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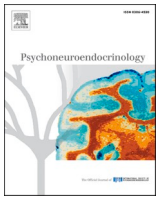

Allostatic load in major depressive disorder: An in-patient clinical study

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ABSTRACT

Introduction: Allostatic load (AL), a cumulative measure of stress, has been implicated in the pathophysiology of major depressive disorder (MDD). However, the relationship between AL and depressive symptoms, treatment response, and metabolic health remains unclear.
Methods: This study investigated AL in unmedicated (>6 weeks) inpatients with MDD (n = 31) at baseline and after 6 weeks of treatment with either Venlafaxine or Mirtazapine. Baseline patients were compared to age- and sex-matched healthy controls. Depressive symptoms and functional status were assessed using the Hamilton Scale for Depression (HAMD) and Global Assessment of Functioning (GAF) rating scales. Furthermore, metabolic syndrome (MetS) was assessed in the MDD patients at baseline and Week 6.
Result: Our findings indicate that AL was significantly elevated in MDD patients compared to healthy controls (HCs; n = 31) at baseline ($p = 0.031$). AL was not associated with functional status at baseline or at Week 6. MetS was prevalent among MDD patients but was not correlated with clinical symptom severity. Lastly, AL significantly ($p = 0.02$) decreased after 6 weeks of antidepressant treatment, although the reduction was not predictive of symptom improvement or functional remission.
Discussion/Conclusion: These findings suggest that AL reflects underlying multisystem dysregulation in MDD rather than symptom severity or treatment responsiveness. The observed decrease in AL during treatment may indicate an effect of antidepressants, although further research with longer follow-up is needed. The observed potential sex difference in AL warrants further investigation using larger sample sets.

1. Introduction

Major depressive disorder (MDD) is one of the most prevalent mental health disorders and a leading cause of disease burden globally (GBD Mental Disorders Collaborators, 2022). It affects 280 million individuals (3.8 %) worldwide, with a higher prevalence among middle-aged adults (5.0 %) and females (61.59 %)(GBD Mental Disorders Collaborators, 2022). Depression has been associated with physiological dysregulation across multiple biological systems involved in the stress response, including cardiovascular, metabolic, immune, and neuroendocrine

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systems (McEwen, 2000). The activation of the autonomic nervous system (ANS), stress hormones, inflammatory cytokines, and other mediators in allostasis is crucial for adapting to stressful events in daily life. When these mediators are released acutely in response to a changing environment, they are beneficial and adaptive to help adjust physiological and behavioral responses to constant change (McEwen, 2000). If they are overused by excessive challenges, left on when no longer needed, or not activated when necessary, the cumulative multisystem changes cause wear-and-tear on the body and brain, known as "allostatic load" (AL) (McEwen, 2003). Chronic exposure to stress is believed to increase AL, which in turn has been shown to predict adverse health indicators. For example, a longitudinal study demonstrated that higher AL was associated with all-cause mortality and cognitive decline in later life (Seeman et al., 2001). Conversely, a decrease in AL is associated with reductions in adverse health outcomes and mortality (Karlamangla et al., 2006).

Increased AL has been associated with acute depressive symptoms in healthy older adults, although this was only a trend after three years and is likely to be driven by increased age after six years (Juster et al., 2011). Another study demonstrated a positive association between AL and both affective and somatic clusters of depressive symptoms in older adults (Kobrosly et al., 2014).

Emerging evidence suggests a significant association between MDD and primary mediators of AL, including cortisol, norepinephrine, epinephrine, and dehydroepiandrosterone sulfate (DHEA-S). Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, a hallmark of MDD, has been partly attributed to impaired glucocorticoid-mediated negative feedback, often resulting from chronic stress exposure. Prolonged activation of these mediators can disrupt both the HPA axis and sympathetic nervous system (SNS) function, thereby contributing to the MDD pathophysiology (Lupien et al., 2009; McEwen, 2003).

The theoretical framework of AL posits that repeated or chronic exposure to stress leads to multisystem dysregulation, particularly affecting the HPA axis and autonomic nervous system (Kinlein and Karatsoreos, 2020). These alterations can manifest in mental disorders such as MDD through a cascade of neurobiological changes, including neuroinflammation, impaired glucocorticoid receptor sensitivity, and hippocampal atrophy (Alper et al., 2023; Anacker et al., 2011; Osei et al., 2024).

The AL is usually measured using a composite index of indicators of cumulative stress on organs and tissues associated with the cardiovascular, metabolic, immune, and neuroendocrine systems (Carbone et al., 2022; Juster et al., 2010). Recent evidence has led to increasing interest in the relationship between depression and Metabolic Syndrome (MetS), linked to insulin resistance, diabetes, and elevated risk of cardiovascular disease (Osei et al., 2024). It has been suggested that MetS and related metabolic biomarkers may be linked to mood disorders, especially depression (Moradi et al., 2021). Building on this growing body of research linking physiological dysregulation and depression, the present study explores the relationship between depression and multisystem dysregulation conceptualised as increased AL.

