ORIGINAL ARTICLE

Allostatic load, emotional hyper-reactivity, and functioning in individuals with bipolar disorder

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Abstract

Objectives: Diagnosis and management of bipolar disorder (BD) are limited by the absence of available biomarkers. Allostatic load (AL) represents the strain that stress, including the effects of acute phases and inter-episode chronic mood instability, exerts on interconnected biological systems. This study aimed to operationalize an AL index and explore whether it could be relevant to better characterize BD patients with and without emotional hyper-reactivity particularly those at higher risk of immune-cardiometabolic dysregulation and functional impairment.

Methods: Levels of biomarkers of chronic inflammation (hsCRP and albumin), cardiovascular (systolic/diastolic blood pressure) and metabolic functions (fasting glucose, glycosylated hemoglobin, total cholesterol, LDL, HDL, and triglycerides) were measured in 1072 adult BD outpatients. Patients were classified in two groups (with/without emotional hyper-reactivity) assessed by the Multidimensional Assessment of

Thymic States scale. An Allostatic Load Index for BD (BALLI), comprising six biomarkers, was constructed using data-driven biomarker selection.

Results: BALLI showed 81.1% accuracy with good sensitivity (81%) and specificity (81.2%) for characterizing BD patients presenting emotional hyper-reactivity, elevated risk of inflammation (increased hsCRP, hypoalbuminemia) and cardiometabolic disturbances (hypertension, hyperglycemia, and hypertriglyceridemia). Patients classified by the BALLI as presenting emotional hyper-reactivity had significantly lower global and cognitive functioning than those without emotional hyper-reactivity (P < .0001).

Conclusions: A multidimensional approach based on a simple AL score (eg, BALLI) and dimensions of behavior (eg, emotional hyper-reactivity) alongside mood is clinically relevant. AL index could be a useful tool to detect multisystemic physiological dysregulations in BD patients with/without emotional hyper-reactivity particularly those at higher risk of immune-cardiometabolic disturbances and functional impairment.

KEYWORDS

allostatic load, biomarkers, bipolar disorder, emotional reactivity, functioning

1 | INTRODUCTION

Bipolar disorder (BD) is a major public health issue associated with premature mortality and increased risk of developing various aging-related diseases, such as hypertension, diabetes and dementia.[1-3] BD patients exhibit a reduced lifespan compared to the general population, a finding that cannot be explained exclusively by high suicide risk and unhealthy lifestyle.[4] The increased premature mortality observed among those patients is thought to result from, among other causes, cardiovascular diseases (CVD) and metabolic syndrome, characterized by hypertension, impaired glucose metabolism, obesity and dyslipidemia, increasing the risk for type 2 diabetes and CVD mortality.[5,6]

Unlike homeostasis, which describes precise regulation of physiological parameters within a narrow range, allostasis refers to dynamic adaptation in response to external stimuli such as stressful life events.[7] Allostatic load (AL) refers to the cost of chronic exposure to fluctuating or heightened immune-endocrine and neural activities resulting from the organism's attempts to deal with repeated or chronic environmental stressors.[7,8] Central to these processes is the brain, which mediates biobehavioral adaptations and is also sensitive to the effects of AL.[9-11] Multiple allostatic mediators function as part of a nonlinear network that contributes to the development of AL, including elevated levels of stress hormones (eg, cortisol, epinephrine), proinflammatory markers (eg, C-reactive protein, Il-6, TNF-a), and oxidative stress.[12,13] These then contribute to damaging effects in the brain and other organs, including altered gene expression,[14] telomere shortening[15] and ultimately playing a role in cognitive, cardiovascular, and immune dysfunction as well as in obesity, bone demineralization and atrophy of cerebral nerve cells, whose association with BD is well established.[16,17]

Allostatic overload has been observed in individuals with psychotic disorders and appears to contribute to the excess mortality observed in those patients.[18-20] Recently, a study found in a small sample of patients with schizophrenia that higher AL was related to positive symptoms severity and impaired functional capacity.[21] However, the complexity involved in measuring AL, including the difficulty associated with obtaining extensive biomarker measurements, has constrained AL research to theoretical models or specific clinical populations.[22,23] In addition, traditional diagnostic categories may be limited to detect the widespread intra- and inter-individual variability in the presentation and/or severity of symptoms observed in individuals with BD.[24] Clinical expression of BD varies in the same individual, not only regarding acute episodes, but also considering the illness course.[25,26] For example, the shortening of the inter-episode interval and the reduced probability of treatment response with illness progression may result from changes in brain circuits, which contribute to behavioral (eg, chronic mood instability, emotional dysregulation), systemic (eg, cardiometabolic disturbances), and functional consequences (eg, cognitive decline).[27]

Persistent deficits in the emotion regulation process as well as abnormal emotional reactivity are frequently observed in individuals with BD.[28,29] Emotional reactivity is defined by the magnitude of change from an emotional baseline state in response to emotion-eliciting stimuli.[30] Using the multidimensional assessment of mood/behavior states (MAThyS),[31] which assess levels of activation (including emotional reactivity) uncoupled from mood, we have recently demonstrated that emotional reactivity is a relevant dimension for characterizing remitted BD patients,[32] and that those patients with emotional hyper-reactivity have increased cardiometabolic risk and chronic inflammation.[16,33]

To approach the problem of inter-individual variability, the Research Domain Criteria project (RDoC) has established that some of these limitations can be mitigated by using multidimensional approaches, including biomarkers, social factors, and fundamental psychological processes, such as fear, motivation, and cognition.[34] They should facilitate the identification of bio-phenotypes that are associated with discrete physiological changes, which result from the organism's adaptation to internal and external states. Despite theoretical literature linking AL composites to mood,[35,36] anxiety,[37] and substance-abuse disorders[38] there is only a paucity of empirical evidence in humans, and no experimental study to date has investigated the AL-mood/behavior links in BD patients. By assessing immune, cardiovascular and metabolic parameters routinely used at clinical practice, we therefore sought to operationalize an AL index and explore whether it could be relevant to better characterize BD patients with and without emotional hyper-reactivity particularly those at higher risk of immune-cardiometabolic dysregulation and functional impairment.

