Psychoneuroendocrinology 194 (2026) 108000

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Differential associations of inflammatory-metabolic markers with depressive symptom dimensions: Towards a clinical phenotyping of immune-metabolic depression

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ARTICLE INFO

Keywords:
Depression
Biological heterogeneity
Clinical phenotypes
Precision psychiatry

ABSTRACT

Background: Depression is increasingly conceptualized as a biologically heterogeneous condition, with immune-inflammatory and metabolic dysregulation implicated in specific symptom dimensions rather than overall depressive severity. However, it remains unclear whether different combinations of inflammatory and metabolic burden define distinct clinical depressive phenotypes.

Methods: In this cross-sectional multicenter study on major depressive episodes (MDE), inflammatory and metabolic burden were indexed by C-reactive protein (CRP) and a composite continuous metabolic syndrome score (cMetS). Participants were classified into four immune-metabolic profiles based on the combination of high/low CRP status and high/low metabolic burden. Somatic symptoms, anhedonia, subjective cognitive complaints, and objective cognitive performance were assessed using standardized psychometric and neuropsychological measures. Associations were examined using covariance and multivariable regression models, including four-category profiles and CRP-cMetS interaction terms, with sensitivity analyses using continuous biomarkers.

Results: Among 221 patients, immune-metabolic profiles differed for somatic symptoms ($p = 0.001$; $\eta^2p = 0.079$), anhedonia ($p = 0.006$; $\eta^2p = 0.065$), and cognition (Digit-Symbol-Substitution Test [DSST]: $p = 0.039$; $\eta^2p = 0.042$). In regression models, the High CRP/High cMetS group was associated with greater somatic symptom burden ($\beta = 5.10$, $p = 0.001$) and poorer cognitive performance (DSST: $\beta = -7.43$, $p = 0.036$; Trail-Making Test-B: $\beta = 41.44$, $p = 0.008$), whereas the High CRP/Low cMetS profile was selectively associated with

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[1] See Appendix A

https://doi.org/10.1016/j.psyneuen.2026.108000
Received 25 May 2026; Received in revised form 24 July 2026; Accepted 14 August 2026
Available online 23 August 2026
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greater anhedonia (β = 2.93, p < 0.001). Significant CRP×cMetS interactions emerged for anhedonia (p = 0.023). Sensitivity analyses using continuous biomarkers showed convergent results.
Conclusions: These findings suggest that distinct combinations of inflammatory and metabolic burden may characterize partly distinct depressive phenotypes across hedonic, somatic, and cognitive domains, supporting the relevance of integrated immune-metabolic profiling for biologically informed stratification and potentially more targeted therapeutic approaches.

1. Introduction

Major depressive disorder (MDD) is a leading cause of disability worldwide (Lu et al., 2024; WHO, 2025) and is increasingly conceptualized as a biologically heterogeneous condition (Maj et al., 2023) characterized by variability in symptom expression, illness trajectory, and treatment response, and encompassing partially distinct clinical and biological phenotypes (Beckett and Lawson, 2026; Cusack et al., 2024; Nguyen et al., 2022). Such heterogeneity is widely regarded as a major challenge for effective treatment and the development of precision-psychiatry approaches (Maj et al., 2020).

Efforts to stratify depressive disorders have progressively focused on biological mechanisms underlying this heterogeneity (Chiappini et al., 2025; Cusack et al., 2024). Immune-inflammatory alterations, particularly elevated C-reactive protein (CRP), have been associated with depression, although findings based on single biomarkers have shown modest and partly inconsistent effects (Horn et al., 2018; Mac Giollabhui et al., 2021; Pinzi et al., 2025). Since elevated CRP is observed in only 20–30% of patients with MDD (Penninx et al., 2024), inflammation may characterize a distinct depressive phenotype. In parallel, metabolic dysregulation, including central adiposity, dyslipidemia, and impaired glucose metabolism, has been implicated in depression, supporting integrated immune-metabolic models (Alshehri et al., 2023; Liu and Zhai, 2025; Meng et al., 2025).

Within this framework, immune-metabolic depression has been proposed as a subtype characterized by co-occurring low-grade inflammation and metabolic dysregulation (Milaneschi et al., 2020; Penninx et al., 2024). Rather than reflecting a general feature of depression, these alterations appear to map onto specific symptom dimensions, including somatic symptoms, energy-related disturbances, and altered reward processing (Aruldass et al., 2025; Lucido et al., 2021). Cognitive dysfunction represents an additional relevant domain, as deficits in processing speed, attention, and executive functioning are associated with poorer functional outcomes in depression (Culpepper et al., 2017; Kriesche et al., 2023; Rhee et al., 2024). Neurobiologically, inflammatory processes may affect dopaminergic signaling and fronto-striatal/prefrontal circuits involved in motivation and cognitive control (Felger and Treadway, 2017; Joyce et al., 2025; Kocamer Şahin and Aslan, 2024), thereby contributing to both motivational and cognitive disturbances (Wu et al., 2026; Yuan et al., 2026).

Despite these advances, inflammatory and metabolic alterations have mostly been examined in isolation rather than within clinically interpretable immune-metabolic profiles (Milaneschi et al., 2020). Moreover, despite increasing interest in immune-metabolic depression, no consensus currently exists regarding its clinical characterization and boundaries as a depressive subtype (Penninx, 2026). Emerging evidence suggests that inflammatory alterations may show symptom-specific rather than global associations within depression (Milaneschi et al., 2020), whereas combined inflammation and metabolic dysregulation may identify a distinct profile characterized by greater anhedonia and treatment resistance (Zwiep et al., 2026). However, few studies have investigated whether isolated inflammation and combined inflammatory–metabolic burden map onto distinct clinical dimensions — including somatic symptoms, anhedonia, and cognition — across both first-onset and recurrent depressive episodes (Donnelly et al., 2025; Lamers et al., 2020).

The present study examined immune-metabolic heterogeneity in a multicenter sample of patients with major depressive episodes (MDE). Using a classification based on CRP status and metabolic burden, we investigated whether isolated and combined inflammatory-metabolic burden would be selectively associated with distinct clinical dimensions of depression, specifically physical symptomatology, anhedonia, and cognitive functioning. This approach was grounded in the hypothesis that different combinations of inflammatory and metabolic burden may underlie partly distinct depressive phenotypes rather than varying levels of severity within the same diagnostic category (Zwiep et al., 2026).

