

Article

Machine Learning-Assisted Identification of Biomarkers Associated with Schizotypal and Cyclothymic Traits

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Abstract

Introduction: Schizotypal traits (unusual perceptual experiences and cognitive-perceptual differences) and cyclothymic traits (mood instability and affective fluctuations) represent subclinical personality dimensions observed in non-clinical populations. Allostatic load (AL), reflecting cumulative multisystem physiological stress, may provide insight into biological processes associated with these traits. This study examined whether individuals with elevated schizotypy or cyclothymic traits show distinct AL-related biomarker patterns. **Methods:** Three groups were defined using validated psychometric measures: 30 individuals with schizotypy traits (PSF), 25 with cyclothymic traits (CF), and 30 control participants (CGs). Machine learning (ML) analyses included a Random Forest model with leave-one-subject-out cross-validation to examine differences in biomarker profiles between groups, and Shapley Additive exPlanations (SHAP) analysis was applied to determine the relative importance of biomarkers. The highest-ranking biomarkers were subsequently used to construct a reduced AL index. **Results:** Significant differences among groups were observed in oxidative stress system markers ($p = 0.014$). SHAP analysis identified creatinine, diastolic blood pressure, uric acid, and low-density lipids as key features for the CF group, and heart rate, TSH, uric acid, and glucose for the PSF group, with uric acid emerging as the strongest shared biomarker. A reduced biomarker panel selected using SHAP achieved subject-level classification accuracy of 63.6% (95% CI 50.9–76.4) and AUC of 0.625 (95% CI 0.469–0.768) and showed comparable performance to the full model. However, label-permutation testing yielded a borderline result ($p = 0.055$), indicating that these findings should be considered exploratory. The AL index derived from the top-ranked biomarkers was significantly lower in the CF than in the CG group ($p = 0.007$), whereas differences between the PSF and CG groups did not remain significant after correction. **Findings are exploratory and require validation in an independent cohort. Conclusions:**



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Distinct biomarker patterns associated with schizotypal and cyclothymic traits were identified in a non-clinical population, highlighting differences in stress-related physiological processes. ML-based feature-importance analysis identified a reduced set of biomarkers associated with trait-related biological profiles; however, these findings remain exploratory and require external validation.

Keywords: allostatic load; biomarkers; psychiatric traits; machine learning

1. Introduction

Personality traits related to unusual perceptual experiences and mood instability can be observed in the general population without reaching the threshold of psychiatric disorders. Schizotypal traits, characterised by atypical perceptual experiences, cognitive-perceptual differences, and interpersonal difficulties, and cyclothymic traits, characterised by fluctuations in mood, energy and activity, represent dimensional personality characteristics that have been widely studied in non-clinical populations [1–3]. These traits reflect variations across social, emotional, cognitive, and behavioural systems that do not meet diagnostic criteria for mental health disorders, but may still be associated with measurable psychological and biological differences [3–5].

Previous research has shown that schizotypal traits represent dimensional personality characteristics within the general population and have been widely studied as a valid putative phenotypic indicator for psychosis-spectrum disorders [6,7]. Epidemiological research supports a continuum model of psychosis in which psychotic-like experiences occur in the general population without necessarily progressing to clinical disorder (Figure 1) [8,9].

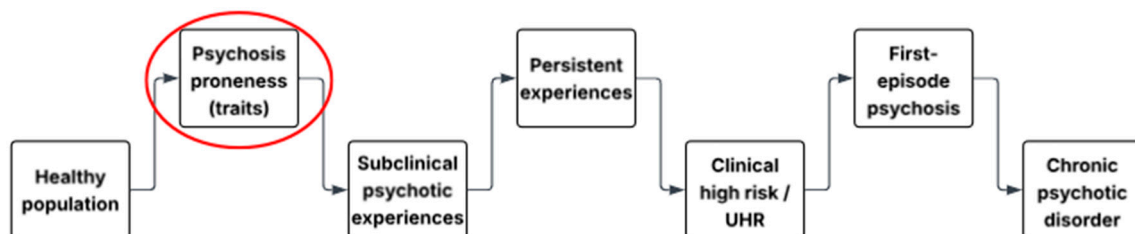


Figure 1. Schematic representation of the psychosis continuum, illustrating the progression from the healthy population through psychosis proneness (trait-level variation) and subclinical psychotic experiences to persistent symptoms, clinical high-risk (UHR) states, first-episode psychosis, and chronic psychotic disorders. The red, highlighted section indicates the trait-based stage examined in the present study.

Evidence from meta-analyses suggests that subclinical psychotic experiences occur in approximately 5–7% of the general population, although the majority (75–90%) are transient and disappear over time [10,11]. Only a small proportion of individuals with such experiences develop persistent symptoms, and an even smaller fraction progresses to clinical psychotic disorders [9,11]. Within this continuum framework, schizotypal traits are thought to reflect stable personality dimensions associated with variations in social, emotional and cognitive functioning rather than a clinical high-risk state for psychosis. Studies have also shown that individuals with elevated schizotypal traits may exhibit subtle similarities to schizophrenia-spectrum conditions in domains such as language processing, neurocognition, and eye-movement control, although typically at a less severe level [5,12].

Comparable dimensional approaches have been applied to affective traits related to cyclothymic features. Cyclothymic traits assessed through self-report questionnaires

capture subclinical characteristics associated with the bipolar spectrum, but at levels that do not meet diagnostic criteria for bipolar disorder. These traits may include depressive mood, mood swings, anxiety, racing thoughts, and irritability [13–15]. Such traits are often conceptualised as temperamental variations, such as cyclothymic temperament, rather than indicators of imminent illness. Although such traits do not represent a prodromal state per se, previous research suggests that bipolar disorder is often preceded by a prolonged period of subthreshold mood symptoms and behavioural changes that may extend over a decade [16,17], with some studies indicating cyclothymic traits as early as 9 years old [18]. Delays in starting treatment have been associated with higher subsequent morbidity [19], and treatment response is better in the early course of the disorder [20]. These observations have contributed to growing interest in identifying trait-based markers and early phenotypic indicators that may help characterise biological processes associated with mood and psychosis-related dimensions [21]. One key component of this approach is identifying individuals who exhibit early vulnerability markers (e.g., schizotypal or cyclothymic traits) as well as those experiencing prodromal symptoms that may precede the onset of a psychiatric disorder [21,22]. In the present study, however, schizotypal and cyclothymic traits are examined specifically as questionnaire-derived dimensions within a non-clinical population rather than as clinical diagnoses or prodromal syndromes.