2 | METHODS

2.1 | Participants

A total of 1072 BD outpatients aged between 18 and 65 years were selected from 1300 patients assessed by semi-structured clinical interview and self-reported questionnaires conducted by trained psychiatrists in the French Network of FondaMental Advanced Centers of Expertise in Bipolar Disorders. Primary diagnosis was confirmed using the SCID, DSM-IV Axis I Disorders.[39] Eligible patients had diagnosed BD type I, II, or Not Otherwise Specified (NOS) and were not in acute mood episode according to DSM-IV criteria. Of the 1300 BD patients evaluated, 228 patients were excluded on account of having medical comorbidities, including autoimmune diseases, hepatic illnesses, immunomodulatory treatment, cancer, or other known conditions associated with peripheral inflammation, or not having available results for the selected biomarkers. The Human Research Ethics Committee, CPP-Ile de France IX, approved the study and all participants received an information letter about this study.

2.2 | Assessments

Severity of depressive and manic symptoms at the time of the assessment was evaluated using Montgomery–Åsberg Depression Rating Scale (MADRS), a 10-item questionnaire, ranging from 0 to 60, with higher scores indicating more severe depression, and the Young Mania Rating Scale (YMRS), an 11-item questionnaire, ranging from 0 to 60, with higher scores indicating severity of (hypo)manic symptoms. Overall functioning was evaluated using the Functioning Assessment Short Test (FAST), which encompasses 24 items to evaluate six functional domains: autonomy, occupational functioning, financial issues, interpersonal relationships, leisure time, and cognitive functioning. Items are rated using a four-point scale from 0 (no difficulty) to 3 (severe difficulty). FAST scores range from 0 to 72, and higher scores indicate poorer functioning and greater disability.[40] Levels of emotional reactivity were measured using the emotional reactivity sub-score of the Multidimensional Assessment of Thymic States (MAThyS), a self-rated scale routinely used in clinical practice in the French Network of Bipolar Expert Centers that assesses levels of activation uncoupled from mood during the preceding week. It quantitatively evaluates five dimensions, including emotional reactivity, sensory-perception, psychomotor activity, motivation, and cognition, each of which can vary from hypo-activation to hyper-activation. Items are rated using a continuous scale ranging from 0 to 10, considering the intensity of emotions and the environmental context (eg, "My emotions are very intense/My emotions are attenuated"). The MAThyS has previously been shown to have validity and internal consistency (Cronbach's alpha coefficient = 0.95).[31] The emotional reactivity score ranges from 0 to 40, and patients were grouped as either with emotional hyper-reactivity (>24-40) or without emotional hyper-reactivity (0-24) based on previously validated cutoffs.[32]

2.3 | Biomarkers and anthropomorphic measurements

A total of 12 biomarkers were primarily selected based on (a) use in previous AL research,[8,12,19,41] (b) availability of data, and (c) representation of multiple physiological systems including markers of chronic inflammation (high-sensitivity C-reactive protein, hsCRP; and albumin), cardiovascular function (systolic and diastolic blood pressure, BP), glucose metabolism (fasting glucose, FG; glycosylated hemoglobin, Hb_{A1c}), lipid metabolism (total cholesterol, TC; low-density lipoprotein, LDL; high-density lipoprotein, HDL; triglycerides, TG), and anthropometric parameters (body mass index, BMI; waist circumference, WC). A fasting blood sample was taken from all patients between 7:00 and 9:00 AM, and hsCRP, fasting glucose, HbA1c, TC, LDL, HDL, and TG levels were measured. Blood samples were centrifuged at 2016 g for 15 minutes, and serum was collected. Patients' height and weight were measured and used to calculate adjusted BMI (kg/m^2). Waist circumference was measured using a tape measure. Blood pressure was assessed after 10 minutes rest period and before the psychiatric assessment.

Rather than classifying participants using cutoffs based on the sample's distribution for a given biomarker, we calculated a subclinical cutoff based on clinical reference ranges accompanying biomarker results, which are used routinely for diagnostic purposes.[12] For each biomarker attaining critical cutoffs (modest deviations from normal) a score of 1 was ascribed, while those within a normal range a score of 0 was ascribed (Table 1).

In the formulation used here, a one-tailed approach is applied using either the lower limit or the higher limit to denote risk. For example, total cholesterol with a normal range between 3.3 and 5.2 nmol/L. First, to determine the range, we subtracted the lower

Biomarker	Normal range	Lower limit	Higher limit
Systolic blood pressure (mm Hg)	90-140	≤102.5 → 0	≥127.5 → 1
Diastolic blood pressure (mm Hg)	60-90	≤67.5 → 0	≥82.5 → 1
C-reactive protein (mg/L)	0-8	<3 → 0	≥3 → 1
Albumin (g/L)	35-48	≤38.25 → 1	≥44.75 → 0
Fasting glucose (mmol/L)	4.0-5.9	≤4.47 → 0	≥5.43 → 1
Glycosylated hemoglobin (mmol/L)	4.6-6.2	≤0.05 → 0	≥0.058 → 1
Triglycerides (mmol/L)	0.4-1.8	≤0.75 → 0	≥1.45 → 1
Total cholesterol (mmol/L)	2.8-5.2	≤3.40 → 0	≥4.60 → 1
High-density lipoprotein cholesterol (mmol/L)	0.9-2.0	≤1.18 → 1	≥1.73 → 0
Low density lipoprotein (mmol/L)	1.0-3.3	≤1.57 → 0	≥2.72 → 1
Body mass index (Kg/m^2)	18.5-25	≤20.125 → 0	≥23.375 → 1
Waist circumference (cm)	♂ 90-102 ♀ 80-88	♂ ≤ 92 → 0 ♀ ≤ 82 → 0	♂ ≥ 100 → 1 ♀ ≥ 86 → 0

Note: The clinical norms may change according to the biochemical assays used and the unit of measurement.