2. Methods

2.1. Study design and participants

The study was conducted within the SFIDE (Subtyping of First-onset and recurrent Depressive Episodes) multicenter Italian project investigating clinical and biological heterogeneity in depressive disorders. This cross-sectional analysis included baseline data collected across mental health facilities in Northern, Central and Southern Italy (listed in supplementary material), coordinated by the Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario "A. Gemelli" IRCCS (Rome). Participants were recruited from different regions to ensure clinical heterogeneity and enhance representativeness of the Italian population.

Adult patients receiving treatment in outpatient, day-hospital, or inpatient psychiatric settings were screened for inclusion based on the following criteria: age between 18 and 75 years; diagnosis of a MDE according to DSM-5-TR criteria (APA, 2022), including both first-onset and recurrent episodes; a Hamilton Depression Rating Scale – 17 items (HDRS-17) total score ≥ 14, indicating at least moderate depressive severity (Hamilton, 1960); and provision of written informed consent. Exclusion criteria included: chronic depressive episodes lasting ≥ 2 years; current hypomanic/manic symptoms (Young Mania Rating Scale score >12); diagnosis of bipolar, schizophrenia, or other psychotic disorders; neurocognitive disorders or other neurological diseases associated with cognitive decline; current alcohol/substance use disorder (except for nicotine); pregnancy or breastfeeding; body mass index (BMI) < 18.5 kg/m^2 or > 29.9 kg/m^2; and any major medical conditions known to contribute to systemic inflammation, not under maintenance pharmacological treatment (i.e., not in remission and/or with significant alterations of monitoring parameters). These eligibility criteria were adopted to minimize biological confounding (as chronic depression, extreme BMI values, and uncontrolled medical conditions may independently influence immune-inflammatory and metabolic burden), while ensuring consistency across cases and preserving the representativeness of the sample.

2.2. Data collection: psychometric measures

Sociodemographic, clinical, and psychopathological data were collected using standardized clinician-rated and self-report instruments validated in Italian populations.

Physical/energy-related symptoms were assessed using the "Physical Symptoms" subscale of the Hamilton Anxiety Rating Scale (HARS), including items 7 (muscular pain), 8 (sensory), 9 (cardiovascular), 10 (respiratory), 11 (gastrointestinal), 12 (genitourinary) and 13

(autonomic) (Hamilton, 1959; Pepe et al., 2025). This subscale was selected because it provides a more comprehensive assessment of bodily symptoms than the somatic items embedded within the HDRS, and was therefore considered more appropriate for capturing the physical symptom dimension investigated in the present study.

Anhedonia was measured using the self-report Snaith–Hamilton Pleasure Scale (SHAPS; range 0–14), with higher scores indicating greater anhedonia and a commonly used cut-off ≥ 3 for clinically relevant symptomatology (Santangelo et al., 2009; Snaith et al., 1995). In this study, continuous SHAPS scores were used in all statistical analyses.

Cognitive functioning was evaluated using both subjective measures and standardized neuropsychological tests (Strauss et al., 2006). Self-reported cognitive complaints were assessed using the Perceived Deficit Questionnaire-5 (PDQ-D5; range 0–20), where higher scores indicate greater impairment in attention/concentration, planning and organization, retrospective, and prospective memory (Lam et al., 2018). The Digit Symbol Substitution Test (DSST) was administered in its paper-and-pencil 90-second version to assess processing speed, attention, visual scanning, and executive functioning; performance was defined as the number of correct symbols (range: 0–90), with higher scores indicating better performance. Executive functioning and cognitive flexibility were further assessed using the Trail Making Test – Part B (TMT-B), with performance recorded as completion time in seconds, where longer times indicate poorer performance.

Additional assessment included the evaluation of overall depressive and anxiety symptoms through the total score of 17-item HDRS and HARS. All clinician-rated questionnaires were performed by trained clinicians at each participating center according to the standardized SFIDE assessment protocol. The psychometric instruments used in the present sample showed good internal consistency and reliability according to Cronbach's α and McDonald's ω coefficients for the HDRS (α=0.853, ω=0.866), the HARS (α=0.733, ω=0.737), the PDQ-D5 (α=0.893, ω=0.897) and for the SHAPS (α=0.809, ω=0.811).

2.3. Data collection: biological variables and definition of immune-metabolic profiles

At study entry, blood samples – performed after overnight fasting - and anthropometric measurements (i.e., body weight, height, waist circumference and body mass index – BMI) were obtained as part of routine clinical assessment. The following variables were extracted from charts for the evaluation of peripheral inflammatory and metabolic indices: C-reactive protein (CRP), fasting glucose, triglycerides, HDL cholesterol, and waist circumference. The continuous metabolic syndrome score (cMetS) was calculated as the sum of standardized values of waist circumference, triglycerides, and fasting glucose, plus the reversed standardized value of HDL cholesterol, with higher scores indicating greater metabolic risk (Meng et al., 2025). Blood pressure was not included in the index due to inconsistent reporting across the dataset and in line with prior evidence. Confirmatory factor analyses of metabolic syndrome demonstrate that blood pressure typically shows the lowest factor loading among MetS components across diverse populations (Honarvar et al., 2023). Moreover, associations between metabolic syndrome and psychiatric disorders appear more strongly driven by abdominal obesity and dyslipidemia than by blood pressure (Penninx and Lange, 2018; Portugal-Nunes et al., 2021). Consistent with this approach, recent immune-metabolic depression research in clinical MDD samples has similarly operationalized metabolic burden without including blood pressure (Zwiep and Milaneschi, 2025).

Due to the skewed distribution, CRP values were log-transformed (log10CRP) for analyses involving continuous inflammatory parameters. CRP was also dichotomized using the clinically established cut-off of 3 mg/L, widely adopted to define low-grade systemic inflammation in both cardiometabolic (Pearson et al., 2003) and psychiatric research (Osimo et al., 2019; Penninx et al., 2024; Rietberg et al., 2026). Values were obtained using either standard or high-sensitivity assays according to local laboratory protocols; however, given the primary reliance on a binary classification, differences in assay sensitivity are unlikely to have substantially influenced the results. CRP values $>$ 10 mg/L were excluded, as generally indicative of acute inflammatory or infectious processes rather than chronic low-grade inflammation (Moriarity et al., 2023; Sălcudean et al., 2025).