We demonstrated previously that AL was significantly elevated in a treatment-responsive manner in first-episode psychosis and schizophrenia (Berger et al., 2018). Extending those findings to allow cross-diagnostic comparison for clinical utility of AL in psychiatry, the aims of the present study were: 1) to investigate whether AL is elevated in unmedicated patients with MDD compared to healthy matched controls (HCs) and whether it predicts clinically relevant outcomes; then to explore whether the AL index was higher in patients with chronic depression relative to recently diagnosed (>1 year) patients. We hypothesised that AL would be elevated and associated with disorder chronicity in depressed patients. 2) We aimed to investigate whether the antidepressants Venlafaxine (a serotonin and noradrenaline reuptake inhibitor) and Mirtazapine (an atypical tetracyclic, noradrenergic and specific serotonergic antidepressant that acts by antagonising the adrenergic alpha2-autoreceptors and by blocking 5-HT2 and 5-HT3 receptors) differed in their clinical outcome measures and effects on the AL index after 6 weeks of treatment. 3) We aimed to assess the prevalence and clinical relevance of MetS in MDD patients, and its potential overlap with AL and depression severity.

2. Methods

2.1. Study design

Participants were enrolled in a naturalistic study involving acutely ill inpatients who were unmedicated for > 6 weeks before inclusion. AL and relevant variables were assessed at baseline (T0) and week 6 (T6).

Exclusion criteria were a history of immune diseases, immunomodulatory treatment, chronic terminal disease, cancer, cardiovascular disorders, dyslipidemia, diabetes mellitus, substance abuse, severe trauma, or clinical/paraclinical findings indicative of these disorders. The study was conducted in accordance with German laws, the Declaration of Helsinki, and guidelines of the local institutional review board (vote 110/07). Written informed consent was obtained from all participants. Details concerning the study design have been published previously by Steiner et al. (2013).

2.2. Sample

Participants included 31 unmedicated patients with MDD (mean disease duration = 2.78 years, standard deviation = 6.62 years) and 31 matched HCs (Table 1). Patients who fulfilled all inclusion criteria and none of the exclusion criteria were recruited from eligible consecutive admissions to the psychiatric inpatient unit between February 2008 and March 2010. No a priori power analysis was performed. Recruitment focused on unmedicated but acutely depressed inpatients to ensure that biological changes reflected the disease state rather than medication effects. The patients received one of the antidepressants, Venlafaxine or Mirtazapine, after inclusion into the study. HCs consisted of university students, blood donors, and hospital staff/their family members, and were recruited from the community. HCs were screened for personal or family history of neuropsychiatric disorders using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998).

2.3. Psychometric assessments

The 21-item Hamilton Scale for Depression (HAMD-21) was used to assess the depression severity in patients (Faries et al., 2000). The HAMD-21 is rated on a 3- or 5-point scale depending on the item and

Table 1
Demographic and psychometric characteristics. GAF = Global Assessment of Functioning; HAMD = Hamilton Scale for Depression. T(0) = Time-point 0 ~ baseline and T(6) = Time-point 6 weeks after the start of treatment. P-value was calculated using the Wilcoxon rank sum test, Fisher's exact test, and Pearson's Chi-squared test.

	HCs (N = 31)	MDD (N = 31)	*p*-value
Sex, female, n (%)	15 (48)	15 (48)	> 0.9
Age in years (T0), mean (SD)	41.13 (11.85)	43.45 (12.77)	0.2
Smoking, yes, n (%)	13 (42)	15 (48)	0.6
Drug screen positive (T0), n (%)	0 (0)	4 (16)	0.11
Drug naïve, n (%)		18 (62)	
Duration of disorder (years), mean (SD)		2.78 (6.62)	
Medication			
Mirtazapine		17 (55)	
Venlafaxine		14 (45)	
Psychometric scales			
GAF score (T0), mean (SD)		48.10 (9.96)	
GAF score (T6), mean (SD)		70.21 (14.44)	
HAMD score (T0), mean (SD)		22.23 (5.85)	
HAMD score (T6), mean (SD)		7.33 (4.87)	

addresses mood, guilt, anxiety, agitation, insomnia, somatic symptoms, and suicidal ideation. The Global Assessment of Functioning (GAF) scale was used to measure occupational, psychological, and social functioning (Startup et al., 2002). The scores range from 0 (severe impairment) to 100 (superior functioning/no symptoms).