limit from the upper limit (5.2-3.3 = 1.9). Second, to determine the quartile, we divided the range by four (1.9/4 = 0.475). Third, to determine the cutoff, either we subtracted the quartile from the upper limit for the upper cutoff (5.2-0.475 = 4.725) or, in the case of biomarkers like albumin and HDL whereby lower levels are deleterious, we added the quartile to the lower limit for the lower cutoff (35 + 3.25 = 38.25). Based on this example, a patient with total cholesterol at 4.725 nmol/L or higher would get a score of 1, whereas values below this cutoff would be scored as 0. While this formula is designed for medical practice, it does not yield cutoffs that are much different from those using biomarker distributions based on the sample distributions generally used in empirical AL studies.[12]

2.4 | Statistical analyses

Demographical and clinical characteristics between patients with emotional hyper-reactivity and those without were compared using one-way ANOVA for continuous variables and chi-squared test for categorical variables. In order to optimize an AL score clinically relevant for BD using the smallest number of biomarkers as possible, algorithms were applied performing 2^{12}-1 permutations to identify the best combination among those twelve biomarkers. Then, the combination of variables yielding the highest predictive performance was selected according to the area under the curve (AUC). Based on six remaining biomarkers, an Allostatic Load Index for BD (BALLI) was constructed, with scores ranging from 0 to 6, where higher scores indicate greater AL. A Mann-Whitney-Wilcoxon test was applied to compare the BALLI scores between the two groups. The composite biomarker score was tested on the sample by receiver operating characteristics (ROC) analysis calculating the AUC of the ROC curve.[42] On assigning a cutoff of 0.5 on the constructed composite score, the accuracy, sensitivity, and specificity were calculated. The resulting P values were adjusted for

multiple comparisons according to the Benjamin and Hochberg procedure. Analyses were conducted using the R statistics package v3.5.1.

3 | RESULTS

3.1 | Study sample description

Characteristics of the study population are described in Table 2. Of the 1072 BD patients included in the study, 638 (59.5%) were female, 499 (46.5%) were diagnosed with BD type I, and the mean age was 41.2 (SD = 12.4) years. Assessment using MAThyS tool found 544 patients (50.7%) presenting with emotional hyper-reactivity who were more likely to have a lower level of education ($F_{1,1072} = 5.75$, $P = .03$), BD-II diagnosis (41.4%), ($F_{1,1072} = 11.86$, $P = .008$), and more comorbid anxiety disorders ($F_{1,1072} = 8.06$, $P = 008$), compared with those without emotional hyper-reactivity. There were no significant differences between groups with respect to age, age at onset, illness duration, and number of previous mood episodes. Both groups had similar levels of depressive subthreshold symptomatology assessed with the MADRS ($F_{1,1072} = 2.258$, $P = .21$). Those with emotional hyper-reactivity had greater YMRS scores ($F_{1,1072} = 99.363$, $P < 1.42 \times 10^{-21}$), levels of anxiety symptoms (STAI scores; $F_{1,1072} = 13.85$, $P < .0006$), and number of suicide attempts ($F_{1,1072} = 31.757$, $P = 1.13\ 10^{-7}$). In terms of medication use, the group with emotional hyper-reactivity was more likely to be prescribed antidepressants and benzodiazepines ($F_{1,1072} = 5.043$, $P = .052$).

3.2 | Allostatic load scores

Figure 1 shows the proportion for each biomarker attained subclinical dysregulation (ie, a score of 1) in the two groups of patients. Except for waist circumference ($P = .5$), significant differences

TABLE 2 Demographic and Clinical Characteristics of 1072 Bipolar Patients with Emotional Hyper-Reactivity and without Emotional Hyper-Reactivity

Variable	Emotional Hyper-reactivity (n = 544)			No emotional hyper-reactivity (n = 528)			t or X^2	df	Adjusted P value
	Mean	SD	%	Mean	SD	%			
Sex (male)			35.5			45.6	11.07	1072	.002
Age (y)	41.45	12.82		42.05	12.67		0.57	1072	.576
Education level (y)	13.62	2.96		14.08	2.88		5.754	1072	.034
Occupation									
Unemployed			20.0			22.7	0.07	1072	.782
Marital status							0.482		.734
Single			33.6			33.5		1072	
Married			45.0			46.2		1072	
Diagnosis							11.868	1072	.008
Bipolar disorder type I			41.4			51.9			
Bipolar disorder type II			41.4			33.1			
Bipolar disorder type NOS			17.2			15.0			
Age-at-onset (y)	24.42	10.04		25.05	10.16		1.009	1072	.447
Illness duration (y)	16.89	11.49		16.77	11.05		0.032	1072	.898
Number of hospitalizations	2.88	3.11		3.05	3.37		0.751	1072	.493
Total number of episodes	6.67	5.99		6.36	5.48		0.731	1072	.493
Total number of depressive episodes	5.72	5.11		5.15	4.73		2.852	1072	.173
Total number of manic episodes	5.69	5.20		5.39	4.74		0.769	1072	.527
Rapid cycling			15.1			10.8	4.289	1072	.173
Number of suicide attempts	2.20	2.38		1.33	2.30		31.75	1072	$.13 \times 10^{-7}$
MADRS score	9.52	8.05		8.77	8.19		2.258	1072	.217
YMRS score	3.27	4.10		1.28	2.07		99.36	1072	1.42×10^{-21}
STAI score	43.57	15.47		40.10	14.65		13.85	1072	.0006
Comorbidities									
Anxiety disorders			45.6			38.4	8.06	1072	.008
Diabetes			4.2			4.9	0.307	1072	.681
Cardiovascular disorders			15.8			12.6	0.498	1072	.284
Dyslipidemia			6.5			5.2	1.345	1072	.781
Substance use disorders			30.9			31.8	0.004	1072	.659
Current smoking			49.8			54.7	1.823	1072	.395
Medications									
Antipsychotics			13.2			15.5	0.968	1072	.492
Lithium			17.3			19.7	0.885	1072	.509
Anticonvulsants			32.4			32.6	0.001	1072	.989
Antidepressants			23.3			20.5	1.144	1072	.477
Benzodiazepines			16.7			11.7	5.043	1072	.052

Note: The resulting P-values were adjusted for multiple comparisons according Benjamin and Hochberg procedure.