To capture the joint contribution of inflammatory and metabolic dysregulation, an immune-metabolic profile variable was constructed combining CRP status (low CRP $\leq$3 mg/L vs. high CRP $>$3 mg/L) and metabolic burden based on cMetS. Because cMetS is intended as a continuous measure of metabolic burden rather than a diagnostic definition of metabolic syndrome, and no universally accepted clinical threshold is available for the modified formulation adopted in the present study (Khazdouz et al., 2021), participants with relatively higher metabolic burden were identified using the upper tertile of the cMetS distribution (cMetS $>$0.775), while preserving adequate subgroup sizes for statistical comparisons. Combining these two dimensions resulted in four immune-metabolic profiles: Low CRP/Low cMetS, Low CRP/High cMetS, High CRP/Low cMetS, and High CRP/High cMetS. This four-group classification allows differentiation between inflammation-only, metabolic-only, and combined immune-metabolic dysregulation.

2.4. Statistical analysis

Descriptive statistics were used to summarize the demographic, clinical, and psychometric characteristics of the sample. Continuous variables were reported as means and standard deviations, whereas categorical variables were expressed as frequencies and percentages. The analytical sample included participants with complete data on both CRP and cMetS. To exclude potential selection bias, patients with and without complete data were preliminary compared using independent-samples *t*-tests for continuous variables and chi-square tests for categorical variables.

Immune-metabolic profiles were first examined descriptively and compared across demographic and clinical characteristics using one-way analysis of variance (ANOVA) for continuous variables and the Chi-square or Fisher's Exact Test, as appropriate, for categorical variables. Because homogeneity of variance was not always met, Welch ANOVA was used when required (e.g., to examine between-group differences in overall depressive severity). Differences in symptom domains (physical symptomatology, anhedonia, subjective and objective cognitive functioning) across the four immune-metabolic profiles were then explored using separate analyses of covariance (ANCOVA). All models were adjusted for a core set of covariates including age, sex, smoking status, presence of medical comorbidity, MDE type (first-onset or recurrent), HDRS total score, and years of education. Estimated marginal means were calculated and pairwise comparisons were tested using Tukey post-hoc correction. Effect sizes are reported as partial eta squared (η^2p).

To further examine the independent and joint contribution of inflammatory and metabolic dysregulation, multivariable linear regression models were estimated using two complementary approaches with: (1) CRP status (CRP $>$3 mg/L vs. $\leq$3 mg/L), cMetS status (high vs. low cMetS) and their interaction term (CRP $\times$ cMetS) as fixed factors; (2) the four-category immune-metabolic profile as the main factor, to facilitate direct clinical interpretation. These models were adjusted for the same set of covariates described above. If significant between-group differences emerged in the distribution of pharmacological treatments, sensitivity analyses were performed by further adjusting these multivariable regression models for the medication class showing significant differences. To account for potential information loss due to dichotomization, additional sensitivity analyses were performed using continuous log10CRP and cMetS values. Collinearity diagnostics were examined for all regression models using variance inflation factors (VIF), with values $\leq$ 2 considered acceptable (O'Brien, 2007).

Statistical significance was set at a two-tailed p-value < 0.05. All analyses were conducted using IBM SPSS Statistics for Windows, v. 28 (IBM Corp., Armonk, New York, USA).

3. Results

3.1. Demographic and clinical characteristics

First, data from 614 participants were screened. After controlling for inclusion/exclusion criteria, the final analytic sample included 221 patients with complete data on variables of interest. This sample was broadly comparable to the initial cohort in terms of sociodemographic (i.e., age, sex distribution, education) and clinical (i.e., BMI, smoking, depressive episode type, medical comorbidity) characteristics (except for lower HDRS total scores). Participants were recruited from Northern (29.9%), Central (34.4%) and Southern (35.7%) Italy, mainly in an outpatient setting (87.2%). Of them, 45 (20.4%) presented with CRP $>$ 3 mg/L and 73 (33%) with high metabolic burden (i.e., cMetS $>$0.775).

The sample was thus divided into the following immune-metabolic profiles: Low CRP/Low cMetS (56.1%), Low CRP/High cMetS (23.5%), High CRP/Low cMetS (10.9%), and High CRP/High cMetS (9.5%). Continuous distributions of inflammatory and metabolic parameters (including BMI, cMetS, CRP, fasting glucose, HDL cholesterol, triglycerides, and waist circumference) are provided in supplementary material (Table S1).

Overall, participants were predominantly females (66.5%), with more than half being employed (61.1%) and without a current relationship (54.3%). Most patients had completed at least secondary education (high school or higher: 70.1%). At study entry, most participants (94.1%) were receiving ongoing psychopharmacological treatment for the current depressive episode, with antidepressants (95.5%), mood stabilizers (25.3%), antipsychotics (46.6%), sedative-hypnotics/anxiolytics (67.3%), either alone or in combination. Among antidepressant treated patients, 61.6% received selective serotonin reuptake inhibitors (SSRIs), 24.6% serotonin-norepinephrine reuptake inhibitors (SNRIs), 8.5% non-SSRI antidepressants with mechanisms potentially relevant to reward processing (i.e., vortioxetine, bupropion), and 20.9% other antidepressants (i.e., mirtazapine, trazodone, tricyclic antidepressants), while 16.2% received combination antidepressant therapy. Mean antidepressant exposure was 29.6 $\pm$ 16.6 mg/day expressed as fluoxetine-equivalent dose. Only a small proportion was drug-naïve (5%) or drug-free at the time of assessment (0.9%). Regarding psychotherapeutic interventions, 19.8% of participants were currently engaged in psychotherapy, 26.3% reported previous treatments, and 53.9% had never received psychotherapy. Detailed sociodemographic, clinical, and psychometric characteristics are reported in Table 1.

Compared with the other profiles, patients with a combined immune-metabolic profile (High CRP/High cMetS) were characterized by older age, lower educational attainment, more clinician-rated physical symptoms and poorer objective cognitive performance. Regarding overall depressive severity, Welch's ANOVA showed significant differences in HDRS total scores, with post-hoc Tukey comparisons indicating a near-significant difference between the Low CRP/Low cMetS and Low CRP/High cMetS groups (mean difference = 4.27, p = 0.05) and a trend-level difference between the Low CRP/Low cMetS and High CRP/High

Table 1
Sociodemographic, clinical, and psychometric characteristics across profiles.