2.4. Allostatic load biomarkers

Biomarkers for the AL index were selected based on previous research (Berger et al., 2018; Finlay et al., 2025; Seeman et al., 2001), and represented multiple physiological systems, including overall metabolic indices (body mass index (BMI) and waist-to-hip ratio (WHR); lipid metabolism (total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides); glucose metabolism (fasting glucose, insulin, and glycosylated hemoglobin (HbA1c)); the immune-inflammatory system (interleukin-6 receptor (IL-6r), which is a gene that encodes the alpha subunit of the IL-6 receptor, tumor necrosis factor-alpha (TNFα), C-reactive protein (CRP), interleukin-12 (IL-12) and adiponectin); the autonomic nervous system (ANS)(diastolic and systolic blood pressure (BP), and heart rate); and the stress neuroendocrine system (serum cortisol and urinary epinephrine and norepinephrine metabolites metanephrine and normetanephrine).

Fasting blood samples were collected between 8:00 and 9:00 a.m. (within 24 h after admission for patients) for both patients and controls, to ensure standardised timing and minimise circadian variation effects. All participants included were overnight fasted before blood collection to control for potential confounding effects of recent food intake on biomarker measurements. Blood was drawn from patients and controls in a sitting position to standardise hemodynamic conditions during sample collection. Blood collection was performed using Becton Dickinson Vacutainer systems, ensuring standardised and sterile collection procedures across all subjects. For serum processing, samples were allowed to clot for 2 h after collection. Samples were then centrifuged at 2000 g for 10 min and aliquoted into 0.5 mL low-protein-binding tubes. For EDTA plasma processing, samples were processed immediately after collection. Samples were centrifuged at 2000 g for 10 min and aliquotted into 0.25 mL low-protein-binding Eppendorf tubes. All samples were stored at −80°C until analysis to preserve sample integrity. Identical storage procedures were used for both patient and control samples to ensure methodological consistency and eliminate potential storage-related bias.

Enzymatic methods were used to determine the concentrations of cholesterol, LDL, HDL, fasting glucose, and triglycerides in a random-access analyser (Hitachi 911, Roche Diagnostics). HbA1c was determined in EDTA whole blood by high-performance liquid chromatography (HPLC) (Variant II, Bio-Rad). Both intra-assay and inter-assay coefficients of variation were less than 5 % for all laboratory assays. The Human DiscoveryMAP™ multiplex immunoassay platform was used to measure serum concentrations of cortisol, TNFα, IL-6R, CRP, insulin, IL-12, and adiponectin (Schwarz et al., 2012). Urinary levels of metanephrine and normetanephrine were measured simultaneously by HPLC with electrochemical detection (Chromsystems Instruments & Chemicals GmbH). A standard (3-hydroxy-2-methylbutanoic acid) was used to compare concentrations in both analytes. The lowest concentrations of metanephrine and normetanephrine were 10 and 30 μg/L, respectively.

2.4.1. The AL index

We used the "Group allostatic load index" approach, which assigns each biomarker a score of "0" (normal) or "1" (high risk) based on whether values fall above the 75th percentile or below the 25th percentile, depending on whether high or low levels confer greater risk (Finlay et al., 2023). The percentiles were derived based on the distribution in the HC group. Because each biomarker is dichotomised as either 0 or 1 depending on cut-offs, each biomarker is allotted an equal weight in the index (Juster et al., 2010). We then used the "scaling" approach to calculate AL indices, in which the sum of biomarkers in each systemic category (anthropometric, stress neuroendocrine, ANS, immune, glucose, and metabolic) was divided by the number of biomarkers in that specific category to ensure equal weighting across the systems (Chen et al., 2012; Juster et al., 2016). Consequently, each systemic category contributes equally to the AL index. This approach, which incorporates a broader set of parameters, minimises the impact of any single biomarker and mitigates the effect of outliers.

2.4.2. Metabolic syndrome

MetS was calculated using systolic and diastolic BP, glucose, WHR, triglycerides, and HDL (Huang, 2009). Each biomarker was assigned a value of "1" if it fell outside the normal range and "0" if it was within the normal range. The six scores were added together, ranging from 0 to 6, and individuals were diagnosed with MetS if they scored ≥ 3 (Alberti et al., 2009).

2.5. Statistical analysis

All analyses were performed using *R version 4.0.3*. Descriptive analyses were performed and stratified by "Diagnosis". Differences in prevalence between categorical variables were tested using chi-square tests, and those between multiple groups were tested appropriately using a paired sample *t*-test (if two groups), analysis of variance (ANOVA), or the Kruskal-Wallis test. As appropriate, we considered age, sex, and smoking as covariates since these are potential confounders and standard covariates in AL studies (Juster et al., 2010). Partial correlations, adjusting for covariates, were used to test associations between AL and the psychological variables, GAF and HAMD. A p-value ≤ 0.05 was considered statistically significant.