The role of stress, ranging from early childhood adversities to challenges during adolescence and ongoing daily stressors, has been consistently shown as a central factor in the pathophysiology of psychotic disorders [23–26]. These stressors are known to interact with neurodevelopmental processes and genetic vulnerabilities, potentially contributing to the onset and progression of the disorder. Given the complex relationship between psychosocial stress and biological systems, there is a growing interest in identifying biomarkers that reflect cumulative stress and physiological dysregulation. Employing an approach that captures various stress-related alterations across multiple biological systems, such as the neuroendocrine, immune, cardiovascular, and metabolic systems, may be particularly useful. This is especially relevant in individuals with either schizotypy or bipolarity traits, which may offer ways to identify predictive, mechanistically relevant biomarkers.

It has been proposed that the allostatic load (AL) concept may help operationalise the multisystem alterations related to chronic stress [27–29]. The term “allostasis” as described by McEwen and Stellar [30] refers to the adaptive processes activated in response to external stimuli, including stressful experiences. These processes release hormones, neurotrophins, oxidative stress markers, neurotransmitters, and proinflammatory cytokines [31,32]. Short-term activation of these processes is essential for survival (via the fight-or-flight response). However, chronic activation of the stress-responsive biological systems or the inability to turn off this activation may result in systemic dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, the autonomic nervous system, inflammatory mediators, and mitochondrial/metabolic functions [28,33]. This concept has been operationalised in the form of the AL index to capture the stress-related changes in various biological processes as a combined score indicating multi-system dysregulation [28,34,35]. In the present study, the biomarker panel was selected to represent multiple physiological systems commonly incorporated into AL models rather than to serve as disorder-specific biomarkers of psychosis or bipolar disorder. The panel included cardiovascular, metabolic, endocrine, renal, oxidative, and immune markers that have previously been linked to physiological adaptation and cumulative stress-related dysregulation. Measures such as blood pressure, glucose, lipid parameters, creatinine, estimated glomerular filtration rate (eGFR), transferrin, thyroid function indices, and oxidative stress markers were therefore considered collectively as indicators of multisystem physiological functioning. Within the allostatic load framework,

the combined pattern across these biomarkers is considered more informative than any individual marker in isolation.

Elevated AL has been consistently reported in individuals with psychotic disorders, including both first-episode and chronic schizophrenia and bipolar disorder [36–38]. However, it remains unclear whether similar alterations are present in otherwise healthy individuals who exhibit schizotypal or cyclothymic-related personality traits. Existing studies have primarily focused on stress-related biomarkers of physiological dysregulation associated with psychotic-like experiences and schizotypal traits in non-clinical populations [12,39], rather than on composite indices, such as AL. In the present study, these traits were assessed using validated questionnaire-derived thresholds and therefore represent subclinical personality or temperamental characteristics rather than clinical prodromal states. Examining AL in individuals with elevated schizotypy or cyclothymic traits may help identify biological correlates of subclinical expressions of these dimensions.

This study aimed to examine whether biomarker profiles can differentiate individuals in a non-clinical population who report elevated schizotypy or cyclothymic traits from those with lower trait levels. Participants were classified, based on thresholds derived from validated psychometric instruments, into three groups: a Positive Schizotypy Factor Group (PSF), a Cyclothymia Factor Group (CF), and a Control Group (CG). Using these questionnaire-defined trait groups, we applied machine learning (ML) methods to assess whether biomarker data could classify individuals based on their current trait expression. By integrating psychometric measures with ML approaches, this study seeks to improve understanding of biological correlates associated with schizotypy and cyclothymic trait dimensions in non-clinical populations.

2. Materials and Methods

2.1. Study Design

This study had the overall aim of examining biological correlations associated with elevated schizotypy and bipolarity traits in a non-clinical population, using a comprehensive set of biomarkers, including actigraphy (monitoring rest and activity cycles), electroencephalography, eye-tracking, cognitive neurophenomenological assessments, self-experience assessments, and stress-related laboratory assessments to quantify allostatic load. The study was approved by the University of Szeged, Szent-Györgyi Albert Clinical Centre, Regional Scientific and Research Ethics Committee for Human Biomedical Sciences (Reg. Number: 267/2018-SZTE and date of approval 26 February 2019). In this paper, we report on the links between the premorbid latent liability and allostatic load. Initial actigraphy results and the detailed study protocol have been published previously by Nagy, Dombi [40].

2.2. Questionnaires for At-Risk Identification

The following questionnaires were used for screening individuals and have demonstrated satisfactory psychometric properties in previous validation studies: the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Auto questionnaire (TEMPS-A), a self-reporting questionnaire that assesses the five affective temperaments: hyperthymic, anxious, irritable, cyclothymic, and depressed [41], which showed good internal consistency and construct validity [42,43]. The 43-item Hungarian version of the shortened Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) was used [44] to assess schizotypal personality traits. This version has demonstrated an appropriate four-factor structure and validity on the schizophrenia–schizotypy continuum [44]. The short version consists of four scales: Unusual Experiences, Introverted Anhedonia, Impulsive Nonconformity [45], and Cognitive Disorganisation. The Delusions Inventory (PDI) [46], comprising

40 questions on various types of delusions, was used to assess delusions in the general population and has demonstrated high reliability and validity in non-clinical populations. To screen for cyclothymic personality traits, the Mood Disorder Questionnaire, a self-reporting questionnaire, was used [47]. The MDQ has shown good screening performance for bipolar spectrum disorders, with reported sensitivity of 73% and specificity of 90% [47]. The Clinician Version of the Structured Clinical Interview for DSM-5 (SCID-5) was used to diagnose current and lifetime mental disorders, such as mood, psychotic, substance use, anxiety, obsessive-compulsive, eating, somatic symptoms, sleep, externalising, trauma-related, and stressor-related disorders [48].

2.3. Participant Selection and Group Formation

The subjects were selected from a pool of healthy university students ($n = 710$), aged 18–25 years, attending the University of Szeged, Hungary, who had not been diagnosed with a mental disorder during their first two years of study. Based on predefined inclusion criteria, 182 students met the preliminary eligibility requirements. After applying exclusion criteria, including current or past psychiatric disorders assessed using the Structured Clinical Interview for DSM-5 (SCID-1/2), substance abuse, neurological conditions, head trauma with loss of consciousness, and medical conditions affecting neurocognitive functioning, 87 participants remained eligible for group formation. Following a face-to-face diagnostic interview, two additional individuals were excluded due to the presence of an acute mental disorder, resulting in 85 participants included in the final analysis. Participants were then tested using the questionnaires described above to form three subgroups: a Positive Schizotypy Factor Group (PSF; latent tendency toward schizotypy), a Cyclothymia Factor Group (CF; latent tendency toward bipolarity), and a Control Group (CG). Figure 2 illustrates the full screening procedure for forming the three subgroups: PSF ($n = 30$), CF ($n = 25$), and CG ($n = 30$).