Characteristics (n, %; M ± SD)	**Total**	**Low CRP / Low cMetS**	**Low CRP / High cMetS**	**High CRP / Low cMetS**	**High CRP / High cMetS**	χ^2/F	p
Overall	221	124 (56.1)	52 (23.5)	24 (10.9)	21 (9.5)		
Sociodemographic data							
Age (years)	47.6 ± 15.4	44.3 ± 15.2	50.2 ± 14.3	49.8 ± 16	59 ± 12.7	8.05	**<0.001**
Gender						11.3	**0.010**
Male	74 (33.5)	37 (29.8)	27 (51.9)	5 (20.8)	5 (23.8)		
Female	147 (66.5)	87 (70.2)	25 (48.1)	19 (79.2)	16 (76.2)		
Education (years)	12.9 ± 3.8	13.3 ± 3.7	13.1 ± 3.8	11.1 ± 3.6	11.5 ± 3.9	3.23	**0.029**
Occupation (employed)	135 (61.1)	83 (66.9)	28 (53.8)	14 (58.3)	10 (47.6)	4.61	0.203
Partner (yes)	101 (45.7)	63 (50.8)	19 (36.5)	12(50)	7 (33.3)	4.53	0.209
Geographic area						19.2	**0.004**
North	66 (29.9)	26 (21.0)	24 (46.2)	7 (29.2)	9 (42.9)		
Centre	76 (34.4)	53 (42.7)	15 (28.8)	5 (20.8)	3 (14.3)		
South	79 (35.7)	45 (36.3)	13 (25.0)	12 (50.0)	9 (42.9)		
Clinical variables							
Current smoking	32 (14.7)	16 (13.1)	5 (9.8)	5 (20.8)	6 (28.6)	5.17	0.160
Medical comorbidity	123 (55.7)	61 (49.2)	32 (61.5)	16 (66.7)	14 (66.7)	5.04	0.169
Age at MDD onset (years)	34.5 ± 15.2	33.4 ± 14.4	32.3 ± 14.2	39.5 ± 16.6	41.1 ± 18.7	2.14	0.106
Age at first psychiatric referral (years)	37.4 ± 15.2	36 ± 14.3	36.2 ± 15.1	41.5 ± 16.3	43.5 ± 17.3	1.81	0.156
MDE type						2.24	0.524
First-onset	70 (32.4)	43 (35.2)	15 (30.6)	8 (33.3)	4 (19)		
Recurrent	146 (67.6)	79 (64.8)	34 (69.4)	16 (66.7)	17 (81)		
Psychiatric comorbidity	91 (42.1)	47 (38.5)	25 (50)	9 (39.1)	10 (47.6)	2.27	0.519
Psychiatric hospitalization (yes)	63 (28.9)	31 (25.4)	16 (30.8)	5 (21.7)	11 (52.4)	7.02	0.071
Psychiatric family history	102 (46.4)	65 (52.8)	18 (34.6)	11 (45.8)	8 (38.1)	5.54	0.136
Psychometric features							
HDRS	23.7 ± 10.2	25.7 ± 11.4	21.5 ± 8.9	21.3 ± 7.3	19.9 ± 5.2	5.54	**0.002**
HARS							
Total	23.8 ± 10.4	24.1 ± 9.9	20.2 ± 9.1	25.9 ± 10.9	29.6 ± 12.6	4.01	**0.012**
Physical Symptoms	11.4 ± 7.3	11.7 ± 7.2	8.8 ± 6.2	12.6 ± 7.7	14.7 ± 8.5	4.01	**0.012**
SHAPS	5.6 ± 3.5	5.1 ± 3.2	5.9 ± 3.9	7.5 ± 3.8	5.7 ± 3.7	2.69	0.057
PDQ-D5	10.9 ± 4.66	11.3 ± 4.5	10.7 ± 5.4	10.9 ± 4.8	10.8 ± 4.1	0.22	0.882
DSST (symbols number)	40.8 ± 15.8	43.9 ± 15.9	37.9 ± 16.1	40.4 ± 13	29.6 ± 10.3	9.72	**<0.001**
TMT-B (seconds)	129 ± 66.9	116.5 ± 56.4	133.2 ± 71.6	137.9 ± 53.5	178.8 ± 97.2	3.66	**0.018**

Significant results in **bold** characters. Abbreviations: cMetS, continuous Metabolic Syndrome score; CRP, C-Reactive Protein; DSST, Digit Symbol Substitution Test; F, Welch's analysis of variance; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; M, mean; MDD, Major Depressive Disorder; MDE, Major Depressive Episode; PDQ-D5, Perceived Deficit Questionnaire–5; SD, standard deviation; SHAPS, Snaith–Hamilton Pleasure Scale; TMT-B, Trail Making Test - part B; χ^2, chi-squared test.

cMetS groups (mean difference = 5.88, p = 0.063). No significant differences across profiles were observed for fluoxetine-equivalent dose (p = 0.288), psychopharmacological treatments (p = 0.390), and psychotherapies (p = 0.716). Neither antidepressant class (SSRIs: p = 0.513; SNRIs: p = 0.934; non-SSRI antidepressants with mechanisms potentially relevant to reward processing: p = 0.334; other antidepressants: p = 0.158), antidepressant combination therapy (p = 0.132), mood stabilizer (p = 0.107) or sedative-hypnotic/anxiolytic use (p = 0.632) differed significantly across immune-metabolic profiles. By contrast, antipsychotic treatment significantly differed across groups (p = 0.010), with the highest proportions observed in the Low CRP/High cMetS (65.4%) and High CRP/High cMetS (52.4%) profiles, compared with the High CRP/Low cMetS (45.8%) and Low CRP/Low cMetS (37.9%) profiles.

3.2. Adjusted comparisons between immune-metabolic profiles and symptom domains

Results of separate ANCOVA models adjusted for the predefined set of covariates are presented in Table 2.

Regarding anxiety-related somatic symptoms (HARS Physical), post-hoc comparisons based on estimated marginal means indicated that the High CRP/High cMetS group had significantly higher scores compared with the Low CRP/High cMetS group (mean difference = 6.10, p = 0.002) and the Low CRP/Low cMetS group (mean difference = 5.10, p = 0.007). In this model, overall depressive severity (HDRS total) also showed a significant effect as a covariate (p < 0.001).

For anhedonia, post-hoc analyses showed that the High CRP/Low cMetS group reported significantly higher SHAPS scores compared with the Low CRP/Low cMetS group (mean difference = 2.93, p = 0.003). No covariates showed significant effects in the adjusted model, although HDRS total score approached statistical significance (p = 0.05).