3. Results

3.1. Demographic data

No significant difference between HCs and MDD patients was observed in age, sex, or smoking. The MDD patients were somewhat, but not statistically significantly, more likely to smoke and consume illicit drugs (Table 1).

3.2. AL in MDD patients and HCs at baseline

A two-sample *t*-test revealed a significantly higher AL index at baseline in individuals with MDD compared to HCs ($t(60) = -1.95$, $p < 0.031$, MDD: 2.15 ± 0.99, HC: 1.66 ± 0.98; Fig. 1). Subgroup analysis revealed no significant difference in the AL between male and female MDD patients ($t(28.40) = 1.84$, $p = 0.076$; males: 2.45 ± 1.05, females: 1.82 ± 0.85).

Grouping participants into "newly diagnosed" (n = 21; diagnosis <1

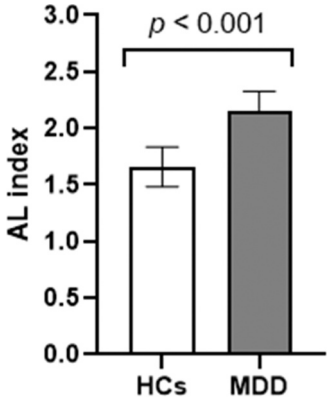

Fig. 1. The mean Allostatic load index (and standard error) at baseline between healthy controls and patients with major depressive disorder (MDD).

year) and "chronic MDD" (n = 6; diagnosis 5–28 years), a non-parametric Wilcoxon rank-sum test was conducted to compare baseline AL between the two groups. There was no significant difference between the groups (newly diagnosed = 2.11 ± 1.09, chronic = 2.14 ± 1.09, W = 77.5, p = 0.41).

3.2.1. Contribution of different biomarkers to the AL index

Comparison of mean biomarker value and their correlations with the AL index (Table 2) showed that ANS- and stress-related biomarkers, including "systolic BP", "diastolic BP", "heart rate", "cortisol", "urinary metanephrine", and "urinary normetanephrine", respectively, were significantly higher in MDD patients compared to HCs.

Biomarkers that correlated significantly with the overall AL index in the HC group included systolic and diastolic BP, CRP, BMI, WHR, HbA1c, glucose, insulin, LDL, and HDL. Biomarkers that correlated significantly with the overall AL index in the MDD group included systolic and diastolic BP, CRP, IL-12, TNF-α, BMI, WHR, HbA1c, LDL, HDL, and triglycerides. The ANS markers, systolic and diastolic BP, showed moderate to strong correlations with the AL index for both groups, indicating consistent contribution to the multisystemic dysregulation across groups. The immune system biomarkers CRP and TNF-α showed a moderate to strong correlation with the AL index in the MDD group, suggesting low-grade inflammation. IL-12 showed a statistically significant moderate negative correlation with the AL index in the MDD group, indicating that higher physiological stress accumulation was associated with reduced IL-12 levels. The anthropometric biomarkers, WHR and BMI, showed a moderate to strong correlation with the AL index in both HC and MDD groups, highlighting their essential role as biomarkers in the AL concept, with no significant difference observed between groups. HbA1c showed a moderate correlation with the AL index in both groups, whereas glucose and insulin showed a moderate correlation with AL in HCs. This suggests that long-term glucose regulation (as measured by HbA1c) is associated with stress burden. In contrast, short-term markers, such as fasting glucose and insulin levels, may be less reflective of physiological stress load. Lipid metabolism showed a statistically significant moderate correlation with the AL index for LDL and HDL for both groups, and for triglycerides in MDD patients.

3.3. MetS in MDD patients

Separation of MDD patients into those with (n = 17) and without (n = 14) MetS at Week 0 showed that for those with MetS at Week 0, 11 (65 %) met the MetS criteria at Week 6, whereas for the 14 individuals who did not have MetS at Week 0, three (21 %) developed MetS by Week 6. (Table 3).

The psychometric scores, GAF and HAMD, did not differ at either time-point for the individuals who had or did not have MetS. Sub-analyses of the correlation between MetS and psychometric measures at baseline and Week 6 did not reach significance (Supplementary Table 1).

3.4. AL index in response to antidepressant treatment and relationship to symptom severity

For all MDD patients on antidepressants, the mean AL index decreased significantly from baseline (1.81 ± 0.90) to Week 6 (2.15 ± 0.99), t(30) = 2.41, $p = 0.02$; Fig. 2.

Further analysis of MDD patients revealed that the biomarkers, diastolic BP, cortisol, metanephrine, BMI, and triglycerides, differed significantly from Week 0 to Week 6 (Supplementary Table 2). Sub-analysis revealed no significant difference in the AL index at Week 6 between patients receiving Mirtazapine (n = 17, $M = 1.95 \pm 0.99$) or Venlafaxine (n = 14, $M = 1.63 \pm 0.79$), t(28.97) = 0.98, $p = 0.33$, 95 % CI [-0.34, 0.97].