Abbreviations: MADRS, Montgomery–Åsberg Depression Rating Scale; STAI, State-Trait Anxiety Inventory; YMRS, Young Mania Rating Scale.

were observed between groups for the biomarkers of inflammation (hsCRP and albumin), cardiovascular function (SystolicBP and DiastolicBP), BMI as well as metabolism of glucose (FG and HbA1c), and lipids (TG, HDL, LDL, TC) P < .0001. Further information on the mean (SD) and statistical differences for each biomarker is presented in Table S1.

The model identified hsCRP, albumin, DiastolicBP, SystolicBP, FG, and TG as the six variables with greater prediction performance
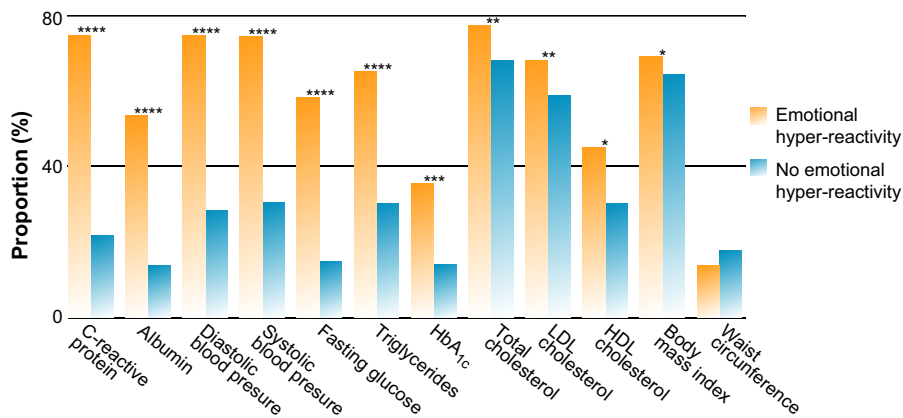
FIGURE 1 Proportion for each biomarker attained subclinical dysregulation in patients with and without emotional hyper-reactivity (N = 1072)
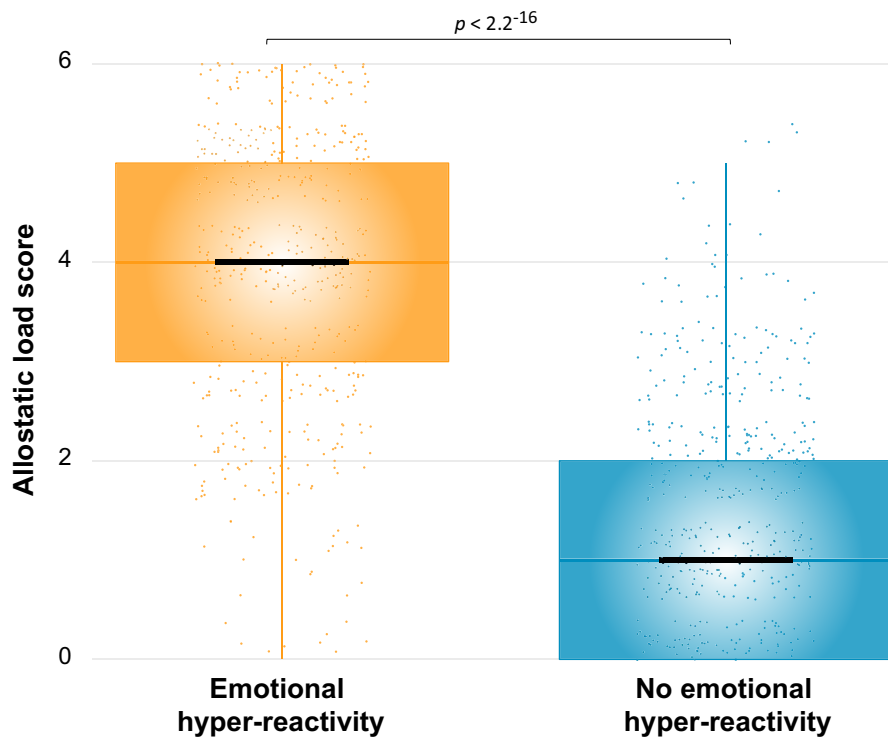

FIGURE 2 Allostatic load score in patients with and without emotional hyper-reactivity (N = 1072)

to identify patients with or without emotional hyper-reactivity states. A Wilcoxon test adjusted for age, sex, and smoking demonstrated that patients with emotional hyper-reactivity had significantly higher AL scores than those without emotional reactivity ($P < 2.2 \times 10^{-16}$, Figure 2).

BD patients who have attempted suicide more than once had significantly increased BALLI scores in comparison with those who have attempted suicide only once or those without suicide attempts ($P < 2 \times 10^{-16}$), independently of their emotional reactivity state, age, sex, and mood symptoms. Also, BD patients that had never attempted suicide presented lower BALLI scores than those who have attempted suicide at least once ($P < .0001$).

The prediction model using the BALLI showed 81.1% accuracy (95% CI; 078, 0.83), with high Sensitivity (81%) and Specificity

(81.2%) to identify patients as either with or without emotional hyper-reactivity (Figure 3).

Furthermore, rather than using the predetermined groups of patients determined by the scale cutoffs, we assessed functioning in the groups of patients predicted by the BALLI. The predicted group with emotional hyper-reactivity presented significantly poorer overall and cognitive functioning compared to those without emotional reactivity using the BALLI (Figure 4).