No significant differences in subjective cognitive complaints were observed across immune-metabolic profiles based on PDQ-D5 (p = 0.955). In this model, HDRS total score (p < 0.001) and smoking status (p = 0.035) were significant covariates. Pairwise comparisons did not reach statistical significance after Tukey correction for DSST performance, while age (p < 0.001) and years of education (p < 0.001) emerged as significant covariates. For TMT-B completion time, the overall effect of the immune-metabolic profile approached statistical significance (p = 0.057), with age (p = 0.005) and years of education (p = 0.005) as significant covariates of the performance. Post-hoc comparisons indicated significantly longer completion times in the High CRP/High cMetS group compared with the Low CRP/Low cMetS group (mean difference = 41.44 s, p = 0.041).

3.3. Regression analyses

In the primary linear regression model for HARS Physical Symptoms, CRP status was significantly associated with greater symptom severity (p = 0.049), whereas metabolic burden (p = 0.353) and the interaction term (p = 0.113) did not reach statistical significance. HDRS total score was the main covariate associated with the outcome (p < 0.001). For SHAPS, CRP status was significantly associated with higher scores (p < 0.001), and a significant CRP-by-metabolic burden interaction was also observed (p = 0.023), whereas metabolic burden alone was not significantly associated with the outcome (p = 0.172). No additional covariates were statistically significant after adjustment. For objective cognitive performance, neither CRP status, metabolic burden, nor their interaction were significantly associated with DSST or TMT-B in the categorical models, whereas higher age was significantly associated with worse performance on both tasks and education showed the expected protective effect in the cognitive models. Results of the primary multivariable regression models are summarized in Table 3.

Additional regression models including the four-category immune-metabolic profile variable (with Low CRP/Low cMetS as the reference level) allowed direct comparison between profiles, as reported in Fig. 1.

The High CRP/High cMetS profile was significantly associated with higher HARS Physical symptom scores compared with the reference group (β = 5.10, SE = 1.55, p = 0.001). For anhedonia, the High CRP/Low cMetS group showed significantly higher SHAPS scores relative to the Low CRP/Low cMetS group (β = 2.93, SE = 0.83, p < 0.001). Regarding cognitive outcomes, the High CRP/High cMetS profile was significantly associated with poorer objective cognitive performance, showing lower DSST scores (β = −7.43, SE = 3.52, p = 0.036) and longer TMT-B completion times (β = 41.44, SE = 15.55, p = 0.008) compared with the reference group. Because antipsychotic treatment

Table 2
Adjusted comparisons of symptom domains across immune-metabolic profiles (ANCOVA).

Outcome	Predictor	F	p	η^2p
Physical Symptoms				
HARS-Physical subscale	Immune-metabolic profile	5.58	**0.001**	0.079
	Covariates			
	Age	0.08	0.781	0.000
	Education	1.12	0.292	0.006
	HDRS total score	59.3	**<0.001**	0.232
	MDE type	0.51	0.474	0.004
	Medical comorbidity	0.01	0.933	0.000
	Sex	2.25	0.135	0.011
	Smoking	0.78	0.377	0.004
Anhedonia				
SHAPS	Immune-metabolic profile	4.26	**0.006**	0.065
	Covariates			
	Age	0.24	0.625	0.001
	Education	1.40	0.237	0.008
	HDRS total score	3.89	**0.050**	0.021
	MDE type	3.59	0.060	0.019
	Medical comorbidity	0.01	0.929	0.000
	Sex	3.52	0.062	0.019
	Smoking	1.69	0.195	0.009
Cognition				
PDQ-D5	Immune-metabolic profile	0.11	0.955	0.002
	Covariates			
	Age	0.78	0.379	0.004
	Education	2.02	0.157	0.010
	HDRS total score	18.23	**<0.001**	0.085
	MDE type	1.42	0.235	0.007
	Medical comorbidity	0.26	0.614	0.001
	Sex	0.74	0.391	0.004
	Smoking	4.52	**0.035**	0.023
DSST	Immune-metabolic profile	2.83	**0.039**	0.042
	Covariates			
	Age	13.01	**<0.001**	0.063
	Education	15.49	**<0.001**	0.074
	HDRS total score	0.12	0.733	0.001
	MDE type	< 0.01	0.968	0.000
	Medical comorbidity	0.06	0.807	0.000
	Sex	1.83	0.178	0.009
	Smoking	1.22	0.271	0.006
TMT-B	Immune-metabolic profile	2.55	0.057	0.038
	Covariates			
	Age	8.20	**0.005**	0.040
	Education	7.99	**0.005**	0.039
	HDRS total score	< 0.01	0.974	0.000
	MDE type	2.03	0.156	0.010
	Medical comorbidity	0.82	0.365	0.004
	Sex	2.13	0.146	0.011
	Smoking	0.29	0.592	0.001

Significant results in **bold** characters. Abbreviations: ANCOVA, analysis of covariance; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; DSST, Digit Symbol Substitution Test; MDE, Major Depressive Episode; PDQ-D5, Perceived Deficit Questionnaire–5; SHAPS, Snaith–Hamilton Pleasure Scale; TMT-B, Trail Making Test – part B. Effect sizes are reported as partial eta squared (η^2p).

Table 3
Primary linear regression models.

