the research unit, a nurse completed a physical exam of each participant, collecting measures of pulse, blood pressure, and anthropometric measures such as waist and hip circumference. Pulse and blood pressure were obtained while the participant was seated (Ryff et al., 2018a; Weinstein et al., 2018a). Urine was collected as part of a 12-hour overnight protocol that occurred starting at 1700 on the first night of the participant's visit and ending at 0700 on the second morning of their visit (Ryff et al., 2018b; Weinstein et al., 2018b). Blood draws were

conducted on the morning of the second day of participant's visit between 0630–0700, with participants being asked to avoid strenuous activity prior to blood collection. Blood was collected via a trained phlebotomist from the participant's non-dominant arm as possible (Ryff et al., 2018b; Weinstein et al., 2018b). ECG data were collected as a part of a laboratory stress protocol to measure stress response, occurring in the morning on the second day of the visit. Our analyses used data during the baseline period, prior to the administration of the stress protocol. ECG electrodes were placed on the participant's left shoulder, right shoulder, and lower left quadrant. Data from ECG measurement were based on the first 300 s epoch of baseline measurement (Ryff et al., 2018c; Weinstein et al., 2018c). Beat-to-beat analog ECG signals were digitized at 500 Hz sampling rate by a 16-bit A/D conversion board (National Instruments, Austin, Texas) installed on a microcomputer. The ECG waveform was submitted to an R-wave detection routine implemented by custom-written software by the MIDUS research group, resulting in an RR interval series. Errors in marking R waves were corrected by visual inspection. Ectopic beats were corrected by interpolation (Ryff et al., 2018c; Weinstein et al., 2018c). See Supplementary Table 3 for additional information on collection and assay methods.

2.2.3. Risk factors for depression

We accounted for three risk factors for depression: Childhood maltreatment history, loneliness, and recent stress. Experiences of childhood maltreatment were measured using 25-items from the childhood trauma questionnaire (CTQ), a retrospective measure of five types of maltreatment: Emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect (Bernstein and Fink, 1998). Each type of maltreatment is measured using five prompts specific to experiencing that form of maltreatment and asks participants to rate how often the experience occurred via Likert scale (1 – never true to 5 – very often true). Summing CTQ items results in a potential score range of 25–125, with greater scores indicating a greater recall of overall childhood maltreatment. Cronbach's α for the sample was 0.92 indicating excellent internal consistency

Loneliness was measured using three items commonly used to measure perceptions of loneliness in the MIDUS data set (Freilich et al., 2023). This included "how much of the time did you feel lonely?", "how much of the time did you feel close to others?", and how "much of the time did you feel like you belong?" over the pasts 30 days. Participants responded to each prompt via Likert scale (1 – all the time to 5 – none of the time). After appropriate reverse coding, summing the three items resulted in a potential score range of 3 – 15, with greater scores indicating greater perceptions of loneliness over the past month. These items closely correspond to items in other common loneliness scales such as the UCLA Loneliness Scale and the de Jong Gierveld Loneliness Scale (Russell et al., 1978; de Jong-Gierveld, 1987). Cronbach's α for the sample was 0.81, indicating good internal consistency.

Recent stress was measured using the Perceived Stress Scale, a 10-item measure of perceptions of stress over the past month (Cohen et al., 1983). Participants respond to each item via Likert scale (0 – never to 4 – very often), resulting in a potential score range of 0–40, with higher scores indicating greater perceptions of stress over the past month. Cronbach's α for the sample was 0.78, indicating acceptable internal consistency.

2.2.4. Health behaviors

We accounted for three health behaviors: Tobacco cigarette smoking status, past month alcohol consumption, and frequent engagement in exercise. Tobacco cigarette smoking status was accounted for categorically as no history of smoking behavior (reference group), prior smoking behavior, or current smoking behavior. Past month alcohol consumption was accounted for continuously with participants reporting no alcohol consumption (0), drinking less than one day per week (1), drinking 1 or 2 days per week (2), drinking 3 or 4 days per week (3), drinking 5 or 6 days per week (4), or drinking everyday (5). Engagement in exercise was measured categorically as currently engaging in any type of exercise for 20 min or more at least three times a week or not (reference group)

2.2.5. Demographics

We accounted four demographic characteristics, each self-reported by participants: age, sex, racial/ethnic identity, and educational status. Participant age was included as a continuous variable. Participant sex was included dichotomously as male (reference group) or female. Participant racial/ethnic identity was included categorically as White (reference group), Black, other or multiple racial/ethnic identities. Educational status was included continuously based on a scale ranging from 1 (no school or some grade school) – 12 (PhD, EdD, MD, DDS, LLB, JD, or other professional degree)

2.3. Analysis plan

Missing data analysis identified that 81.47 % of participants had complete data, with the majority of univariate missingness being driven by the four PNS markers – each of which were missing for 12.80 % of participants. Analysis of patterns of missingness in the data identified that 10.90 % of participants had missing data for these same four markers of the PNS, only. Given the theoretical relevance of PNS markers to allostatic measurement, we chose to impute missing data using a random forest algorithm as implemented in the missForest package (Stekhoven and Bühlmann, 2012). The random forest imputation method implemented in missForrest has been found to perform as well or outperform other common imputation methods in the context of biological data (Stekhoven and Bühlmann, 2012).