4 | DISCUSSION

To the best of our knowledge, this is the first study to operationalize an allostatic load score to characterize emotional hyper-reactivity
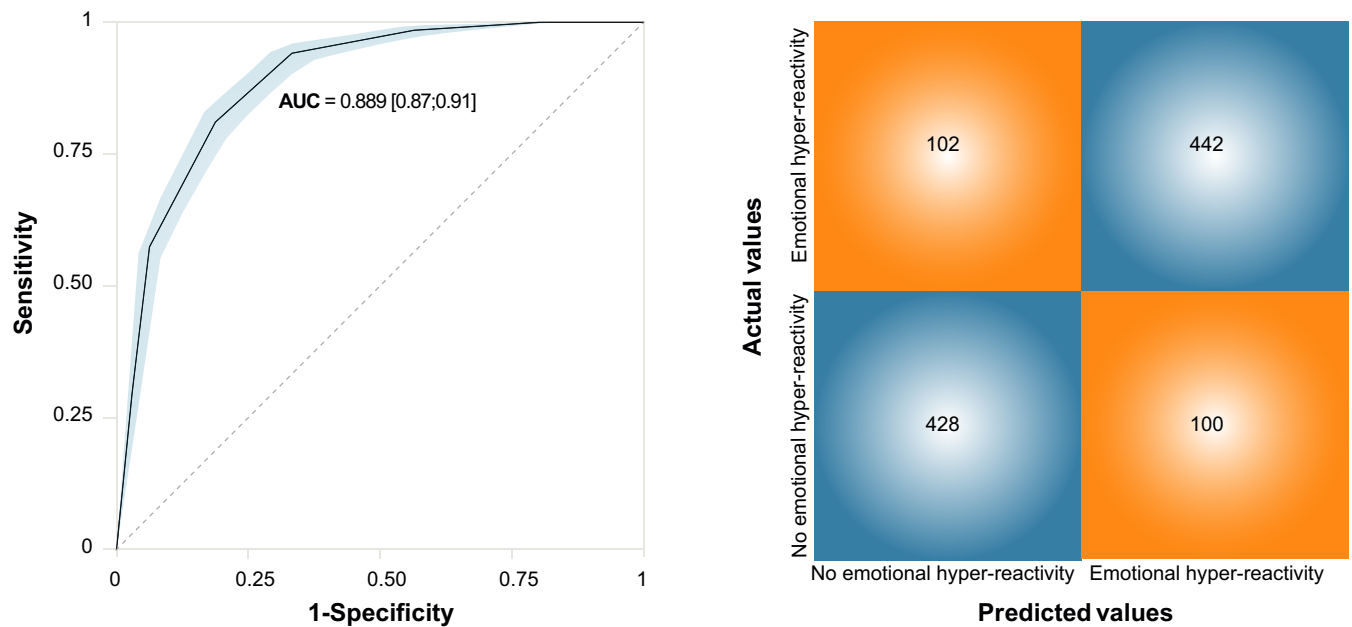
FIGURE 3 Prediction accuracy, specificity and sensitivity of the Allostatic Load Index for Bipolar Disorder, BALLI (N = 1072)
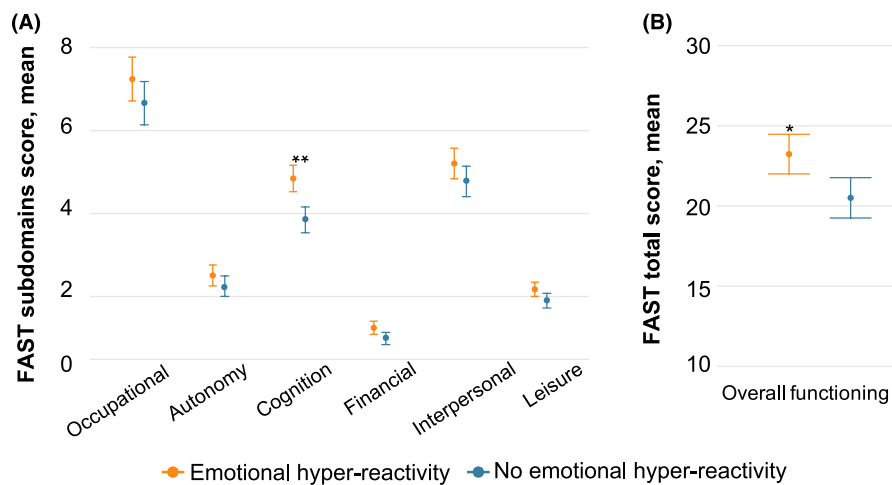

FIGURE 4 Psychosocial functioning in patients classified by the Allostatic Load Index for Bipolar Disorder (BALLI) as presenting with or without emotional hyper-reactivity (N = 1072); A, FAST subdomains score, B, FAST total score

states and functional outcomes in BD patients. The use of data-driven approaches enabled us to establish the BALLI, a simple score based on six biomarkers routinely used in clinical settings that showed 81.1% accuracy for characterizing a specific group of BD patients presenting emotional hyper-reactivity, elevated risk of chronic inflammation (increased hsCRP, hypoalbuminemia), cardiometabolic disturbances (hypertension, hyperglycemia, and hypertriglyceridemia), and poorer cognitive functioning. Biomarkers are not subject to reporting biases and can provide insight into physiological mechanisms through which both immune-metabolic and behavioral disturbances may have an impact on health,[43] thus improving confidence that observed relationships are not spurious. These findings are consistent with the AL concept, which postulates that a composite of

multisystem biological signatures would provide better prediction of health risks than individual parameters.[44] As routine blood tests and measurement of blood pressure are widely accessible and could be easily used in clinical practice, these parameters may inform practitioners of changes in AL, aiding earlier detection of subjects with increased risk of CVD, metabolic syndrome, and chronic inflammation.

Although BD patients included in this study were not in acute episode based on the traditional diagnostic categories, about half of them presented with emotional hyper-reactivity independently of age, sex, and mood symptoms severity. Moreover, there were no significant differences regarding the number of mood episodes between groups, suggesting that it is not solely the result of acute mood episodes but the chronic emotional hyper-reactivity during

the inter-episodes' periods that would exacerbate some of the measures obtained (eg, CRP, FG, BP) in this sample. The effects of emotional/mood dysregulation as well as of other factors such as medication adjustments, treatment compliance, stressful life events, and changes in lifestyle behaviors (diet, sleep, physical activity, smoking/drugs) during the inter-episodes' periods may contribute to the allostatic (over)load owing to prolonged/sustained brain arousal and over-activation of neuroendocrine, immune and sympathetic nervous systems that may in turn lead to inflammation, endothelial dysfunction, and oxidative stress,[13,36] conferring risk for hypertension, diabetes, cancer as well as premature aging and early mortality.[4,44] Clinically, assessing dimensions of behavior associated with relatively affordable biomarkers (blood pressure-CRP-glycaemia), in addition to the assessment of mood symptoms in BD patients, may facilitate interventions that are closer to the BD pathophysiology.