Outcome	Factor	β	SE	p
HARS-Physical subscale				
	CRP > 3 mg/L	2.72	1.37	**0.049**
	High cMetS	-1.00	1.07	0.353
	CRP × cMetS	3.38	2.12	0.113
	HDRS total score	0.33	0.04	**<0.001**
	Age	-0.01	0.03	0.781
	Education	-0.12	0.12	0.292
	Sex*	1.39	0.93	0.135
	Medical comorbidity	0.08	0.97	0.933
	Smoking	−1.07	1.21	0.377
	MDE type*	−0.68	0.94	0.474
SHAPS				
	CRP > 3 mg/L	2.93	0.83	**<0.001**
	High cMetS	0.87	0.63	0.172
	CRP × cMetS	−2.87	1.25	**0.023**
	HDRS total score	0.05	0.03	**0.050**
	Age	−0.01	0.02	0.625
	Education	0.08	0.07	0.237
	Sex*	−1.06	0.56	0.062
	Medical comorbidity	0.05	0.58	0.929
	Smoking	0.91	0.70	0.195
	MDE type*	1.08	0.57	0.060
DSST				
	CRP > 3 mg/L	2.24	3.27	0.495
	High cMetS	-4.97	2.62	0.059
	CRP × cMetS	−4.71	4.94	0.342
	Age	−0.28	0.08	**<0.001**
	Education	1.11	0.28	**<0.001**
	Sex*	−3.01	2.23	0.178
	Medical comorbidity	−0.57	2.33	0.807
	Smoking	−3.10	2.81	0.271
	HDRS total score	0.04	0.11	0.733
	MDE type*	0.09	2.28	0.968
TMT-B				
	CRP > 3 mg/L	4.45	14.4	0.758
	High cMetS	14.8	11.5	0.201
	CRP × cMetS	22.2	21.8	0.309
	Age	0.97	0.34	**0.005**
	Education	−3.52	1.25	**0.005**
	Sex*	14.3	9.79	0.146
	Medical comorbidity	9.32	10.2	0.365
	Smoking	-6.65	12.4	0.592
	HDRS total score	-0.02	0.48	0.974
	MDE type*	-14.3	10.0	0.156

Significant results in **bold** characters. Abbreviations: cMetS, continuous Metabolic Syndrome score; CRP, C-Reactive Protein; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; DSST, Digit Symbol Substitution Test; MDE, Major Depressive Episode; SHAPS, Snaith Hamilton Pleasure Scale; TMT-B, Trail Making Test – part B. *Reference levels: male for sex; first-onset for MDE type.

significantly differed across immune-metabolic profiles, additional analyses were performed including this variable among covariates. The overall pattern of findings remained substantially unchanged, confirming the observed associations between immune-metabolic burden and depressive symptom dimensions, which are fully detailed in supplementary material (Table S2).

Finally, sensitivity analyses using continuous values yielded a substantially convergent pattern. Higher log10CRP values were associated with greater HARS Physical symptoms ($\beta = 1.76$, $p = 0.005$) and greater anhedonia severity ($\beta = 0.74$, $p = 0.032$), whereas higher continuous cMetS values were associated with poorer DSST performance ($\beta = -0.97$, $p = 0.023$). Collinearity diagnostics indicated acceptable VIF across all models.

4. Discussion

The present study indicates that immune-metabolic profiles, derived from routinely available markers, are differentially associated with specific clinical dimensions of depression. Combined inflammatory and metabolic dysregulation was primarily linked to somatic symptom burden and objective cognitive impairment, whereas inflammatory burden in the absence of marked metabolic dysregulation was more specifically related to anhedonia. This pattern supports a dimensional rather than unitary view of depression, consistent with models proposing partially distinct biological phenotypes, whose clinical expression may vary across symptom domains rather than simply tracking overall severity (Beckett and Lawson, 2026; Milaneschi et al., 2020; Penninx et al., 2024).

Although CRP is one of the most extensively validated peripheral biomarkers of low-grade systemic inflammation with potential clinical applicability, it also reflects adiposity-related metabolic processes (Craveiro et al., 2025). Integrating CRP with cMetS therefore provides a pragmatic characterization of immune-metabolic burden while accounting for the overlap between inflammatory and metabolic pathways. This approach is further supported by evidence indicating visceral adiposity as a major driver of chronic low-grade inflammation and metabolic dysfunction, with increasing relevance across adulthood as body fat progressively redistributes toward a more central pattern (Portugal-Nunes et al., 2020; Sun et al., 2025). This consideration is particularly relevant in the context of the present sample, in which immune-metabolic profiles differed according to age, further supporting the prioritization of abdominal adiposity over blood pressure when characterizing metabolic burden. Consistent with this framework, our findings support the view that the interplay between inflammatory and metabolic burden may contribute to distinct depressive symptom dimensions. Recent evidence also suggests that immune-metabolic mechanisms underlying depression may differ between males and females, with sex-specific biological drivers potentially contributing to distinct inflammatory and metabolic phenotypes (Rietberg et al., 2026). All multivariable models in this study were adjusted for sex; however, the available sample size precluded adequately powered sex-stratified analyses. Future studies with larger, adequately powered cohorts will be important to further disentangle immune-specific and metabolic contributions to depression (ideally including other inflammatory biomarkers, e.g., cytokines), to clarify potential sex-specific immune-metabolic phenotypes, and to determine whether age-related changes in metabolic burden further influence these relationships.

A first relevant finding of the present study was the greater somatic symptom burden in patients with combined immune-metabolic dysregulation, even after adjustment for relevant covariates. This is consistent with evidence linking inflammatory and immune-metabolic alterations to energy-related and somatic dimensions of depression, including fatigue, bodily discomfort, and autonomic symptoms (Lamers et al., 2020; Pepe et al., 2025; Zwiep et al., 2026). Within current immune-metabolic models of depression, these features are considered part of a clinically recognizable phenotype characterized by the convergence of psychiatric and systemic dysregulation (Milaneschi et al., 2020; Penninx et al., 2024). Chronic low-grade inflammation may promote sickness-behavior-like states through effects on interoceptive processing, autonomic regulation, and neural pathways involved in fatigue and bodily distress, while metabolic dysregulation may further contribute through altered energy availability, insulin signaling, and vascular burden (Liu and Zhai, 2025; Meng et al., 2025; Moriarity et al., 2023). The greater somatic burden observed in the combined profile supports the view that depression-related biological vulnerability is often multi-systemic rather than confined to isolated pathways (Penninx et al., 2024; Pinzi et al., 2025). Overall depressive severity remained a strong covariate of the model, suggesting that somatic symptoms are partly embedded in broader depressive burden, yet not fully reducible to it.