As antidepressant administration caused significant improvement in symptoms (Supplementary Figure 1) and AL index decreased from baseline to Week 6 (Fig. 2), we examined the associations between AL and psychometric variables informative of symptom severity to test for a possible relationship of AL with social and occupational functioning, and depressive symptoms for MDD patients (n = 31). We found that GAF and HAMD scores were non-significantly negatively correlated with AL at baseline (Supplementary Table 3). For Week 6, GAF was non-

Table 2
Mean and standard deviation (SD) for individual biomarkers for the healthy controls (HCs) and the individuals with major depressive disorder (MDD), and their group difference (HCs vs MDD) and correlation with the AL index using Pearson's r. * = p-value 0.05, ** = p-value 0.005, *** = p-value 0.001. Significant p-values are highlighted.

Biomarker	HCs (n = 31) Means (± SD)	MDD (n = 31)	Group comparison (*p-value*)	Correlation with AL index (HCs)	Correlation with AL index (MDD)
Autonomic Nervous System					
***Systolic Blood Pressure** [mmHg]*	118.84 (14.62)	127.29 (15.44)	**0.016**	**0.648*****	**0.433***
***Diastolic Blood Pressure** [mmHg]*	73.55 (9.68)	81.39 (9.50)	**0.003**	**0.578*****	**0.363***
***Heart Rate** [bpm]*	67.74 (9.41)	80.52 (12.41)	**< 0.001**	0.267	0.243
Stress Neuroendocrine					
***Cortisol** [nmol/L]*	229.48 (137.51)	444.0 (408.05)	**0.025**	0.279	0.262
***Metanephrine** [μg/L]*	58.06 (41.57)	106.72 (92.56)	**0.003**	0.233	−0.093
***Normetanephrine** [μg/L]*	104.33 (65.78)	262.91 (310.51)	**0.003**	0.311	−0.070
Immune System					
***CRP** [mg/L]*	1.44 (1.74)	1.41 (1.73)	> 0.9	**0.383***	**0.394***
***IL−12** [pg/mL]*	0.15 (0.08)	0.16 (0.07)	0.5	0.107	**−0.380***
***IL−6r** [ng/mL]*	26.20 (8.10)	23.36 (7.38)	0.11	0.219	0.217
***TNFα** [pg/mL]*	6.70 (6.58)	5.83 (6.64)	0.6	0.183	**0.581*****
***Adiponectin** [μg/mL]*	4.45 (1.91)	4.87 (2.62)	0.7	−0.305	0.026
Anthropometric					
***BMI** [kg/m^2]*	25.15 (3.39)	23.98 (3.87)	0.11	**0.547*****	**0.505****
WHR	0.88 (0.09)	0.88 (0.10)	0.7	**0.518****	**0.709*****
Glucose Metabolism					
***HbA1c** [%]*	5.31 (0.48)	5.31 (0.42)	> 0.9	**0.510****	**0.463***
***Glucose** [mmol/L]*	4.81 (0.59)	4.95 (0.71)	0.8	**0.509****	0.306
***Insulin** [μIU/mL]*	2.51 (1.32)	3.12 (2.94)	0.8	**0.655*****	0.016
Lipid Metabolism					
***Cholesterol** [mmol/L]*	5.16 (0.90)	5.36 (0.81)	0.3	0.295	0.334
***LDL** [mmol/L]*	3.09 (0.80)	3.21 (0.70)	0.4	**0.412***	**0.408***
***HDL** [mmol/L]*	1.52 (0.36)	1.52 (0.54)	0.6	**−0.352***	**−0.409***
***Triglycerides** [mmol/L]*	1.21 (0.53)	1.27 (0.62)	0.8	0.265	**0.573*****

Table 3
Metabolic Syndrome (MetS) scores and psychometric characteristics for MDD individuals with or without MetS at Week 0 (T0). GAF = Global Assessment of Functioning; HAMD = Hamilton Scale for Depression. T(0) = Time-point 0 ~ baseline, T(6) = Time-point 6 weeks after the start of treatment. Continuous variables are presented as mean (SD) and were compared using independent-samples *t*-tests, with test statistics (t), degrees of freedom (df), p-values, and 95 % confidence interval (CI). Categorical variables (MetS present at T6) were analysed using Pearson's Chi-square test, with corresponding χ^2, p-values and 95 % CI reported.