Our findings suggest that the presence of higher AL may be an indicator of states of body-brain dysfunction in BD patients, particularly those presenting emotional hyper-reactivity and anxiety states, which are reflected in cardiovascular (eg, hypertension) and immune-metabolic regulatory systems (eg, increased hsCRP, hyperglycemia, hypertriglyceridemia, and hypoalbuminemia). A preclinical study has shown that elevated levels of CRP may induce a disruptive effect in the blood-brain-barrier, increasing its permeability and facilitating the cross of proinflammatory cytokines through the barrier, making the brain more susceptible to the effects of inflammation.[45] Recently, increased levels of inflammatory markers (eg, CRP, IL-6, TNF-a) were associated with reduced functional connectivity in reward and motor brain circuitry in depressive patients, and are likely to be related to neuroinflammatory and metabolic processes within the brain, including the blood-brain barrier, leading to altered monoamine levels and over-activation of microglial cells.[46] The net effect of these changes may be disrupted neuroplasticity in key brain regions, which may lead to the phenotypic and functional changes observed in BD patients. Since it is a relatively low-cost biomarker and widely available in clinical settings, measurement of CRP levels might be an easy, cost-effective way to assess peripheral levels of chronic inflammation in BD patients, and, indirectly, alterations in proinflammatory cytokines, which are known to modulate CRP levels.

This study also found that BD patients with higher AL scores presented poorer functioning independently of age, sex, and mood symptoms severity. Rather than using the groups of patients predetermined by the scale cutoffs, we assessed functioning in the groups of patients predicted by the BALLI. Patients classified as presenting emotional hyper-reactivity had significantly lower overall and cognitive functioning than those without emotional hyper-reactivity. This finding is particularly relevant given that the groups included in this analysis were determined using data-driven approaches based on objective markers, which allow for the classification of individuals based not simply on single variables/symptoms, but on distinct clinical/functional profiles. Understanding the dynamic relationship between AL, emotional hyper-reactivity and functioning alongside mood may contribute to enhancing therapeutic interventions such

as psychoeducation and mindfulness for emotional/stress management, and cognitive remediation, to improve cognitive and functional performances. These nonpharmacological interventions may help to arrest the cycle of AL and decrease emotional hyper-reactivity, which complicates the BD course by contributing to cognitive impairment and comorbid pathologies.

Beyond associations of AL with adverse physical and functional outcomes, the multisystem biological signatures encompassed by the AL framework may change with treatment. In our study, patients with emotional hyper-reactivity (those also presenting higher AL levels) were more likely to receive antidepressants and benzodiazepines that could contribute to chronic mood/emotional instability in BD. Recently, Berger et al, have shown that elevated AL among psychotic patients could be lowered over 3 months with antipsychotic medication.[18] Evidences suggest that lithium determines a decrease in proinflammatory mediators in BD,[47] and that a TNF antagonist (infliximab) reduced the levels of glucose and cholesterols as well as depressive symptoms in treatment-resistant depressive patients with high baseline CRP levels.[48] The associations of AL with increased risk of cardiometabolic, liver and inflammatory disturbances observed in our study add to the evidence that AL may contribute to the multisystemic (neuro)progression frameworks,[35,49,50] and could be useful to objectively assess the efficacy of pharmacological and psychosocial interventions in BD patients.

Limitations of this study include the cross-sectional design, which prevented us from examining directionality between levels of AL, emotional hyper-reactivity, and functioning. Our measurements of biomarkers represent snapshots of the activity of physiologic systems. BALLI is an initial operational measure, which was restricted to the biomarkers that were available in our dataset and based on clinical practice guidelines that may provide a crude measure of biological dysfunction. Although we did not include other typical AL components, such as neuroendocrine (eg, cortisol, epinephrine) and inflammatory (eg, IL-6, TNF-a) markers,[12] these parameters are rarely assayed in routine clinical practice. As such, having an AL index that works without such parameters is more accessible and useful in clinical settings. Mood/behavior as well as AL are not static and change overtime, and also are related to acute mood episodes of mania or depression as well as individual experiences during life (eg, stress, trauma)[36] that were not examined in this research and could eventually be the focus of another study. Big data approaches, in combination with digital technologies to measure psychophysiological and context correlates of mood/behavior in a continuous way, might provide a more detailed understanding of the links between AL, affective instability, and how such fluctuations may correspond with increased chronic inflammation, CVD, diabetes, and accelerated aging, affecting the overall health of BD patients over time. In addition, we assessed BD patients under various therapeutic regimens, which could impact AL levels (eg, blood pressure, triglycerides) as well as mood/emotion regulation (eg, patients with emotional hyper-reactivity were more likely to receive antidepressants).

Strengths of this study include its relatively large cohort of BD patients and the use of robust data-driven approaches to operationalize an AL score, including biomarkers of inflammation and cardiometabolic dysfunction routinely used in clinical practice. Although we could not know the directions of these associations, our findings document that a multisystem composite of biological markers may serve as a marker for mood instability, cardiometabolic risk and functional outcomes in BD patients, and would be better at predicting overall health than individual markers. Our study expands on the previous general AL risk formulation,[20,23] applying mathematical approaches to optimize and build a simple AL score specific for BD. This may contribute for extension of the concept of AL in BD research and clinical practice, as the BALLI can be implemented in more settings using fewer resources. As such, BALLI may be a proxy of an allostatic environmental load as well as a marker of noncommunicable disorders, many of which share blood pressure-CRP-glucose-triglycerides as biomarkers.[51] Our approach is also in line with the RDoC perspective,[34] which advocates for a multidimensional approach including psychophysiological parameters alongside mood-behavior profiles that may provide insights into etiological mechanisms and for identifying individuals at high-risk of further physiological and functional deterioration.