A second major finding concerns anhedonia. Here, the profile with high CRP without high metabolic burden showed the clearest association with SHAPS scores, while regression models confirmed both a significant CRP effect and a CRP-by-metabolic burden interaction, suggesting a direct link between inflammatory burden and reward dysfunction. Such an interpretation is supported by experimental and

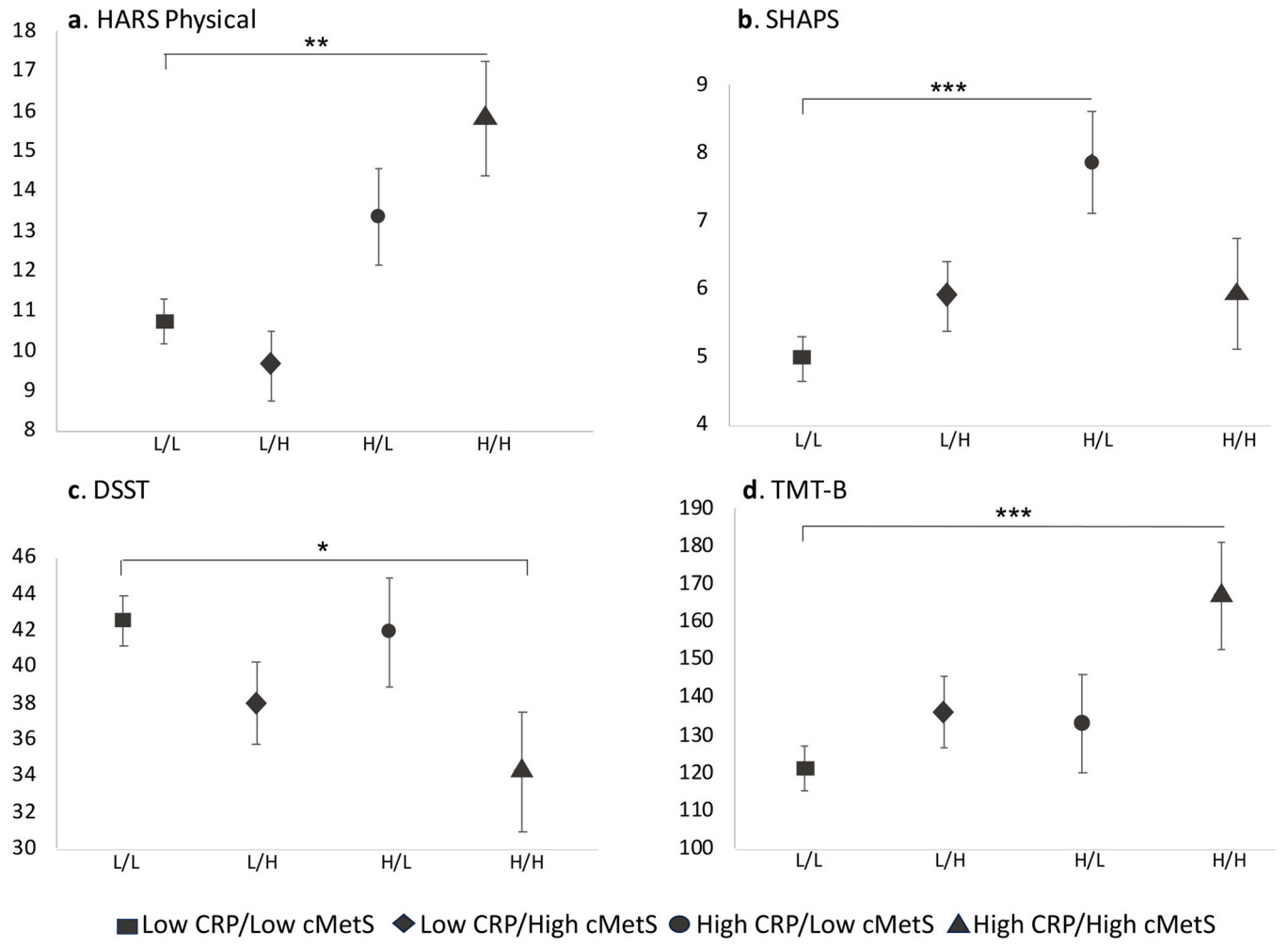


Fig. 1. Adjusted marginal means of symptom domains across immune-metabolic profiles. Estimated marginal means (± standard error) derived from multivariable regression models are shown for four immune-metabolic profiles: Low CRP/Low cMetS (L/L), Low CRP/High cMetS (L/H), High CRP/Low cMetS (H/L), and High CRP/High cMetS (H/H). Panels display adjusted values for (a) HARS Physical symptoms, (b) SHAPS, (c) DSST, and (d) TMT-B. Asterisks indicate statistically significant differences relative to the reference group (Low CRP/Low cMetS) in regression analyses (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$).

translational literature indicating that inflammation can reduce dopaminergic signaling within mesolimbic and fronto-striatal circuits, thereby impairing reward anticipation, effort allocation, and motivational salience (Felger and Treadway, 2017; Lucido et al., 2021). Neuroimaging studies further reinforce this view, as higher CRP levels have been associated with reduced activation of reward-related striatal regions (Aruldass et al., 2025). Accordingly, the present data are consistent with the notion that anhedonia may represent one of the most inflammation-sensitive dimensions of depression (Lucido et al., 2021; Zwiep et al., 2026). At the same time, the significant interaction with metabolic burden suggests that the relationship between elevated inflammation and hedonic dysfunction varies across metabolic contexts rather than reflecting a simple additive effect. Specifically, this association was more pronounced in patients with low metabolic burden and attenuated when inflammatory and metabolic burden co-occurred, in line with recent profiling approaches showing non-linear interactions between these pathways in depressive phenotypes (Donnelly et al., 2025; Sforzini et al., 2025).

A third clinically meaningful result concerns objective cognition. Although ANCOVA findings were modest, regression models showed that the combined High CRP/High cMetS group was associated with poorer DSST and TMT-B performance, while sensitivity analyses linked continuous metabolic burden to lower DSST scores. Together, these findings suggest that cognitive impairment in depression may be especially evident when combined inflammatory and metabolic burden is present, consistent with previous evidence in MDD (Sanchez-Carro et al., 2022). Present findings extend this framework by suggesting that combined immune-metabolic burden may be linked not only to global cognitive inefficiency, but more specifically to executive and processing-speed dimensions, increasingly recognized as determinants of functional outcome in depression (Culpepper et al., 2017; Kriesche et al., 2023; Rhee et al., 2024).

Several mechanisms may account for this pattern. Neuroinflammatory processes can impair prefrontal functioning through effects on synaptic plasticity, neurovascular coupling, and catecholaminergic regulation, thereby weakening cognitive control (Joyce et al., 2025; Kocamer Şahin and Aslan, 2024). Metabolic dysregulation may contribute through vascular dysfunction, oxidative stress, reduced metabolic efficiency, and impaired energetic coupling (Yuan et al., 2026). This interpretation is compatible with neuroimaging literature in mood disorders linking elevated CRP to structural and diffusion MRI abnormalities in fronto-striatal and prefrontal circuits involved in executive performance (Valizadeh et al., 2025; Zacková et al., 2021), and with the proposed cognitive biotype of depression, characterized by objective neurocognitive deficits and circuit-level alterations (Hack et al., 2023).