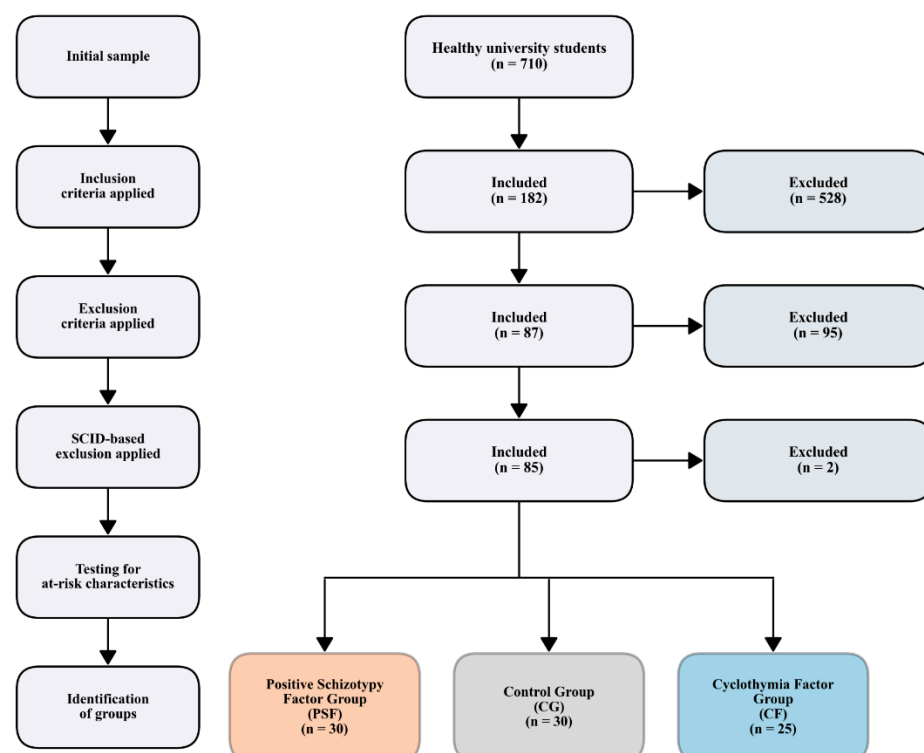


Figure 2. The initial sample ($n = 710$) underwent inclusion and exclusion criteria before psychometric testing for at-risk characteristics, which identified 30 individuals with positive schizotypy traits, 25 individuals with bipolarity traits, and 30 control individuals.

The inclusion and exclusion criteria for each group were described in detail in the publication by Nagy, Dombi [40]. Briefly, the PSF group consisted of participants with O-LIFE ≥ 5 , PDI-21 > 10 , and TEMPS-A Cyclothymia scores < 12 . The group showed higher values on the O-LIFE and PDI scales, indicating increased psychopathological risk, while the TEMPS-A scale remained within the normal range. In contrast, the CF group had O-LIFE < 6 and TEMPS-A Cyclothymia = 11, with lower O-LIFE and PDI scores and higher TEMPS-A scores compared to the CG, suggesting emotional instability, but without a high level of psychopathological risk. The CG showed no psychopathological deviations, and their scores remained within the normal range [40]. For ML training and analysis, the CG subjects were assigned the label “0”, and the PSF or CF subjects were assigned the label “1”.

2.4. The Allostatic Load Index

Biomarkers were selected a priori to represent major physiological systems commonly incorporated into allostatic load models (cardiovascular, metabolic, endocrine, renal, oxidative, and nutritional domains) rather than as disorder-specific biomarkers. This study used 21 biomarkers representing eight biological systems, including (1) the anthropometric system using Body Mass Index (BMI); (2) the cardiovascular system using systolic and diastolic blood pressure and heart rate; (3) the glucose metabolism system using glucose and glycosylated haemoglobin (HbA1c); (4) the immune system using C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-12 (IL-12), and albumin; (5) the lipid metabolism system using total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, total protein; (6) the neuroendocrine system using cortisol and thyroid stimulating hormone (TSH); (7) the oxidative system using uric acid and transferrin; and (8) the renal system using creatinine and glomerular filtration rate (eGFR) [35,49].

The AL index was calculated using the “norm allostatic load index” approach, which scores each biomarker using quartiles (i.e., upper or lower quartiles depending on whether low or high values confer a greater risk for health) based on the clinical practice values for each biomarker [35]. Each biomarker was assigned a score of 0 (normal value) or 1 (above the 75th percentile or below the 25th percentile, depending on the biomarker’s risk ranking). Scores were then summed together for a total score ranging from 0 to 21. Higher AL total scores indicate more profound physiological dysregulation.

2.5. Data Analysis and Machine Learning

All statistical analyses and data processing were conducted using R version 4.6.1. Three binary classification machine learning models were constructed using the Random Forest (RF) algorithm [50]. The machine learning component of this study was designed primarily for biomarker feature-importance analysis rather than predictive model deployment. The analytical framework followed methodological principles [51] which emphasise the use of machine learning for stable feature ranking in small biomedical datasets. Within this framework, model interpretability and stability of feature-importance rankings were prioritised over predictive performance metrics. RF is used here as a non-linear feature-attribution engine, not as a clinical predictor. SHAP values are the primary outcome, and classification metrics (accuracy, AUC, sensitivity, specificity, F1) are reported only to demonstrate that the model is exploiting signal rather than noise. We make no claim of generalizable predictive performance, and the bipolar- and schizotypy-trait separations that follow should be read as hypothesis-generating biomarker discovery, rather than as a clinical decision-support tool.

Although RF supports multi-class classification, separate binary models were implemented to facilitate clearer interpretation of biomarker contributions associated with specific fatigue phenotypes. Binary comparisons allow feature importance and SHAP

values to be interpreted relative to a single class boundary, whereas multi-class models may distribute feature importance across multiple competing boundaries. Accordingly, the first model classified the CG from the CF group, the second classified the CG from the PSF group, and the third classified the CF group from the PSF group.

RF constructs multiple decision trees using bootstrap samples randomly drawn with replacement from the training data. For each tree, a random subset of features (biomarkers) is used to determine optimal node splits. Final predictions are obtained by aggregating tree outputs using majority voting. RF was selected because it provides robust estimation of feature importance while accommodating non-linear relationships and interactions among biomarkers. A single RF architecture was used across all analyses to avoid model selection bias and ensure comparable feature-importance rankings. No data preprocessing was required, and all observations were complete. Before model training, a covariance matrix was calculated to examine relationships among the 21 biomarkers. No strong correlations ($r > 0.8$) were detected, indicating an absence of problematic collinearity and suggesting that each biomarker contributed unique information to the models.

Given the limited cohort size, leave-one-subject-out (LOSO) cross-validation was used to evaluate model robustness. In each iteration, the model was trained on data from all subjects except one, which served as the test observation. This process was repeated until each subject had been used once as the test set. LOSO maximises the amount of training data in each fold while preserving subject-level independence and is commonly recommended when independent validation cohorts are unavailable. The primary aim is exploratory biomarker discovery.