After imputation, we conducted a latent profile analysis (LPA) of the 23 allostatic markers to identify biological profiles within individuals currently experiencing depression. Prior to entry into the model, markers were z-transformed, setting means to zero while retaining the same distribution, allowing for a visual comparison of biomarkers with different ranges (for instance: CRP vs triglycerides). After z-transformation, allostatic markers were then winsorized within ±3 standard deviations, reducing the risk of identifying profiles with a small *n* due to the influence of outliers (Spurk et al., 2020). After z-transformation and winsorization, we used the MCLUST package to calculate Bayesian information criterion (BIC) and integrated complete-data likelihood (ICL) comparative fit indices for 1–9 profile solutions for all 14 potential methods of handling distribution, volume, shape, and orientation of within-groups covariance (Scrucca et al., 2016). After identifying potential solutions via BIC and ICL, we then selected a final model based on theoretical considerations.

LPA is a statistical technique used to identify subgroups of individuals who share similar patterns across a set of characteristics. LPA assumes that there are underlying (latent) subgroups in the population. An LPA model estimates the probability that each participant belongs to each possible group, based on their responses to variables included in a specified model. Individuals are then assigned to the group for which they have the highest probability of membership (Ferguson et al., 2020). In this way, LPA is a person-centered approach, focusing on how variables cluster within individuals. To determine how many groups best represent the data, models are compared using different numbers of groups. Fit indices guide how many latent groups exist (Bauer, 2022). Once the best-fitting model is chosen, each group can be described by its unique profile of characteristics.

Once we had identified biological profiles, we aimed to understand the differences between these groups. First, we used ANOVA and chi-square tests to understand mean and proportion differences between the groups. We then engaged in a multivariate model building process to understand how risk factors for depression may differ by biological profile using four multinomial logistic regression models. The first three models explored how depression risk factors, health behaviors, and demographics differently associated with biological groups. We then ran a final fourth regression model, including only variables that were

significant in the prior three models.

To better understand the robustness of our results we conducted two sensitivity analyses. First, some evidence suggests that LFHRV should not be included in models simultaneously with HFHRV (Heathers, 2014). Thus, we re-estimated the LPA model while excluding LFHRV from the model. To facilitate comparison between models, we re-estimated the model using the same method as the first LPA. Second, the multivariable modeling strategy used to understand different predictors of biological profiles, while maximizing power to detect differences when the smallest profile has a low *n*, may risk excluding age and sex. Age and sex both have substantive relevance due to the influence of sex-hormones as well as immunosenescence. Therefore, we re-estimated the risk factors model, health behaviors model, and the final model while including both age and sex consistently across all models.

3. Results

3.1. Sample description

The sample had a mean age of 49.259 years (SD = 11.458), was 59.67 % female and 60.49 % White. Mean past-week depressive symptoms as measured by the CES-D were 23.060 (SD = 6.938) with a right skew (1.381) indicating greater representation of moderate rather than severe depressive symptoms in the sample. See Table 1 for a full review of sample descriptive statistics.

3.2. Latent profile analysis and profile comparison

After estimating profiles 1–9 using the 14 different methods for model estimation, we identified that the following methods produced the strongest results based on BIC and ICL: diagonal distribution, variable volume, variable shape, and coordinate axes orientation (VVI); ellipsoidal distribution, equal volume, variable shape, and equal orientation (EVE); and ellipsoidal distribution, variable volume, variable shape, and equal orientation (VVE). Across these three methodologies, BIC and ICL both indicated that solutions between 3 and 6 profiles yielded the best results (See Supplementary Figs. 1 and 2). We then compared solutions, selecting a 5-profile VVI (BIC = −16301.080, ICL = −16323.390) solution based on theoretical considerations (see Fig. 1). The first group was named High Inflammation and Glucose (n = 74, 20.16 %) based on having greater levels of CRP, IL6, fibrinogen, ICAM-1, and, sE-selectin, as well as fasting glucose, HbA1C, and insulin resistance. The Low PNS (n = 83, 22.61 %) group was named based on having lower LFHRV, HFHRV, SDRR, and RMSSD. Conversely, the High PNS (n = 73, 19.81 %) group was found to have elevated LFHRV, HFHRV, RMSSD, and SDDR relative to other groups. The Healthy Depression (n = 67, 18.25 %) group had lower levels of CRP, IL6, fibrinogen, sICAM1, sE-selectin, and greater levels of HDL. Last, the High HPA-Axis (n = 70, 19.07 %) group had elevated epinephrine and norepinephrine. Triglycerides, LDL, resting heart rate, DHEAs, cortisol, SBP, and pulse pressure did not clearly distinguish between groups.