By contrast, no significant association emerged between immune-metabolic profiles and PDQ-D5 scores, in line with evidence showing

only partial overlap between self-reported and performance-based cognitive measures in depression (Rhee et al., 2024). Subjective complaints are often shaped by depressive severity, anxiety, expectancy, and negative cognitive bias, whereas objective tests more directly reflect specific neurocognitive processes (Hack et al., 2023). In our data, HDRS total score and smoking status significantly contributed to PDQ-D5 variability, reinforcing the view that perceived cognitive inefficiency may be influenced by affective burden and behavioral factors even in the absence of a clear biological signal, as well as the importance of combining subjective and objective assessments in depression (Pepe et al., 2023).

Taken together, these results indicate that inflammatory and metabolic alterations show partially distinct and interacting associations across somatic, affective, and cognitive features. CRP appeared more closely related to somatic symptoms and anhedonia, whereas metabolic burden contributed more consistently to objective cognitive performance, and their combination identified the subgroup with the broadest pattern of impairment. This pattern is consistent with immune-metabolic models emphasizing interactions among immune, endocrine, and metabolic systems rather than one-to-one relationships between single biomarkers and symptoms (Milaneschi et al., 2020; Penninx et al., 2024). More broadly, the findings support integrated biological profiling over isolated biomarker approaches, whose associations with depression have often been modest and inconsistent (Horn et al., 2018; Mac Giollabhui et al., 2021; Moriarity et al., 2023). Indeed, our results suggest that isolated inflammation and combined inflammatory-metabolic burden may index partly distinct depressive phenotypes, with implications for how the construct of immune-metabolic depression should be refined and how stratification-based interventions could be designed.

From a clinical perspective, similar immune-metabolic phenotyping could have implications for precision psychiatry. Simple immune-metabolic profiles based on routinely available biomarkers may identify patients with greater somatic and cognitive burden, both closely linked to functional outcomes (Culpepper et al., 2017; Kriesche et al., 2023). In turn, biologically informed stratification may help guide targeted interventions, as anti-inflammatory strategies appear more effective in patients with elevated inflammatory markers (Miller et al., 2025; Elbakary et al., 2025), whereas interventions targeting metabolic dysfunction may be particularly relevant in patients with combined immune-metabolic burden (Di Nicola et al., 2025, Di Nicola et al., 2025; Penninx et al., 2024; Pinzi et al., 2025).

Some limitations should be acknowledged. First, the cross-sectional design prevents causal inference and does not allow assessment of whether these profiles are stable over time or predictive of clinical outcomes (Mac Giollabhui et al., 2021; Penninx et al., 2024). At the same time, the present study should be viewed as a foundational analysis within the broader longitudinal SFIDE project, which may help clarify the temporal stability and prognostic relevance of these immune-metabolic profiles in future investigations. Second, the lack of a healthy control group precludes determining whether the identified immune-metabolic profiles are specific to MDE or reflect patterns also observable in the general population. In addition, the relatively small size of some immune-metabolic subgroups, particularly those characterized by elevated CRP levels, may have reduced statistical power for subgroup-specific analyses. Third, the study relied on peripheral markers only and did not include transcriptomic, imaging, or other multimodal biological measures that may better refine mechanistic stratification (Sforzini et al., 2025; Valizadeh et al., 2025). Finally, the predefined exclusion of clinically relevant populations based on chronic MDE duration, extreme BMI values and major uncontrolled medical conditions may limit the generalizability of the present findings. Moreover, although all multivariable analyses were adjusted for sex, the available sample size within each subgroup precluded adequately powered sex-stratified analyses. Nevertheless, strengths include the multicenter design, which increased clinical heterogeneity and ecological validity; the use of a clinically interpretable immune-metabolic classification based on routine biomarkers, enhancing potential translational value; the simultaneous examination of multiple symptom dimensions; and the integration of categorical and continuous biomarker analyses.

5. Conclusions

In conclusion, immune-metabolic profiles derived from routine biomarkers were differentially associated with specific clinical dimensions of depression. Combined inflammatory and metabolic dysregulation was linked to greater somatic symptom burden and poorer objective cognition, whereas inflammatory burden without marked metabolic dysregulation was more specifically associated with anhedonia. These findings support contemporary immune-metabolic models of depression, emphasizing interacting inflammatory and metabolic pathways rather than isolated biomarkers alone (Milaneschi et al., 2020; Penninx et al., 2024; Pinzi et al., 2025), and suggest that immune-metabolic profiling may help refine depressive phenotyping and support stratified treatment approaches (Chiappini et al., 2025; Miller et al., 2025).

Author contributions

All persons who meet the authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. **MDN**, **MP, GSani** and **AF** conceptualized the design of the study. **AA**, **UA**, **FB**, **EAC**, **GCastellini**, **PDF**, **GDL**, **MDN**, **CG**, **ML**, **LO**, **GSampogna**, **AV** were responsible for the patient recruitment and the collection of clinical data. The **SFIDE Study Group** contributed to the collection and curation of clinical data. **MP** and **MDN** performed the statistical analysis, carried out data interpretation, and wrote the first draft of the manuscript. **AF**, **GCarrà**, **GM**, **GSani**, and **GSerafini** revised the manuscript and provided substantial comments. All authors contributed and approved the final manuscript.

Ethics declaration

Written informed consent to take part in the study and to publish the article has been obtained from all participants or their legal representatives. The privacy rights of participants have been observed.

This study was performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place. This study was approved by the Università Cattolica del Sacro Cuore, Rome, Italy. (Approval No. 5147)

Institutional review board statement

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (1964) and subsequent revisions and was approved by the institutional review board of the Università Cattolica del Sacro Cuore, Rome, Italy, on 28th July 2022 (protocol number 5147).

Informed consent statement

Anonymity was guaranteed to all participants, who gave written informed consent before their enrollment and did not receive any form of compensation.

Funding

This research received no external funding.

Declaration of Competing Interest

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

Acknowledgments

This work was conceived during the Star Academy Initiative and implemented among the sites of the Star Academy participants.

Appendix A

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Appendix B. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2026.108000.

Data availability

Authors do not have permission to share these data.

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