As group sizes were relatively similar (25–30 participants), no oversampling, under-sampling, or class weighting was applied. Default Random Forest hyperparameters were used throughout. We deliberately did not tune hyperparameters on this small dataset to avoid the optimistic bias that arises from selecting hyperparameters on the same data used for SHAP attribution, consistent with the observation that RF defaults are competitive without tuning for feature-attribution use cases [52]. With 21 features, each split considers a random subset of approximately 4–5 features, which acts as a structural regularizer.

Feature importance was evaluated using SHapley Additive exPlanations (SHAP), which estimates the contribution of each feature to model predictions by comparing model outputs with and without that feature across different feature combinations [53]. In the present analysis, SHAP values were aggregated across all leave-one-subject-out (LOSO) trials and all subjects, irrespective of whether the held-out subject was classified correctly. This full-cohort aggregation was adopted as the primary SHAP analysis to avoid survivorship bias that may arise when restricting analyses to correctly classified subjects only. As a sensitivity analysis, SHAP values were additionally computed using only the subset of correctly classified subjects reported previously (first model: 19 CG and 19 PSF participants; second model: 21 CG and 10 CF participants). The resulting feature rankings showed strong agreement with the full-cohort analysis (Spearman's ρ : CG vs. Bipolar = 0.961; CG vs. Schizophrenia = 0.935; Schizophrenia vs. Bipolar = 0.982; Top-10 reduced model = 0.952; Top-6 reduced model = 1.000). Furthermore, overlap among the five highest-ranked features was at least 3/5 across all comparisons, and the top-ranked feature remained unchanged in every model. Detailed feature-rank tables for each pipeline are provided in Table S2.

Because group sizes were relatively similar (25–30 participants), no oversampling, undersampling, or class weighting was applied. Hyperparameter tuning was also avoided to reduce the risk of overfitting to individual subjects during cross-validation. Default parameters were therefore used to ensure that model behaviour reflected generalisation across subjects rather than optimisation to specific observations.

Feature importance was evaluated using SHapley Additive exPlanations (SHAP), which estimates each feature's contribution to model predictions by comparing model outputs with and without that feature across possible feature combinations [53]. SHAP analysis focused on subjects for whom model predictions were stable across cross-validation folds. Subjects for whom the first or second models failed to correctly predict the assigned label at least once were excluded from feature importance calculations to reduce noise arising from unstable predictions. Following this filtering step, the first model retained 19 CG and 19 PSF subjects, and the second model retained 21 CG and 10 CF subjects for feature importance analysis.

To evaluate the stability of feature importance estimates, the modelling and SHAP analysis procedure was repeated multiple times with different random seeds, and importance values were aggregated across iterations to produce final feature rankings for the 21 biomarkers [51]. Spearman correlation analysis was subsequently performed using biomarker data from subjects for whom the corresponding model produced at least one correct prediction, and these correlations were interpreted alongside the ML-derived feature rankings.

Features were then reduced to the ten highest-ranked biomarkers for each model, and the modelling procedure was repeated using this reduced feature set to assess consistency of feature-importance rankings. The third model was subsequently trained using the top ten features to classify latent bipolar subjects from latent schizophrenia subjects, with feature importance again determined using SHAP.

Robustness of the reduced-panel result was assessed both by repeated LOSO cross-validation (400 trials per subject) and by a label-permutation null. Specifically, the diagnosis label was randomly shuffled across subjects 200 times, and the full Top-10 LOSO procedure was re-run on each shuffle to generate an empirical null distribution of subject-level accuracies. Each null shuffle used a single RF random seed (versus 400 trials for the observed value) to keep total compute tractable; this widens the null distribution and renders the resulting one-sided permutation p -value slightly conservative. Using the results from the three models, the six and ten highest-ranking biomarkers were identified and used to construct two targeted allostatic load indices (AL6 and AL10).

3. Results

3.1. Descriptive Statistics

Based on psychometric measures, participants were classified into three trait-defined groups: 25 individuals with elevated cyclothymic traits (CF group), 30 individuals with elevated schizotypy traits (PSF group), and 30 individuals assigned to the Control Group (CG). There was no significant difference ($p = 0.9$) in sex distribution between the three groups: CG (43% female), PSF (50%), and CF (44%). Significant differences were observed in the "oxidative system" ($p = 0.014$) (Table S1). No significance was found between groups in the anthropometric system ($p = 0.5$), the cardiovascular system ($p = 0.6$), glucose metabolism ($p = 0.7$), the immune system ($p = 0.8$), the lipid metabolism ($p = 0.5$), the neuroendocrine system ($p = 0.4$), or the renal system ($p = 0.4$) between the groups (Table S1).

3.2. Correlation Plot for PSF and CF Groups

Figure 3 illustrates the correlation table of the 21 biomarkers prior to model training.

The correlation matrix analysis revealed that diastolic blood pressure and uric acid exhibited the strongest positive correlations with the PSF group. In contrast, glucose and estimated glomerular filtration rate (eGFR) showed the strongest negative correlations. Interestingly, the CF group displayed the opposite pattern, with the strongest positive correlations observed for glucose and eGFR and the strongest negative correlation for

diastolic blood pressure and uric acid. Overall, biomarkers that were positively correlated with one trait-defined group tended to be negatively correlated with the other. For example, cortisol showed a negative correlation with the CF group and a positive correlation with the PSF group, whereas LDL displayed the opposite pattern.