Future studies need to decompose the multi-dynamic interactions between allostatic processes associated with BD. In this endeavor, metabolomic approaches,[52] models of glucose allostasis,[53] and immune and renin-angiotensin systems pathway analysis[54] as well as the incorporation of biomarkers not currently included in the AL concept (eg, adiponectin, leptin, resistin)[55] may be essential for BD research and clinical practice. Moreover, definition of specific dimensions of BD would facilitate study of the relative benefit of one or a combination of medications in different bio-phenotypes. In contrast to categorical diagnoses, such approaches are more clearly linked to brain circuitry and endophenotypes (eg, anhedonia, type A behavior, cognitive control, and immune-endocrine axis dysfunction),[34] which are more likely to be medication targets.

In conclusion, a multidimensional approach based on a simple AL score (eg, BALLI) and dimensions of behavior (eg, emotional hyper-reactivity) alongside mood is clinically relevant and may contribute for extension of the concept of AL in BD research and clinical practice. Future studies should consider AL parameters to investigate mood/behavioral changes over time among BD patients, which may in turn contribute to our understanding of BD bio-phenotypes and inform the implementation of early, more individualized interventions to improve the health and quality-of-life of these patients.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

DATA AVAILABILITY STATEMENT

Authors elect to not share data. Research data are not shared.

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REFERENCES

1. Hayes JF, Marston L, Walters K, King MB, Osborn DPJJ. Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000–2014. *Br J Psychiatry*. 2017;211(3):175-181.
2. Kessing LV, Andersen PK. Evidence for clinical progression of unipolar and bipolar disorders. *Acta Psychiatr Scand*. 2017;135(1): 51-64.
3. Sylvia LG, Shelton RC, Kemp DE, et al. Medical burden in bipolar disorder: findings from the Clinical and Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder study (Bipolar CHOICE). *Bipolar Disord*. 2015;17(2):212-223.
4. Amann BL, Radua J, Wunsch C, König B, Simhandl C. Psychiatric and physical comorbidities and their impact on the course of bipolar disorder: A prospective, naturalistic 4-year follow-up study. *Bipolar Disord*. 2017;19(3):225-234.
5. Goldstein BI, Carnethon MR, Matthews KA, et al. Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2015;132(10):965-986.
6. Vancampfort D, Stubbs B, Mitchell AJ, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: A systematic review and meta-analysis. *World Psychiatry*. 2015;14(3):339-347.
7. McEwen BS. Stress, adaptation, and disease: allostasis and allostatic load. *Ann N Y Acad Sci*. 1998;840(1):33-44.
8. Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proc Natl Acad Sci*. 2001;98(8):4770-4775.
9. Moghaddam B. Stress activation of glutamate neurotransmission in the prefrontal cortex: implications for dopamine-associated psychiatric disorders. *Biol Psychiatry*. 2002;51(10):775-787.
10. McEwen BS. The brain is the central organ of stress and adaptation. *NeuroImage*. 2009;47(3):911-913.
11. Vieta E, Popovic D, Rosa AR, et al. The clinical implications of cognitive impairment and allostatic load in bipolar disorder. *Eur Psychiatry*. 2013;28(1):21-29.
12. Juster R-PP, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neurosci Biobehav Rev*. 2010;35(1):2-16.
13. Picard M, Juster R-P, McEwen BS. Mitochondrial allostatic load puts the "gluc" back in glucocorticoids. *Nat Rev Endocrinol*. 2014;10(5):303-310.

14. Mansur RB, Fries GR, Trevizol AP, et al. The effect of body mass index on glucagon-like peptide receptor gene expression in the post mortem brain from individuals with mood and psychotic disorders. *Eur Neuropsychopharm*. 2019;29(1):137-146..

15. Zalli A, Carvalho LA, Lin J, et al. Shorter telomeres with high telomerase activity are associated with raised allostatic load and impoverished psychosocial resources. *Proc Natl Acad Sci USA*. 2014;111(12):4519-4524.

16. Dargél AA, Roussel F, Volant S, et al. Emotional hyper-reactivity and cardiometabolic risk in remitted bipolar patients: A machine learning approach. *Acta Psychiatr Scand*. 2018;138(4):348-359.

17. Rosenblat JD, McIntyre RS. Bipolar Disorder and Inflammation. *Psychiatr Clin North Am*. 2016;39(1):125-137.

18. Berger M, Juster R-P, Westphal S, et al. Allostatic load is associated with psychotic symptoms and decreases with antipsychotic treatment in patients with schizophrenia and first-episode psychosis. *Psychoneuroendocrinology*. 2018;90:35-42.

19. Juster R-P, Marin M-F, Sindi S, et al. Allostatic load associations to acute, 3-year and 6-year prospective depressive symptoms in healthy older adults. *Physiol Behav*. 2011;104(2):360-364.

20. Juster RP, Sasseville M, Giguère CÉ, Consortium S, Lupien SJ Elevated allostatic load in individuals presenting at psychiatric emergency services. *J Psychosom Res*. 2018;115(April):101-109.

21. Nugent KL, Chiappelli J, Rowland LM, Hong LE. Cumulative stress pathophysiology in schizophrenia as indexed by allostatic load. *Psychoneuroendocrinology*. 2015;60:120-129.

22. Beckie TM. A Systematic Review of Allostatic Load, Health, and Health Disparities. *Biol Res Nurs*. 2012;14(4):311-346.

23. Nobel L, Roblin DW, Becker ER, Druss BG, Joski PI, Allison JJ Index of cardiometabolic health: a new method of measuring allostatic load using electronic health records. *Biomarkers Biochem Indic Expo Response, Susceptibility to Chem*. 2016:1-9.

24. Hawken ER, Brietzke E, Soares CN. Intra - individual variability in animal models of bipolar disorder. *Int J Bipolar Disord*. 2019;7(1):4-5.

25. Malhi GS, Irwin L, Hamilton A, et al. Modelling mood disorders: An ACE solution? *Bipolar Disord*. 2018;20:4-16.

26. Judd LL, Akiskal HS, Schettler PJ, et al. The Long-term Natural History of the Weekly Symptomatic Status of Bipolar I Disorder. *Arch Gen Psychiatry*. 2002;59(6):530.