	MetS (n = 17)	No MetS (n = 14)	Test stats	df	*p* - value	95 % CI
Metabolic Syndrome						
MetS Score (T0), mean (STD)	3.65 (0.93)	1.29 (0.83)	**t = 7.48**	**28.82**	**< 0.001**	**1.72–3.01**
MetS Score (T6), mean (STD)	3.18 (1.24)	1.36 (1.34)	**t = 3.90**	**26.92**	**0.002**	**0.86 – 2.77**
Metabolic Syndrome (T6) = Yes, n (%)	11 (65)	3 (21)	**χ^2 = 4.19**	**1**	**0.041**	**1.08 – 49.42**
Psychometric scales						
GAF score (T0), mean (STD)	46.35 (10.99)	50.38 (8.28)	**t = −1.14**	**27.99**	**0.26**	**−11.24 – 3.17**
GAF score (T6), mean (STD)	70.29 (12.75)	70.08 (12.54)	**t = 0.04**	**24.08**	**0.96**	**−9.61 – 10.0**
HAMD score (T0), mean (STD)	21.65 (6.74)	22.93 (4.70)	**t = −0.62**	**28.32**	**0.53**	**−5.49 – 2.93**
HAMD score (T6), mean (STD)	7.24 (5.73)	7.46 (3.69)	**t = −0.13**	**27.33**	**0.89**	**−3.76 – 3.31**

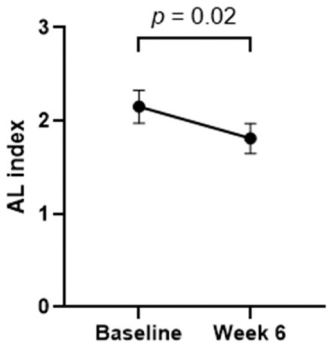

Fig. 2. Mean allostatic load index (with standard error) in patients with MDD (n = 31) at baseline (T0), and week 6 (Time-point 6 weeks after the start of treatment).

significantly positively correlated with AL, and HAMD was non-significantly negatively correlated with AL (Supplementary Table 3). We examined the relationships between baseline allostatic load (AL) and HAMD symptom clusters at both baseline and Week 6. No subscore showed a statistically significant relationship with AL. These results suggest that baseline AL was not strongly linked to specific symptom domains in this sample.

Using the AL index distribution in the MDD group, participants were divided at the median (AL index = 2.0) into two groups: "Low AL" (AL index < 2.0) and "High AL" (AL index > 2.1) at baseline. At Week 6, the High AL group (n = 12) showed a significantly higher GAF score ($p = 0.049$). No other significant differences were found between groups for the psychometric scores at baseline or Week 6 (Supplementary Table 4).

4. Discussion

This is the first study to demonstrate that AL decreases with treatment of MDD patients compared to matched controls. We also identified a modest but significant reduction in AL after 6 weeks of treatment with antidepressants, but no association of AL with symptom severity. Furthermore, we showed, along with published literature, a high prevalence of MetS in patients with MDD. These results gave increased understanding beyond existing research by examining both baseline and longitudinal AL changes, while disentangling symptom severity, disease contribution, and MetS.

In line with our present findings, a recent study has further highlighted the role of AL in mood disorders, including longitudinal findings linking elevated AL to poor health outcomes and recurrence risk in MDD (Gou et al., 2025), emphasizing the need for integrative models that consider biological, psychological, and social contributors to depression.

Our results confirm the findings of previous studies, which report elevated AL in patients with MDD compared to HCs (Honkalampi et al., 2021; Juster et al., 2011). Furthermore, our study is an extension of a study showing that the AL index was elevated in patients with schizophrenia (SCZ) and first-episode psychosis (FEP) relative to controls, and that AL decreased with 6 weeks of antipsychotic treatment (Berger et al., 2018). A list of key differences and similarities is shown in Table 4. The multisystemic biomarker panel and scaled AL index approach ensure methodological consistency and the ability to compare results across different diagnostic categories.

Both studies showed elevated AL at baseline in unmedicated psychiatric inpatients (SCZ/FEP and MDD) and reductions in AL over time with pharmacological treatment. In both studies, AL was not predictive of treatment response, although some symptom-domain-specific associations emerged in SCZ in the earlier study (Berger et al., 2018).

The AL index is a cumulative score representing dysregulation resulting from repeated exposure to stress (McEwen and Stellar, 1993). Elevated AL has been hypothesised to contribute to the development of MDD through dysregulation of the SNS and HPA axis. This dysregulation leads to persistent elevation of stress hormones, such as cortisol, which can negatively impact brain regions involved in mood regulation, including the hippocampus, amygdala, and prefrontal cortex (Gold et al., 2015; McEwen, 2003). Over time, this "wear-and-tear" may result in structural and functional impairments in brain structures like the amygdala, which regulates ANS function and cortisol production

Table 4
Descriptive statistics of the current study investigating patients with Major Depressive Disorder (MDD) and the study by Berger et al. (2018) investigating patients with first-episode psychosis (FEP) and schizophrenia.