Mean and frequency comparisons between subgroups yielded several insights. First, there was no difference in mean past-week depressive symptom severity between subgroups (p = 0.287) as measured by the CES-D. Interestingly, we did observe differences in mean recalled-childhood maltreatment experiences as measured by the CTQ ($F(4)$ = 4.619, $p < 0.001$), with post-hoc analyses indicating that the Low PNS group had greater experiences of recalled childhood maltreatment experiences (m = 51.356, SD = 16.928) than the High PNS group (m = 43.044, SD = 15.435) and the Healthy Depression group (m = 42.550, SD = 13.492). However, the subgroups had no significant differences in perceptions of loneliness as measured by the MIDUS loneliness measures or recent stress as measured by the PSS. We also observed significant differences in health behaviors, with the High PNS group having the greatest proportion of individuals who currently smoke (39.72 %) and the Healthy Depression group had the greatest proportion of individuals who had never smoked (62.68 %). Additionally, the High Inflammation and Glucose group had the lowest proportion of individuals engaging in regular exercise (45.94 %) whereas the Healthy Depression Group had the greatest proportion (79.10 %). See Tables 2 and 3 for a full report of mean and frequency comparisons.

Table 1
Sample description.

	Mean (*SD*) or *n*	Range or %
Depressive symptoms (CES-D)	23.060 (6.938)	16–54
Risk Factors:		
Childhood maltreatment (CTQ)	46.678 (16.621)	25–106
Loneliness	8.398 (2.931)	3–15
Recent stress (PSS)	30.251 (5.383)	14–48
Health Behaviors:		
Alcohol	1.433 (1.491)	0–5
Smoking history: none	176	47.95 %
Smoking history: prior	95	25.88 %
Smoking history: current	96	26.15 %
No or infrequent exercise	134	
Frequent exercise	233	63.5 %
Demographics:		
Sex: male	148	40.32 %
Sex: female	219	59.67 %
Racial identity: White	222	60.49 %
Racial identity: Black	115	31.33 %
Racial identity: other	30	8.17 %
Age (years)	49.259 (11.458)	25–83
Education	7.134 (2.443)	2–12

CES-D: center for epidemiologic studies depression scale; CTQ: childhood trauma questionnaire; PSS: perceived stress scale. Alcohol consumption measured by Likert scale ranging from 0 (drinking less than 1 day per week) – 5 (daily drinking). Education measured by Likert scale ranging from 1 (no school or some grade school) – 12 (PHD, EdD, MDD, DDS, LLB, JD, or other professional degree). Exercise is qualified by engagement in at least 20 min of physical activity for at least three times per week. Variables should be interpreted within the context of the methods section.

3.3. Multinomial regression

The first model exploring differences in the associations between risk factors for depression and biological profiles identified that only childhood maltreatment differently predicted biological profiles. For each 1-point increase in recalled childhood maltreatment experiences as measured by the CTQ, participants were at a 1.031 (b = 0.031, SE = 0.011, $p < 0.01$) increased risk for membership in the High Inflammation and Glucose group and a 1.033 (b = 0.033, SE = 0.011, $p < 0.01$) increased in the risk for membership in the Low PNS group relative to the Healthy Depression group. No other risk factors emerged as differentially predicting group membership.

The second model exploring differences in the associations between health behaviors and biological profiles identified several significant predictors. Both prior smoking status (b = 0.970, SE = 0.439, $p < 0.05$) and current smoking status (b = 1.464, SE = 0.447, $p < 0.01$) were associated with an increased risk of membership for the High PNS group relative to the Healthy Depression group. Engagement in exercise for at least 20 min per day at least three times per week was associated with lower risk of membership to the High Inflammation and Glucose group (b = -1.406, SE = 0.385, $p < 0.001$) as well as the High PNS group (b = −80.982, SE = 0.392, $p < 0.05$) relative to the Healthy Depression group.

The third model exploring demographic differences also identified several significant differences in profile membership. Individuals who identified as Black were more likely to be in the High Inflammation and Glucose group (b = 1.300, SE = 0.437, $p < 0.01$) and the High PNS group