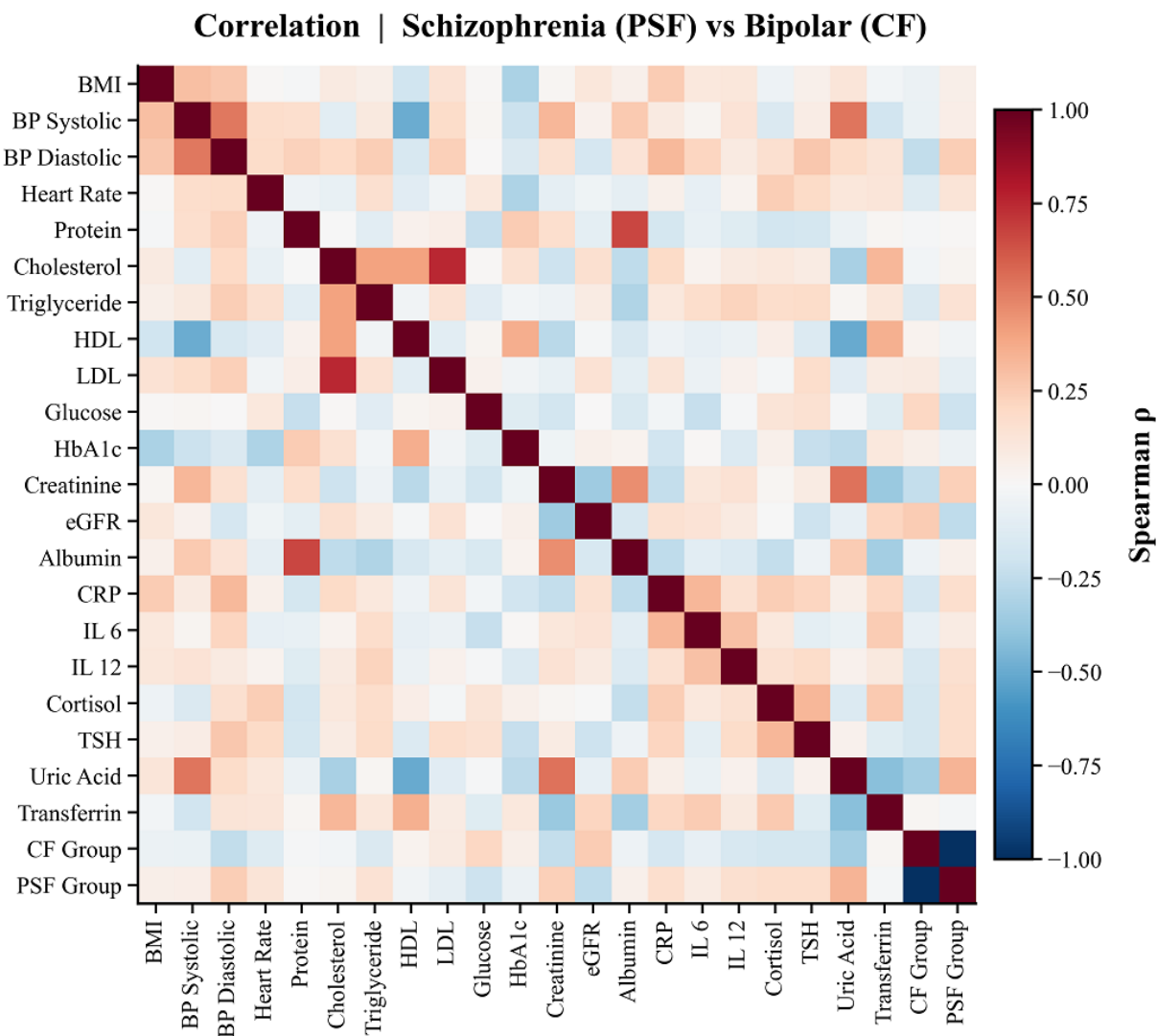


Figure 3. Correlation plot showing the relationships between the 21 biomarkers and group membership variables for the Cyclothymia Factor (CF) and Positive Schizotypy Factor (PSF) groups.

3.3. Feature Importance for Distinguishing Elevated Bipolarity Traits (CF Group)

For the comparison between the bipolarity trait (CF) group and controls, SHAP analysis indicated that creatinine was the most influential biomarker contributing to the differentiation of individuals with elevated bipolarity traits (Figure 4).

In addition, features reflecting cardiovascular (BP diastolic), oxidative stress (uric acid), and metabolism (LDL) were among the most influential features to distinguish the CF group from controls. The direction and magnitude of these feature contributions are presented in Table S2.

3.4. Feature Importance for Distinguishing Elevated Schizotypy Traits (PSF Group)

For the comparison between the CG and the PSF group, SHAP analysis indicated that heart rate was the most influential feature contributing to the differentiation of individuals with schizotypy traits (Figure 5).

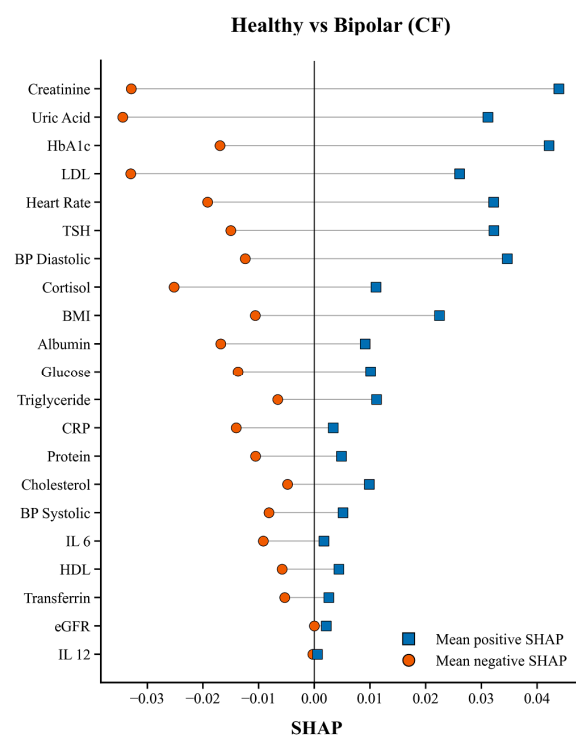


Figure 4. Mean positive (blue squares) and negative (orange circles) SHAP values for features differentiating healthy controls and bipolar disorder (CF). Features are ranked by their contribution to model predictions. Creatinine, uric acid, HbA1c, LDL, and heart rate showed the strongest discriminative effects. Positive SHAP values favour bipolar disorder classification, whereas negative SHAP values favour healthy control classification. The vertical line indicates SHAP = 0.

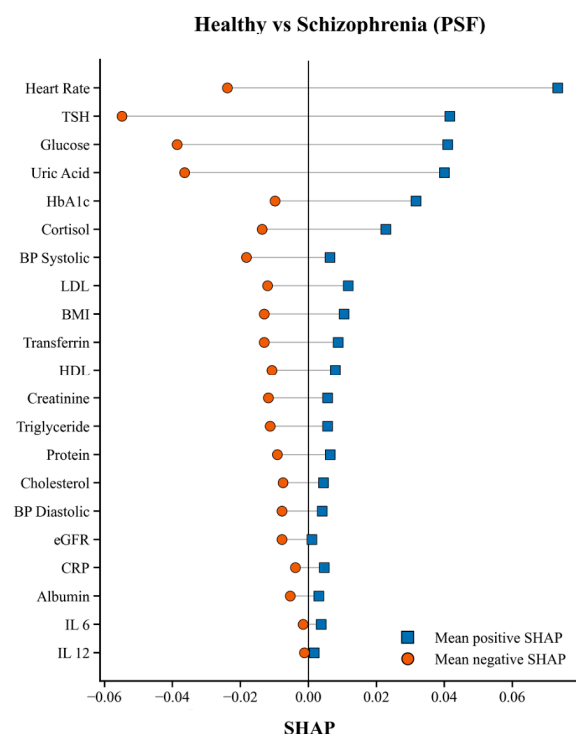


Figure 5. Mean positive (blue squares) and negative (orange circles) SHAP values for features differentiating healthy controls and schizophrenia (PSF). Features are ranked by their contribution to model predictions. Heart rate, TSH, glucose, uric acid, and HbA1c showed the strongest discriminative effects. Positive SHAP values favour schizophrenia classification, whereas negative SHAP values favour healthy control classification. The vertical line indicates SHAP = 0.