	Major Depressive Disorder Current study	First-episode Psychosis and Schizophrenia Berger et al. (2018)
Diagnosis	MDD	SCZ + FEP
Sample size	31 MDD + 28 HCs	28 SCZ + 28 FEP + 53 HCs
Duration of follow-up (weeks)	6	6 + 12
Clinical focus	MDD + MetS + antidepressants	SCZ + FEP + antipsychotics
Psychometrics	HAMD + GAF + YMRS	PANSS + GAF
Drug comparisons	Venlafaxine + Mirtazapine	Olanzapine + Risperidone + Quetiapine
Inflammatory biomarkers	IL−6r + IL−12 + TNF-α + CRP + adiponectin	IL−6r + TNF-α + CRP + e-selectin
Main findings	- AL was increased in MDD compared to HCs - Antidepressants decreased AL over 6 weeks - AL is not associated with depressive symptoms and functional scores - MetS is prevalent in MDD patients	- AL was elevated in SCZ and FEP compared to HCs - Antipsychotics decreased AL over 12 weeks - AL was associated with more positive symptoms (PANSS) and lower GAF

(Trousselard, 2025). Prolonged MDD has been linked to volumetric changes in the amygdala (Roddy et al., 2021), with evidence suggesting that initial hypertrophy may be followed by atrophy (Sheline et al., 1999). This neurobiological deterioration may be compounded by elevated AL, which has been linked to persistent low-grade inflammation and immune system impairment, both of which have been identified in MDD (Slavich and Irwin, 2014). Therefore, the high AL at baseline in MDD patients in our study may reflect long-term systemic dysregulation, which ultimately contributes to the disorder.

It is important to note that the current evidence regarding the relationship between AL and depression remains inconclusive. For example, a study reported a cross-sectional but not longitudinal association between depression and AL, which suggests an acute response (Juster et al., 2011). However, that study included fewer AL biomarkers, only one stress neuroendocrine biomarker (cortisol), and no inflammatory biomarkers, which limited their ability to assess multisystemic dysregulation, compared to our investigation (Juster et al., 2011). Another recent study found that elevated AL was positively associated with the risk of depression 13 years after the initial assessment, particularly among those with moderate to high AL, who showed a higher risk of comorbid anxiety and depression (Gou et al., 2024).

It is also important to recognise that potential reverse pathways may exist. MDD may be associated with HPA-axis dysregulation, partly due to disrupted sleep and structural remodeling/atrophy of the hippocampus and prefrontal cortex (Sharan and Vellapandian, 2024), which have a critical role in mood and emotion regulation (Tartt et al., 2022). The hippocampus plays a crucial role in the HPA axis feedback mechanism by inhibiting hypothalamic corticotropin-releasing hormone (CRH) secretion, thereby downregulating the HPA axis (Dahmen et al., 2018; Kageyama et al., 2021; Smith and Vale, 2006). Thus, presumed structural and functional changes in the hippocampus associated with MDD may result in impaired negative feedback and dysregulation of the HPA axis, resulting in increased cortisol, metanephrine, and normetanephrine levels (Table 2) (Dahmen et al., 2018; McEwen, 2003; Mikulska et al., 2021).

We found in this study that AL was increased in MDD patients compared to HCs, but this was not associated with disease duration, contrary to our hypothesis. Similar findings were reported in the study by Berger et al. (2018), who found that the AL was not associated with duration of illness in SCZ or FEP. The relationship between AL and disease duration is complex, involving factors such as support system, illness type, and individual stress responses (Guidi et al., 2020; Schneiderman et al., 2005). Medications and psychological support, also mitigate stress and physiological burden, thereby reducing the AL (Nakao et al., 2021).

A notable finding of our study was the lack of association between AL and psychometric symptom severity. This apparent dissociation may reflect the fundamental different temporal and conceptual nature of these constructs: While AL is a chronic, 'trait-like' measure, clinical symptoms captured by instruments like the HAMD and GAF primarily assess transient 'state-like' phenomena (Juster et al., 2011; McEwen and Akil, 2020). Moreover, AL may align more closely with somatic symptoms (e.g., sleep, appetite, energy levels) rather than with affective or cognitive domains (Kobrosly et al., 2014). In fact, a previous study from our group showed that PHQ-9 scores were unrelated to AL when age, sex, and smoking were taken into account, but anhedonia and insomnia sub-scores were significantly associated with AL (Berger et al., 2019). Furthermore, the temporal lag effect may play a role, as biological changes could precede symptom changes. The study by Berger et al. (2018) noted stronger associations between AL and clinical improvement after 12 weeks of treatment, which suggests that our 6-week window may have been insufficient.