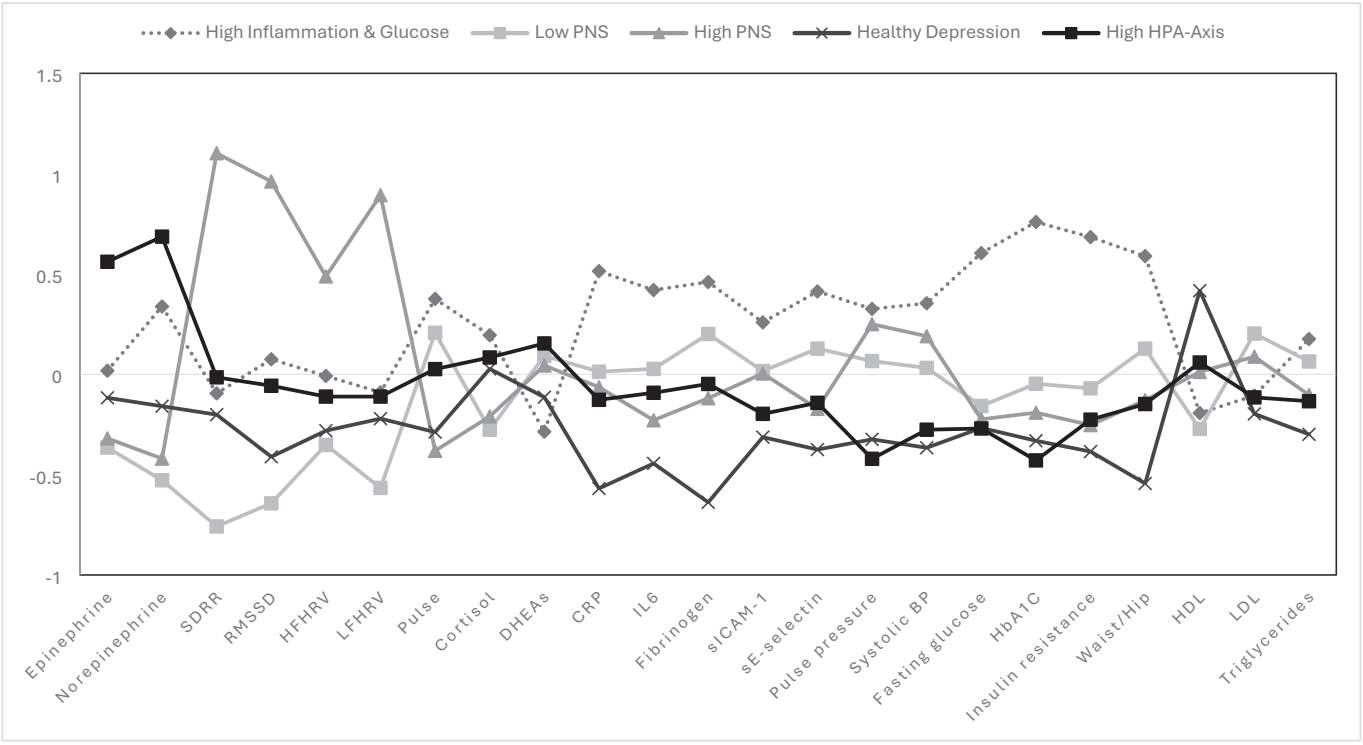

Fig. 1. Latent Profile Analysis of Allostatic Markers. PNS: parasympathetic nervous system; HPA-axis: hypothalamic pituitary adrenal-axis; CRP: C-reactive protein; IL6: interleukin-6; sICAM-1: soluble intercellular adhesion molecule-1; sE-selectin: soluble E-selectin; HFHRV: high frequency heart rate variability; LFHRV: low frequency heart rate variability; RMSSD: root mean square of successive differences; SDRR: standard deviation of R-R interval; DHEAs: dehydroepiandrosterone sulfate; Systolic BP: systolic blood pressure; HbA1c: hemoglobin A1c; WHR: waist-hip ratio; HDL: high density lipoprotein; LDL: low density lipoprotein.

Table 2
Mean comparisons between allostatic profiles.

	High Inflammation & Glucose ($n = 74$)	Low PNS ($n = 83$)	High PNS ($n = 73$)	High HPA-Axis ($n = 70$)	Healthy Depression ($n = 67$)	ANOVA Result
	m (SD)	*m (SD)*	*m (SD)*	*m (SD)*	*m (SD)*	*F*
Depressive symptoms (CES-D)	22.864 (7.608)	24.534 (6.414)	22.503 (6.824)	22.443 (6.820)	22.701 (6.978)	1.256
Childhood maltreatment (CTQ)	50.071 (18.646)	51.356 (16.928)	43.044 (15.435)	45.286 (16.221)	42.550 (13.492)	4.619***
Loneliness	8.568 (2.938)	8.639 (2.648)	8.288 (3.093)	8.529 (3.039)	7.896 (2.980)	0.753
Recent stress (PSS)	29.770 (5.656)	30.597 (5.251)	29.781 (5.606)	30.626 (5.137)	30.477 (5.321)	0.484
Alcohol consumption	0.973 (1.249)	1.627 (1.651)	1.616 (1.515)	1.557 (1.400)	1.373 (1.526)	2.577*
Age (years)	51.797 (11.480)	50.747 (9.706)	48.137 (12.959)	46.543 (11.525)	48.672 (11.118)	2.501*
Education	6.851 (2.568)	6.855 (2.420)	6.699 (2.240)	7.471 (2.506)	7.910 (2.314)	3.198*

CES-D: center for epidemiologic studies depression scale; CTQ: childhood trauma questionnaire; PSS: perceived stress scale; PNS: parasympathetic nervous system; HPA: hypothalamic-pituitary-adrenal.

All ANOVAs are based on 4 degrees of freedom. Alcohol consumption measured by Likert scale ranging from 0 (drinking less than 1 day per week) – 5 (daily drinking). Education measured by Likert scale ranging from 1 (no school or some grade school) – 12 (PHD, EdD, MDD, DDS, LLB, JD, or other professional degree). Exercise is qualified by engagement in at least 20 min of physical activity for at least three times per week. Variables should be interpreted within the context of the methods section.

Tukey post hoc analysis found yielded the following significant associations: Low PNS group had greater childhood maltreatment experiences than the High PNS group ($p < 0.05$) and the High HPA-Axis group ($p < 0.05$); Low PNS group had lower alcohol consumption than the High Inflammation & Glucose group ($p < 0.05$); High Inflammation & Glucose group was older than the High HPA-Axis group ($p < 0.05$). High PNS group had lower education than the Healthy Depression group ($p < 0.05$).

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

($b = 1.250$, $SE = 0.433$, $p < 0.01$) relative to the Healthy Depression group. Increasing age was associated with an increased risk for membership to the High Inflammation and Glucose group ($b = 0.031$, $SE = 0.015$, $p < 0.05$) relative to the Healthy Depression group. Increasing educational status was associated with a decreased risk for membership to the Low PNS ($b = -0.175$, $SE = 0.072$, $p < 0.05$) and High PNS ($b = -0.163$, $SE = 0.075$, $p < 0.05$) groups relative to the Healthy Depression group.