In addition, features reflecting neuroendocrine activity (TSH), oxidative stress (uric acid), and glucose metabolism (glucose) were among the most influential features in distinguishing the PSF group from controls. The direction and magnitude of these feature contributions are presented in Table S3.

3.5. Feature Importance for Distinguishing Elevated Schizotypy and Bipolarity Traits (PSF and CF Groups)

Combining the conditions CF and PSF, excluding the CG, we observed that uric acid was the most influential feature for distinguishing CF and PSF traits (Figure 6).

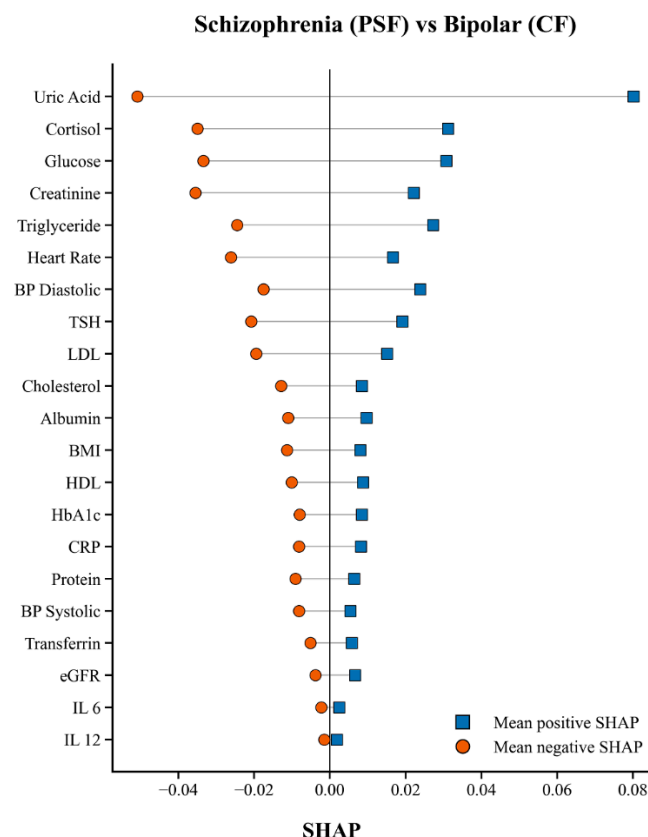


Figure 6. Mean positive (blue squares) and negative (orange circles) SHAP values for features differentiating schizophrenia (PSF) and bipolar disorder (CF). Features are ranked by their contribution to model predictions. Uric acid, cortisol, glucose, creatinine, and triglycerides showed the strongest discriminative effects. Positive SHAP values favour bipolar disorder classification, whereas negative SHAP values favour schizophrenia classification. The vertical line indicates SHAP = 0.

Following this, biomarkers reflecting neuroendocrine activity (cortisol), metabolism (triglycerides), and glucose metabolism (glucose) were among the most influential features for distinguishing the PSF group from the CF group. The direction and magnitude of these feature contributions are presented in Table S4.

3.6. Using the Top Biomarkers to Create the Optimal AL Index

The classification performance of each panel is summarised in Table 1.

The full 21-biomarker PSF-vs-CF model achieved an accuracy of 58.2% (95% bootstrap CI: 45.5–70.9), an AUC of 0.557 (0.396–0.707), a sensitivity of 56.0% (36.0–76.0), a specificity of 60.0% (43.3–76.7), and an F1 score of 0.549 (0.383–0.691). The top-ten panel achieved an accuracy of 63.6%, while the top-six panel achieved an accuracy of 58.2%. Because the reduced panels were selected from the same data on which they were evaluated, an independent label-permutation null distribution was constructed by shuffling the diagnosis

labels 200 times and re-running the top-ten LOSO procedure. The observed accuracy (0.636) exceeded the null mean (0.487 ± 0.084) at a borderline one-sided permutation $p = 0.055$ (Table 2).

Table 1. Subject-level classification metrics under leave-one-subject-out (LOSO) cross-validation with majority voting across 400 Random Forest retrains. Point estimates with 95% bootstrap confidence intervals (2000 stratified resamples preserving class balance). CG = control group; PSF = positive-schizotypy-factor group; CF = cyclothymia-factor group.

Pipeline	Accuracy	AUC	Sensitivity	Specificity	F1
CG vs. CF (21 biomarkers)	0.382 [0.255, 0.491]	0.339 [0.197, 0.488]	0.200 [0.040, 0.360]	0.533 [0.367, 0.700]	0.277 [0.051, 0.383]
CG vs. PSF (21 biomarkers)	0.433 [0.317, 0.550]	0.390 [0.254, 0.534]	0.367 [0.200, 0.533]	0.500 [0.333, 0.700]	0.393 [0.235, 0.533]
PSF vs. CF (21 biomarkers)	0.582 [0.455, 0.709]	0.557 [0.396, 0.707]	0.560 [0.360, 0.760]	0.600 [0.433, 0.767]	0.549 [0.383, 0.691]
PSF vs. CF (Top-10 SHAP panel)	0.636 [0.509, 0.764]	0.625 [0.469, 0.768]	0.560 [0.360, 0.760]	0.700 [0.533, 0.867]	0.583 [0.471, 0.735]
PSF vs. CF (Top-6 SHAP panel)	0.582 [0.455, 0.709]	0.608 [0.456, 0.751]	0.560 [0.360, 0.760]	0.600 [0.433, 0.767]	0.549 [0.391, 0.691]

Table 2. Label-permutation null test for the Top-10 reduced PSF-vs-CF panel. The diagnosis label was randomly shuffled across subjects $n_{perm} = 200$ times, and the full LOSO procedure was re-run on each shuffle to construct an empirical null distribution of subject-level accuracies. Each null shuffle was evaluated with a single RF random seed (versus 400 trials for the observed value), which widens the null distribution and renders the resulting one-sided permutation p -value slightly conservative.

Statistic	Value
Number of permutations	200
Observed subject-level accuracy	0.636
Null distribution mean	0.487
Null distribution SD	0.084
Null distribution maximum	0.727
One-sided permutation p -value	0.055

We interpret this as exploratory evidence that the top-ten panel captures a signal above chance in this cohort, but emphasise that out-of-sample validation in an independent cohort remains an essential next step before any clinical or screening claim.

Based on the feature-importance results from the SHAP models, the AL index was recalculated using the top 6 and top 10 most influential biomarkers for each group (CG, PSF, and CF), as shown in Figure 7A,B.

As the AL index is a bounded ordinal score (range: 0–21), and the Shapiro–Wilk test indicated non-normality in the PSF group ($p = 0.043$; CG: $p = 0.141$; CF: $p = 0.067$), group differences were assessed using a non-parametric approach. Specifically, an omnibus Kruskal–Wallis test was followed by pairwise Mann–Whitney U tests with Bonferroni correction for three comparisons. Descriptive statistics are reported as median [IQR], and effect sizes as Hedges' g (parametric, small-sample corrected) and Cliff's δ (non-parametric).