Our findings demonstrated a reduction in AL over a 6-week period of antidepressant medication combined with psychosocial therapy, prompting the inquiry into whether antidepressants may mitigate AL. The consistent decrease in AL observed in the MDD patients during the follow-up period suggests a potential link between the acute phase of depression and AL. Alternatively, it is plausible that antidepressant medications genuinely lower AL, which contradicts the idea that these medications may exacerbate AL due to their negative metabolic side effects (Bizik et al., 2013). Nonetheless, the 6-week duration of observation may not be sufficient to detect any adverse changes in AL. Furthermore, in the absence of a placebo group, it is not possible to disentangle the effects of antidepressant treatment from regression to the mean, natural recovery, or the effects of the inpatient environment; therefore, this finding should be interpreted with caution.

MetS were identified in more than half of the MDD individuals at baseline, consistent with previous studies (Marazziti et al., 2014; Osei et al., 2024; Zhang et al., 2021). Long-term dysregulation of stress hormones and inflammation are associated with elevated blood platelet reactivity, thromboembolic events, and increased blood pressure (Sandrini et al., 2020), contributing to an elevated cardiovascular risk (Krittanawong et al., 2023; McEwen, 2003). Similarly, MDD has been associated with a greater risk of diabetes due to elevated levels of proinflammatory cytokines, which may contribute to insulin resistance and therefore glucose dysregulation (Watson et al., 2021). Likewise, a bidirectional relationship between depressive symptoms and glucose metabolism, posited through the HPA axis and inflammatory biomarkers, has also been demonstrated and plays a significant role in MetS (Bodnaruc et al., 2024; Demakakos et al., 2014). Our results indicate that the number of individuals with MetS at baseline (n = 17) decreased slightly (n = 11) by Week 6, although three new cases emerged in individuals who were initially unaffected. Adding MetS to models predicting symptom severity did not significantly improve the prediction of depressive symptoms (HAMD) or functional status (GAF) at Week 6, suggesting that MetS does not provide additional information beyond AL in this sample, though the small sample size limits interpretation of the results.

Limitations of this study include the relatively small sample size (n = 31 MDD patients) and the absence of an a priori power analysis. However, recruitment was intentionally restricted to unmedicated, acutely depressed inpatients to minimise medication-related confounding effects, making such samples challenging to obtain. High attrition at Week 12 prevented more extended longitudinal analysis, and the brief 6-week window may not be sufficient to capture longer-term trends. Finally, there is currently no universally accepted method for quantifying AL, and variations in the selection and weighting of biomarkers can influence the results. This lack of standardisation poses challenges for comparing findings across studies and may affect the robustness. While our use of the "scaling approach" incorporated a large number of biomarkers, which reduces the influence of individual parameters and mitigates the effects of outliers or transient fluctuations (e.g., blood pressure reflecting acute stress), alternative formulations of allostatic load indices might yield different results. Therefore, our findings should be interpreted with caution, and future studies could explore the impact of using different AL calculation methods. In contrast to several other studies on AL in psychiatry, which used a more limited selection of AL biomarkers (Nugent et al., 2015; Savransky et al., 2017), we calculated the AL index using 20 biomarkers that cover all major physiological systems to ensure a more comprehensive representation of systemic dysregulation.

Future research should involve larger, multicenter samples with extended follow-up, testing of symptom domains, and AL standardisation to enhance clinical relevance.

5. Conclusion

This study shows that AL is significantly elevated in unmedicated MDD patients compared to HCs, indicating widespread physiological dysregulation. However, AL was not linked to depressive symptoms or treatment response, suggesting a dissociation between clinical symptoms and the underlying biological stress. Furthermore, the

neuroendocrine stress biomarkers, cortisol, epinephrine, and norepinephrine, were significantly elevated in patients with MDD, reinforcing the role of HPA axis dysfunction. MetS was highly prevalent at baseline and persisted after 6 weeks of antidepressant treatment in the MDD patients, despite a modest decrease in some patients. These findings suggest that antidepressants may reduce physiological stress, but are insufficient to reverse metabolic abnormalities in response to a short-term antidepressant regimen. Our results highlight the complex relationship between mental and physical health in MDD, and the need for a more integrative approach that incorporates both pharmacological and lifestyle interventions. This study underscores the critical role of metabolic health, particularly the risk of metabolic syndrome, in the management of depression, highlighting the need for integrated treatment strategies that address both psychological and physiological outcomes.

Disclosure of Interest

SB is a director of Psynova Neurotech Ltd and PsyOmics Ltd. The other authors declare no conflict of interest.

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Declaration of Competing Interest

SB is a director of Psynova Neurotech Ltd and PsyOmics Ltd. The other authors declare no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2025.107653.

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