The final model continued to demonstrate several significant associations which were identified in prior models. Experiences of recalled childhood maltreatment as measured by the CTQ were still associated with an increased risk for membership to the High Inflammation and Glucose ($b = 0.026$, $SE = 0.011$, $p < 0.05$) and Low PNS ($b = 0.031$, $SE = 0.011$, $p < 0.01$) groups relative to the Healthy Depression group. Both prior smoking status ($b = 1.048$, $SE = 0.455$, $p < 0.05$) and current smoking status ($b = 1.218$, $SE = 0.474$, $p < 0.05$) were associated with

Table 3
Frequency comparisons between allostatic profiles.

	High Inflammation & Glucose ($n = 74$)	Low PNS ($n = 83$)	High PNS ($n = 73$)	High HPA-Axis ($n = 70$)	Healthy Depression ($n = 67$)	Chi-Square Test
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	χ^2 (*df*)
No smoking history	36 (48.64 %)	37 (44.58 %)	23 (31.51 %)	38 (54.29 %)	42 (62.69 %)	17.593 (8)*
Prior smoking history	19 (25.68 %)	23 (27.71 %)	21 (28.77 %)	18 (25.71 %)	14 (20.90 %)	
Current smoking status	19 (25.68 %)	23 (27.71 %)	29 (39.72 %)	14 (20.00 %)	11 (16.41 %)	
Frequent exercise	34 (45.95 %)	57 (68.67 %)	42 (57.53 %)	47 (67.14 %)	53 (79.10 %)	19.355 (4)***
No or non-frequent exercise	40 (54.05 %)	26 (31.33 %)	31 (42.47 %)	23 (32.86 %)	14 (20.90 %)	
Male	30 (40.54 %)	36 (43.37 %)	33 (45.21 %)	25 (35.71 %)	24 (35.82 %)	2.358 (4)
Female	44 (59.46 %)	47 (56.63 %)	40 (54.79 %)	46 (64.29 %)	42 (64.18 %)	
White	37 (50.00 %)	55 (66.26 %)	37 (50.68 %)	43 (61.43 %)	50 (74.63 %)	17.600 (8)*
Black	30 (40.54 %)	22 (26.51 %)	32 (43.84 %)	20 (28.57 %)	11 (16.41 %)	
Other	7 (9.46 %)	6 (7.23 %)	4 (5.48 %)	7 (10.00 %)	6 (8.96 %)	

PNS: parasympathetic nervous system; HPA: hypothalamic-pituitary-adrenal.
Percentages represent the proportion of the frequency within each group (column), not the total sample. Please interpret carefully when comparing between groups.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

Table 4
Multinomial regression models exploring how risk factors, behaviors, and demographics are associated with allostatic profile membership.

	High Inflammation & Glucose ($n = 74$)	Low PNS ($n = 83$)	High PNS ($n = 73$)	High HPA-Axis ($n = 70$)
	b (SE)	*b (SE)*	*b (SE)*	*b (SE)*
Model 1: Risk Factors				
Maltreatment (CTQ)	0.031 (0.011)**	0.033 (0.011)**	0.002 (0.012)	0.010 (0.012)
Loneliness	0.067 (0.061)	0.058 (0.060)	0.05 (0.061)	0.068 (0.061)
Stress (PSS)	−0.056 (0.033)	−0.027 (0.032)	−0.032 (0.033)	−0.010 (0.033)
Model 2: Behavioral Factors				
Alcohol	−0.212 (0.134)	0.091 (0.113)	0.073 (0.119)	0.087 (0.117)
Prior smoking	0.562 (0.432)	0.576 (0.412)	0.970 (0.439)*	0.306 (0.426)
Current smoking	0.685 (0.458)	0.781 (0.436)	1.464 (0.447)**	0.252 (0.467)
Exercise	−1.406 (0.385)***	−0.545 (0.388)	−0.982 (0.392)*	−0.641 (0.397)
Model 3: Demographics				
Male sex	0.319 (0.361)	0.363 (0.345)	0.593 (0.361)	−0.008 (0.363)
Black racial identity	1.300 (0.437)**	0.481 (0.439)	1.250 (0.433)**	0.635 (0.446)
Other racial identity	0.517 (0.604)	−0.087 (0.616)	−0.119 (0.687)	0.266 (0.596)
Age (years)	0.031 (0.015)*	0.017 (0.014)	0.001 (0.015)	−0.014 (0.015)
Education	−0.136 (0.074)	−0.175 (0.072)*	−0.163 (0.075)*	−0.049 (0.074)