For the AL index derived from all 21 biomarkers, median [IQR] values were 3.0 [2.0–5.8] for CG, 4.0 [2.2–5.0] for PSF, and 2.0 [1.0–3.0] for CF. The omnibus test indicated significant group differences ($H = 8.793$, exact $p = 0.012$). Pairwise comparisons showed no significant differences between CG and PSF ($p_{Bonf} = 1.000$, Hedges' $g = -0.15$, Cliff's $\delta = -0.10$) or between CG and CF ($p_{Bonf} = 0.144$, Hedges' $g = 0.63$, Cliff's $\delta = 0.31$). In contrast, the PSF–CF comparison remained significant after correction ($p_{Bonf} = 0.007$, Hedges' $g = 0.89$, Cliff's $\delta = 0.47$).

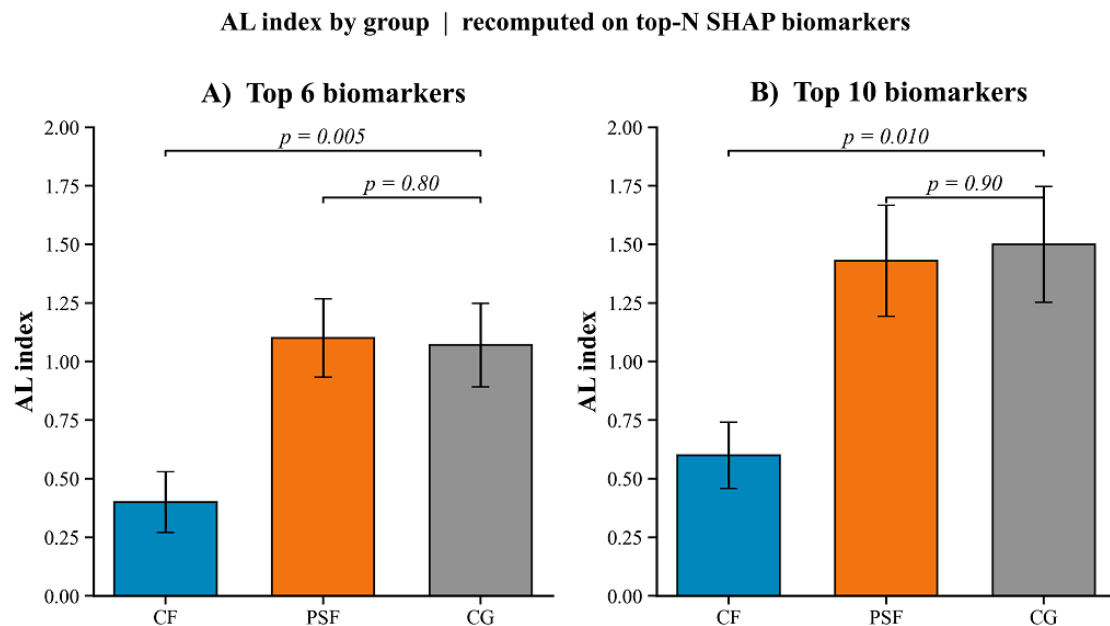


Figure 7. (A) The mean allostatic load index and 95% Confidence Interval (CI) in the groups: Cyclothymic features (CF), psychosis-schizotypy features (PSF), and the Control Group (CG) using the top 6 features. (B) The mean allostatic load index and 95% CI for the groups CF, PSF, and CG using the top 10 features. Significance levels between groups are displayed on the graphs.

4. Discussion

We studied a non-clinical population of university students using self-reported and guided questionnaires to identify individuals with traits of either schizotypy or cyclothymia. The present study demonstrates that individuals with schizotypal (PSF) and cyclothymic (CF) traits exhibit both shared and distinct patterns of physiological variation across AL biomarkers. The correlation analyses and machine learning (ML) feature-importance analyses suggest that these trait-defined groups share a common biological core involving metabolic, neuroendocrine, and oxidative stress-related processes, while differing in the relative organisation and contribution of specific physiological systems.

The most consistent finding across analyses was the importance of uric acid. Correlation analyses identified uric acid as one of the biomarkers most strongly associated with both trait-defined groups, and SHAP analyses further demonstrated that it was among the most influential features distinguishing CF from controls, PSF from controls, and CF from PSF. This suggests that oxidative stress and related inflammatory processes may represent a common systemic biological component underlying both PSF and CF traits. Supporting our findings, previous studies have linked elevated uric acid levels to altered purinergic signalling, neuroinflammation, and oxidative imbalance in both schizophrenia-spectrum and bipolar-spectrum disorders [54–56].

Despite this shared core, the two trait-defined groups displayed markedly different biomarker profiles. Correlation analyses revealed an almost inverse pattern of associations across many biomarkers. For the PSF group, diastolic blood pressure and uric acid showed the strongest positive correlations, whereas these biomarkers were negatively correlated in the CF group. On the other hand, glucose and eGFR demonstrated strong positive correlations with the CF group and negative correlations with the PSF group. This inverse correlation pattern may suggest that the physiological profiles associated with the two personality traits are biologically distinct, with different systems dysregulated. For example, the elevated glucose and eGFR levels observed in the CF group are consistent with metabolic processes previously implicated in bipolar-spectrum conditions [57]. Like-

wise, the prominence of elevated blood pressure and uric acid within the PSF-associated biomarker profile may indicate inflammatory and cardiovascular processes that have been associated with schizophrenia-spectrum disorder [58,59], although the present findings related to trait-defined groups in a non-clinical population. The findings support the emerging understanding that traits in bipolar disorder and schizophrenia, although they share some clinical features, may arise from different pathophysiological pathways [60,61].

The SHAP analyses reinforced this distinction. For cyclothymic traits, the most influential biomarkers included creatinine, uric acid, blood pressure, LDL cholesterol, and total cholesterol. Creatinine is generally associated with renal function, but evidence suggests an important role in systemic metabolic health [62,63]. Altered creatinine levels may serve as a peripheral biomarker of mitochondrial dysfunction and bioenergetic abnormalities that have previously been highlighted in bipolar disorder [64,65]. Another important feature was uric acid, which has been consistently associated with manic episodes and increased impulsivity in bipolar disorder due to its role in oxidative imbalance [54,56]. Also, blood pressure, LDL, and cholesterol were among the highest-ranking features supporting the growing recognition of cardiometabolic dysfunction in mood disorders [66,67].