27. Vieta E, Berk M, Schulze TG, et al. Bipolar disorders. *Nat Rev Dis Prim*. 2018;4(1):18008.

28. Gruber J, Harvey AG, Purcell A. What goes up can come down? A preliminary investigation of emotion reactivity and emotion recovery in bipolar disorder. *J Affect Disord*. 2011;133(3):457-466.

29. Phillips ML, Ladouceur CD, Drevets WC. Drevets WC. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Mol Psychiatry*. 2008;13(9):833-857.

30. Gross JJ. The emerging field of emotion regulation: An integrative review. *Rev Gen Psychol*. 1998;2(3):271-299.

31. Henry C, Mbailara K, Mathieu F, Poinsot R, Falissard B. Construction and validation of a dimensional scale exploring mood disorders: MAThyS (Multidimensional Assessment of Thymic States). *BMC Psychiatry*. 2008;8(1):82.

32. Dargél AA, Godin O, Etain B, et al. Emotional reactivity, functioning, and C-reactive protein alterations in remitted bipolar patients: clinical relevance of a dimensional approach - draft. *Aust New Zeal J Psychiatry*. 2017;51(8):788-798.

33. Dargél A, Volant S, Saha S, et al. Activation Levels, Cardiovascular Risk, and Functional Impairment in Remitted Bipolar Patients: Clinical Relevance of a Dimensional Approach. *Psychother Psychosom*. 2019;88(1):45-47.

34. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. 2010;167(7):748-751.

35. Kapczinski F, Vieta E, Andreazza AC, et al. Allostatic load in bipolar disorder: Implications for pathophysiology and treatment. *Neurosci Biobehav Rev*. 2008;32(4):675-692.

36. McEwen BS. Mood disorders and allostatic load. *Biol Psychiatry*. 2003;54(3):200-207.

37. Schulkin J, Gold PW, McEwen BS. Induction of corticotropin-releasing hormone gene expression by glucocorticoids: implication for understanding the states of fear and anxiety and allostatic load. *Psychoneuroendocrinology*. 1998;23(3):219-243. http://www.ncbi.nlm.nih.gov/pubmed/9695128. Accessed July 20, 2019.

38. Koob GF. Alcoholism: allostasis and beyond. *Alcohol Clin Exp Res*. 2003;27(2):232-243.

39. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version*, Patient edn. New York: Biometrics Research, New York State Psychiatric Institute; 2002.

40. Rosa AR, Reinares M, Amann B, et al. Six-month functional outcome of a bipolar disorder cohort in the context of a specialized-care program. *Bipolar Disord*. 2011;13(7–8):679-686.

41. Bizik G, Picard M, Nijjar R, et al. Allostatic load as a tool for monitoring physiological dysregulations and comorbidities in patients with severe mental illnesses. *Harv Rev Psychiatry*. 2013;21(6):296-313.

42. Greiner M, Pfeiffer D, Smith RD. Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. *Prev Vet Med*. 2000;45(1–2):23-41. http://www.ncbi.nlm.nih.gov/pubmed/10802332. Accessed July 20, 2019.

43. Davis J, Maes M, Andreazza A, McGrath JJ, Tye SJ, Berk M. Towards a classification of biomarkers of neuropsychiatric disease: from encompass to compass. *Mol Psychiatry*. 2015;20(2):152-153.

44. Karlamangla AS, Singer BH, McEwen BS, Rowe JW, Seeman TE. Allostatic load as a predictor of functional decline. MacArthur studies of successful aging. *J Clin Epidemiol*. 2002;55(7):696-710. http://www.ncbi.nlm.nih.gov/pubmed/12160918. Accessed July 20, 2019.

45. Hsuchou H, Kastin AJ, Mishra PK, Pan W. C-Reactive Protein Increases BBB Permeability: Implications for Obesity and Neuroinflammation. *Cell Physiol Biochem*. 2012;30(5):1109-1119.

46. Felger JC, Li Z, Haroon E, et al. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. *Mol Psychiatry*. 2016;21(10):1358-1365.

47. Manchia M, Rybakowski JK, Sani G, et al. Lithium and bipolar depression. *Bipolar Disord*. 2019;21(5):458-459.

48. Bekhbat M, Chu K, Le N-A, et al. Glucose and lipid-related biomarkers and the antidepressant response to infliximab in patients with treatment-resistant depression. *Psychoneuroendocrinology*. 2018;98:222-229.

49. Grande I, Magalhães PV, Kunz M, Vieta E, Kapczinski F. Mediators of allostasis and systemic toxicity in bipolar disorder. *Physiol Behav*. 2012;106(1):46-50.

50. Frank E, Nimgaonkar VL, Phillips ML, Kupfer DJ. All the world's a (clinical) stage: rethinking bipolar disorder from a longitudinal perspective. *Mol Psychiatry*. 2015;20(1):23-31.

51. O'Neil A, Jacka FN, Quirk SE, et al. A shared framework for the common mental disorders and Non-Communicable Disease: key considerations for disease prevention and control. *BMC Psychiatry*. 2015;15(1):15.

52. Pedrini M, Cao B, Nani JVS, et al. Advances and challenges in development of precision psychiatry through clinical metabolomics on mood and psychotic disorders. *Prog Neuro-Psychopharmacology Biol Psychiatry*. 2019;93:182-188.

53. Stumvoll M, Tataranni PA, Stefan N, Vozarova B, Bogardus C. Glucose Allostasis. *Diabetes*. 2003;52(4):903-909.

54. Smith AK, Maloney EM, Falkenberg VR, Dimulescu I, Rajeevan MS. An angiotensin-1 converting enzyme polymorphism is associated

with allostatic load mediated by C-reactive protein, interleukin-6 and cortisol. *Psychoneuroendocrinology.* 2009;34(4):597-606.

55. Guo M, Li C, Lei Y, Xu S, Zhao D, Lu XY. Role of the adipose PPARÎ 3-adiponectin axis in susceptibility to stress and depression/anxiety-related behaviors. *Mol Psychiatry.* 2017;22(7):1056-1068.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.