CTQ: childhood trauma questionnaire; PSS: perceived stress scale; PNS: parasympathetic nervous system; HPA: hypothalamic-pituitary-adrenal.
Healthy Depression (n = 67) is a reference group for the dependent variable. Alcohol consumption measured by Likert scale ranging from 0 (drinking less than 1 day per week) – 5 (daily drinking). Education measured by Likert scale ranging from 1 (no school or some grade school) – 12 (PHD, EdD, MDD, DDS, LLB, JD, or other professional degree). Exercise is qualified by engagement in at least 20 min of physical activity for at least three times per week. Variables should be interpreted within the context of the methods section.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

increased risk for membership to the High PNS group relative to the Healthy Depression group. Exercise for at least 20 min per day at least three times per week was significantly associated with a lower risk for membership to the High Inflammation and Glucose group ($b = -1.202$, $SE = 0.396$, $p < 0.01$) relative to the Healthy Depression group, but was no longer significantly associated with membership to the High PNS group. Black racial identity continued to indicate an increased risk for membership to the High Inflammation and Glucose ($b = 1.025$, $SE = 0.451$, $p < 0.05$) and the High PNS ($b = 0.974$, $SE = 0.445$, $p < 0.05$) groups relative to the Healthy Depression group. Age also continued to show an increased risk for membership to the High Inflammation & Glucose ($b = 0.032$, $SE = 0.016$, $p < 0.05$) group relative to the Healthy Depression group. Education was no longer a significant predictor of group membership. Tables 4 and 5 provide a complete review of model parameters. Supplementary Table 4 reports raw values for each biomarker across each profile.

3.4. Sensitivity analysis 1: excluding LF-HRV from LPA

Estimation of the LPA while excluding LFHRV yielded a model with strong overlap in differentiated profiles to the first LPA model which included HFHRV. The new model continued to indicate a group best characterized as High Inflammation & Glucose ($n = 73$) per greater levels of CRP, IL6, sICAM-1, sE-selectin, fasting glucose, HbA1C, and insulin resistance. Groups characterized by High PNS ($n = 48$) and Low PNS ($n = 62$) also emerged per respectively high and low HFHRV, SDRR,

Table 5
Multinomial regression models exploring how risk factors, behaviors, and demographics are associated with allostatic profile membership.

	High Inflammation & Glucose ($n = 74$)	Low PNS ($n = 83$)	High PNS ($n = 73$)	High HPA-Axis ($n = 70$)
	b (SE)	*b (SE)*	*b (SE)*	*b (SE)*
Maltreatment (CTQ)	0.026 (0.011)*	0.031 (0.011)**	−0.004 (0.012)	0.009 (0.012)
Prior smoking	0.261 (0.452)	0.463 (0.429)	1.048 (0.455)*	0.479 (0.438)
Current smoking	0.161 (0.486)	0.445 (0.464)	1.218 (0.474)*	0.153 (0.492)
Exercise	−1.202 (0.396)**	−0.332 (0.399)	−0.742 (0.402)	−0.474 (0.406)
Black racial identity	1.025 (0.451)*	0.346 (0.451)	0.974 (0.445)*	0.565 (0.454)
Other racial identity	0.387 (0.625)	−0.208 (0.634)	−0.059 (0.704)	0.275 (0.605)
Age (years)	0.032 (0.016)*	0.018 (0.015)	−0.006 (0.016)	−0.017 (0.015)
Education	−0.078 (0.080)	−0.110 (0.077)	−0.080 (0.082)	−0.027 (0.080)

CTQ: childhood trauma questionnaire; PNS: parasympathetic nervous system; HPA: hypothalamic-pituitary-adrenal.
Healthy Depression ($n = 67$) is a reference group for the dependent variable. Education measured by Likert scale ranging from 1 (no school or some grade school) – 12 (PHD, EdD, MDD, DDS, LLB, JD, or other professional degree). Exercise is qualified by engagement in at least 20 min of physical activity for at least three times per week. Variables should be interpreted within the context of the methods section.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

and RMSSD. Notably, the High PNS group also continued to have the lowest pulse. A fourth group continued to be best characterized as High HPA-Axis ($n = 81$) per the greatest epinephrine and norepinephrine levels, and the second greatest cortisol level. However, the Healthy Depression group ($n = 103$) was less clearly differentiated when the model did not account for LFHRV. For instance, the Healthy Depression group had the second lowest waist to hip ratio and second highest HDL cholesterol, while the High HPA-Axis had the lowest waist to hip ratio, LDL cholesterol, and triglyceride, and the highest HDL cholesterol. Although, the Healthy Depression group still had low levels across measures of inflammation, glucose, and HPA-axis. Supplementary Fig. 3 depicts the plotted profiles.

3.5. Sensitivity analysis 2: inclusion of sex and age in all multivariable models

Inclusion of age and sex consistently across regression models yielded no change in predictor significance across the risk factors model and the health behaviors model; however, several differences were noted in the final model. First, exercise was now associated with a decreased risk for membership to the High PNS group relative to the Healthy Depression group ($b = -0.805$, $SE = 0.406$, $p < 0.05$). Second, age was no longer a significant predictor of membership to the High Inflammation & Glucose group relative to the Healthy Depression group ($p = 0.054$). Notably, a self-reported history of childhood maltreatment was still associated with an increased risk for membership to the High Inflammation & Glucose group ($b = 0.029$, $SE = 0.011$, $p < 0.05$) as well as the Low PNS group ($b = 0.034$, $SE = 0.011$, $p < 0.01$) relative to the Healthy Depression group. Supplementary Table 5 contains a complete report of coefficients for multivariable models consistently controlling for sex and age.