In contrast, schizotypal traits were most strongly characterised by heart rate, TSH, glucose, and uric acid. Elevated resting heart rate is associated with dysfunction in the autonomic nervous system and could reflect heightened arousal, which has been observed in individuals with schizophrenia-spectrum traits [68]. Another top-ranking feature was TSH, which suggests altered function of the hypothalamic-pituitary-thyroid (HPT) axis. This alteration has previously been implicated in the pathogenesis of psychotic disorders [69,70]. Furthermore, glucose and uric acid were amongst the top-ranking features. Glucose metabolism dysregulation has been convincingly demonstrated by large systematic reviews and meta-analyses in first-episode, never-medicated individuals with psychosis [71]. Overall, these findings suggest that CF and PSF may be associated with differing patterns of multisystem physiological variation [72].

Comparing CF and PSF traits highlights uric acid as the most influential biomarker for predicting the presence of either psychiatric traits. As high levels of uric acid have been linked to neuroinflammation, alteration in purinergic signalling, and increased oxidative stress, all of which are implicated in the pathophysiology of schizophrenia and bipolar disorder, it is not surprising that this biomarker ranks at the top [54,56]. Other top-ranking biomarkers reflected the metabolic (triglycerides and glucose) and neuroendocrine (cortisol) systems. Cortisol has been associated with chronic stress and stress sensitivity, and its importance in this paper highlights the central role of stress response in the emergence of psychiatric symptoms [39,73].

Although critical differences exist between elevated schizotypy or bipolarity traits and clinical psychotic disorders, examining biological correlates of these traits may contribute to understanding mechanisms related to psychosis-spectrum conditions [4,74]. Chronic stress has been implicated in the development and course of psychotic disorders [75,76]. Understanding the relative importance of stress-related biomarkers associated with schizotypy and bipolarity traits may therefore provide insight into physiological processes linked to these. In this context, ML for simultaneously examining the contributions of several biomarkers to the AL index is an emerging and valuable approach. Machine learning methods are increasingly being applied across various areas of medical research, including studies of mental health conditions and biomarker discovery [77,78]. In particular, the use of feature importance measures derived from ML models has recently gained attention as a way to identify biomarkers that contribute most strongly to distinguishing biological or clinical phenotypes [79].

Compared to traditional statistical methods, ML algorithms offer enhanced versatility and predictive power [55]. However, this increase in power is often accompanied by greater model complexity and decreased interpretability of results. The field of XAI, or interpretable machine learning, has emerged to address these challenges. XAI focuses on developing methods to provide post hoc, human-interpretable explanations for machine learning models, enabling validation against known “gold standards” where prior knowledge exists [78].

The ML analyses further demonstrated that a reduced set of 10 biomarkers yielded classification performance comparable to that of the full panel. However, because feature selection and evaluation were performed within the same cohort, this observation should be regarded as exploratory and requires independent validation. To our knowledge, this finding has not been previously reported and may pave the way for the ongoing efforts to establish a consensus on the selection of biomarkers to calculate the AL index. The original AL index by McEwen and Stellar [30] was not proposed as quintessential, but rather as the first attempt to use AL in a population. Since then, numerous studies have added to and revised the selected biomarkers, resulting in substantial variance in the biomarkers used to calculate the AL index [80]. Nevertheless, there is a general agreement that the AL index should include neuroendocrine and immune biomarkers due to their involvement in stress response and adaptation [35]. Notably, the reduced panel included the neuroendocrine biomarkers cortisol and TSH, supporting the view that stress-regulatory systems are central components of allostatic load. In contrast, no immune biomarkers were retained among the most influential features, suggesting that, within this cohort, neuroendocrine and metabolic factors may have contributed more strongly to group differentiation than inflammatory markers.

The interpretation of group differences in allostatic load requires caution. Following non-parametric testing and correction for multiple comparisons, only the PSF–CF comparison remained statistically significant, whereas differences between the control group and either trait-defined group did not survive correction. The observed biomarker patterns should be interpreted as exploratory associations rather than evidence of specific physiological mechanisms. Nevertheless, the finding that biomarker profiles differentiated the two trait-defined groups suggests that schizotypal and cyclothymic traits may be associated with distinct patterns of multisystem physiological dysregulation, a possibility that warrants investigation in larger, independently validated cohorts.

Limitations

Several methodological limitations should be considered when interpreting these findings. First, the relatively small sample size increases the potential risk of model overfitting and limits the generalizability of predictive performance metrics. Although leave-one-subject-out cross-validation reduces information leakage between training and test samples, the ML results should be interpreted as exploratory and hypothesis-generating rather than confirmatory. Second, an independent validation cohort was not available. External validation on larger datasets will therefore be necessary to confirm the patterns of biomarker importance identified in the present study. Third, the primary SHAP analysis aggregates feature attributions across all 400 LOSO trials and all subjects, regardless of prediction correctness, to avoid survivorship bias. A sensitivity analysis using only the previously reported subset of correctly predicted cases is provided in the Table S1B. The two rankings agree closely, demonstrating that the qualitative biomarker conclusions are robust to the choice of subset. Fourth, the analysis used binary comparisons rather than a single multi-class model. This approach was chosen to maximise interpretability of biomarker importance patterns; however, future studies with larger cohorts should explore multi-class

modelling strategies. Another limitation is that factors known to influence AL biomarkers, including menstrual cycle phase, oral contraceptive use, recent physical activity, caffeine and alcohol consumption, smoking behaviour, fasting status, and time of blood sampling, were not systematically assessed. Consequently, residual confounding cannot be excluded, and some of the observed biomarker differences may reflect unmeasured physiological or behavioural variation rather than trait-related biological processes. Future studies should incorporate standardised sampling protocols and adjustment for these variables. Finally, the reduced biomarker-based AL index derived from the ML analysis was evaluated within the same cohort used for feature discovery. Independent validation will therefore be required to determine whether this reduced biomarker index generalises to other patient populations.

5. Conclusions

This study demonstrates the value of combining ML and physiological biomarkers to examine biological differences associated with schizotypy and bipolarity trait expression in a non-clinical population of young adults. By analysing self-reported traits related to schizotypy or bipolarity, we identified distinct and biologically meaningful patterns of multisystem dysregulation across the trait-defined groups. Specifically, distinct biomarker profiles were observed in the CF and PSF groups, suggesting that a unique trait dimension may be associated with distinct physiological processes. Feature importance analysis highlighted uric acid, TSH, cortisol, and glucose markers as key contributors to the AL index, reflecting the involvement of multiple systems in stress-related regulation [72].

Models trained with the ten most influential biomarkers achieved subject-level classification metrics comparable to those of the full 21-biomarker panel under LOSO cross-validation, with confidence intervals overlapping the full-panel intervals. Because the reduced panel was selected on the same cohort, this comparability should be regarded as an internal-consistency check rather than as external validation, and the targeted AL index is best read as a hypothesis-generating candidate for replication and prospective testing in an independent cohort.

Overall, these findings support the use of ML for exploring complex biomarker patterns associated with variation in schizotypy and bipolarity traits and highlight the potential value of physiological markers for understanding stress-related processes in non-clinical populations.

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