4. Discussion

The present study examined data-driven subgroups of MDD using 23 biomarkers across 7 biological systems, guided by AL theory in a group of community dwelling U.S. adults. We identified five distinct biological profiles, and consistent with our hypotheses, several groups were characterized by inflammation and metabolic dysfunction, PNS dysfunction, or relatively healthy functioning. Also consistent with our initial hypotheses, childhood maltreatment differentially predicted membership to the High Inflammation and Glucose group as well as the Low PNS group. However, neither loneliness nor recent stress predicted group membership. Thus, for the first time to our knowledge we have shown how experiences of childhood maltreatment may relate to different biological subtypes of MDD.

Although increasing research activity has focused on data-driven subtyping of MDD, a review of the literature identified that studies yielded inconsistent findings and that more recent studies had foregone the use of biochemical markers in favor of psychometric and neuroimaging approaches (Beijers et al., 2019). Despite this, both our analysis and the handful of other data-driven AL studies, which include biochemical markers (catecholamines, inflammatory molecules) have begun to point towards some consistencies in the field. For instance, both our work and prior data-drive AL studies have consistently pointed towards a group characterized by elevated inflammatory molecules and adipose tissue as indicated by increased CRP and BMI, respectively (Carbone, 2021; Twait et al, 2023; Carbone and Casement, 2024; Spiegler et al., 2024). Additionally, our work confirmed the identification of a relatively healthy group of individuals with a current depressive episode while also expanding the number of AL markers based on an established measure of AL, reducing the risk that this finding may be due to an excluded biomarker. Interestingly, our work does use similar AL markers to Carbone's (2021) study which also used the MIDUS data set; however, Carbone's study included individuals with and without MDD. Our work built off Carbone's finding that two different groups, one characterized by high inflammation and the other by low PNS, have greater depressive symptoms by showing that among people with MDD, these are still two distinct profiles.

Distinct from prior work, our study makes the important contribution of finding that experiences of childhood maltreatment, but not recent stress or loneliness, differentially predict AL profiles of MDD. One explanation for our results is that childhood maltreatment relates to MDD through two distinct vulnerability pathways. The High Inflammation and High Glucose group may indicate vulnerability to blood brain barrier (BBB) permeability following the experience of childhood maltreatment. Recent meta-analytic work suggests that childhood maltreatment is associated with greater levels of adipose tissue in adulthood which in turn increase levels of inflammation in the periphery that then relate to greater depressive symptoms (Zagaria et al., 2024). Greater levels of adipose tissue as seen in individuals with both obesity and poor metabolic health have been found to have greater levels of sE-selectin and sICAM-1 which increases the permeability of the BBB, allowing more proinflammatory molecules to target the brain, inducing depressive symptoms (Liu et al., 2023). Additionally, some evidence suggests that social stress such as childhood maltreatment is associated with reduced levels of proteins in the tight-junction space between endothelial cells, also increasing permeability of the BBB (Menard et al.,

2017). The High Inflammation and High Glucose group had the greatest overall adiposity (proxied by WHR), helping to explain why it also had the greatest levels proinflammatory markers (CRP, IL6, fibrinogen, and TNF-a). For the High Inflammation and High Glucose group, this greater inflammation may be targeting the brain through a more permeable BBB due to the effects of childhood maltreatment on tight junction proteins in addition to poorer metabolic health in the context of greater adiposity that leads to higher levels of sE-selectin and sICAM-1.

At the same time, the Low PNS group may indicate a vulnerability to the dysregulation of stress response systems in the body, particularly as it relates to the role of the HPA-axis and vagus nerve in stimulating immune cells during the stress response. Several reviews have pointed towards experiences of childhood maltreatment being associated with lower HRV (Young-Southward et al., 2020), and lower HRV also being associated with MDD (Kemp and Quintana, 2013; Koenig et al., 2016; Brown et al., 2018; Koch et al., 2019). While causal pathways have been slow to develop, some evidence suggests that lower HRV precedes depressive symptoms, implicating the role of vagus nerve dysfunction in the production of cognitive symptoms during a prodromal period of MDD (Jandackova et al., 2016). Specific to stress responsivity, the efferent vagus nerve is implicated in the production of acetylcholine which stimulates peripheral immune cells to release proinflammatory cytokines that in turn stimulate the afferent vagus nerve, causing microglia and astrocytes to start producing proinflammatory cytokines throughout the brain (Slavich and Irwin, 2014). Notably, the Low PNS group also had the lowest levels of cortisol in the study while having the second greatest levels of inflammation. Given that cortisol is needed to both stop the stress response via a negative feedback loop to the HPA-axis and is immunosuppressive during the stress response via the targeting of immune cells (Slavich and Irwin, 2014; Gjerstad et al., 2018), this would contribute to more chronic or prolonged inflammation in the periphery that could then target the vagus nerve. Thus, while the High Inflammation and High Glucose group may show vulnerability pathways through BBB permeability, the Low PNS group may be more related to vulnerabilities in HPA-axis and vagus nerve activity during the stress response.

Results indicating differing biological pathways towards MDD are at the heart of Allostatic Load's theoretical background. Some of the earliest papers proposed that exposure to a stressor could cause differences in stress responsivity between people (McEwen, 1998a; McEwen 1998b). Results indicating that childhood maltreatment differentially predicts these differences in systems related to stress responsivity confirm some of the earliest foundations in the field. Further, these results confirm aspects of the Social Signal Transduction Theory of Depression as well as the Differential Susceptibility Theory in that childhood maltreatment may be associated with increased inflammation targeting the brain through several different pathways to produce depressive symptoms, and that these different pathways may be related to different vulnerabilities across the central nervous system (Belsky and Pluess, 2009; Slavich and Irwin, 2014). Unfortunately, much of the work around AL collapses markers into a single index, with greater scores in an index indicating greater overall dysfunction (Finlay et al., 2021). Although theoretically tenable and useful in identifying an initial bridge between the social environment and health outcomes, results from the present study caution against this practice as important information in pathophysiological processes may be obfuscated, delaying the translation of findings into future treatment research.

Experiences of childhood maltreatment are a risk factor for an overall worse course of MDD, characterized by greater depressive symptoms, resistance to frontline antidepressants, and increased risk for suicide (Nanni et al., 2012; Nelson et al., 2017). Results from the present study suggest that childhood maltreatment may be related to distinct pathophysiological processes which have been associated with specific symptom patterns. For instance, low HRV may correlate with cognitive symptoms of MDD while high inflammation may correlate with somatic and interpersonal symptoms of MDD (Jandackova et al., 2016; O'Shields et al., 2023). At the same time, we know from numerous psychometric network models that depressive symptoms themselves, as well as many mental health symptoms are intercorrelated (See McNally, 2021). Furthermore, relying on accurate client/patient recall of depressive symptom onset patterns when most MDD diagnoses are made years after first onset is unreasonable and unreliable (Wang et al., 2005). The collection of HRV, inflammation, and metabolic data, in addition to routine psychological interviewing may be one method for identifying treatment targets in those who have experienced both MDD and childhood maltreatment.

4.1. Strengths

The present study has several strengths. First, biomarker data, particularly those used in AL studies, are measured continuously but frequently collapsed into categorical data. The present study retained the continuous nature of the data, estimating subgroups using LPA. This allows for the observation of not only high and low levels of various biomarkers, but also moderate elevation such as the moderate degree of inflammation in the Low PNS group. Second, the present study used a robust number of biomarkers, many of which can be assessed through non-invasive measures, bypassing the need for imaging tools which may be less available in some areas. Third, the present study explored several risk factors for MDD rather than isolating a single risk factor. Although loneliness and recent stress most likely still play an important role in MDD, we were able to identify that experiences of childhood maltreatment may have important utility in identifying biological subgroups of MDD.

4.2. Limitations

While the present study both confirms prior findings in the field and makes important advancements, results should be considered in light of several limitations. First, the data used here are largely cross-sectional. Although the CTQ is a retrospective measure of childhood maltreatment recent evidence suggests that retrospective studies may underestimate the effects of childhood maltreatment relative to objective measures such as case reports (Baldwin et al., 2019). Second, data from the present are older relative to similar data sets, and indeed, some data from the present study were collected as early as 2004. Still, few studies offer the same breadth of biomarker measurement and the diagnostic criteria for MDD have been consistent for several decades now. Third, the sample size from the present study is relatively small. Recommendations for LPA typically perform best with an n of at least 500 and the number of predictors that can be included in a multinomial regression are constrained by the n of the smallest group in the dependent variable (Spurk et al., 2020). While some of our results are confirmatory of larger studies, which we believe indicates some reliability in our results, replication with larger data sets is still needed. Fourth, our analysis relied on selecting participants likely to have current MDD based on CES-D scores of 16 or greater. Although this measure has been used in numerous depression studies, the CES-D may under-detect cases of atypical depression where vegetative symptoms such as hypersomnia and wight gain are likely to be present. Future studies should aim to replicate analyses using other screening instruments that can provide a more comprehensive measurement of depressive symptoms (See Fried 2017b for a review of symptom measurement across common depression measures). Last, the present study does not include healthy or non-MDD affected participants. As demonstrated by Cole et al. (2010), selecting participants based on potential MDD status first may introduce bias into models through conditioning on a collider. Results from the present study should be carefully interpreted as differences between individuals with probable MDD at a single point in time, *not* as a comparison between those with and without MDD. For instance, while our results indicate that childhood maltreatment differentially predicted two distinct biological profiles of MDD, each profile of MDD had greater

mean childhood maltreatment experiences than the non-MDD participants that were excluded from analyses. Future studies exploring mechanisms that link the risk factors to MDD through biological mechanisms may be able to improve causal inference through the inclusion of non-MDD controls.

4.3. Conclusion

Our analysis identified that childhood maltreatment, but not perceptions of recent stress or loneliness, differentially predict allostatic profiles of MDD. Recalled childhood maltreatment seems to differentially predict two groups: Low PNS vs High Inflammation and High Glucose. The clustering of biomarkers in these two groups indicates that childhood maltreatment may be associated with distinct pathophysiological differences, and treatments that differentially target these pathways may be one pathway forward for improving treatment outcomes for those who experience MDD.

CRediT authorship contribution statement

Jay O'Shields: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Helisha Soni:** Writing – review & editing, Writing – original draft. **Orion Mowbray:** Writing – review & editing, Supervision, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2025.106243.

Data availability

Data is publicly available via the Inter-university Consortium for Political and Social Research (ICPSR)

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