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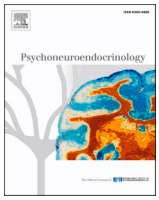

Baseline circulating biomarkers, their changes, and subsequent suicidal ideation and depression severity at 6 months: A prospective analysis in patients with mood disorders

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ABSTRACT

Background: Identifying circulating biomarkers associated with prospective suicidal ideation (SI) and depression could help better understand the dynamics of these phenomena and identify people in need of intense care. In this study, we investigated the associations between baseline peripheral biomarkers implicated in neuroplasticity, vascular homeostasis and inflammation, and prospective SI and depression severity during 6 months of follow-up in patients with mood disorders.

Methods: 149 patients underwent a psychiatric evaluation and gave blood to measure 32 plasma soluble proteins. At follow-up, SI incidence over six months was measured with the Columbia Suicide Severity Rating Scale, and depressive symptoms were assessed with the Inventory for Depressive Symptomatology. Ninety-six patients provided repeated blood samples. Statistical analyses included Spearman partial correlation and Elastic Net regression, followed by the covariate-adjusted regression models.

Results: 51.4 % (N = 71) of patients reported SI during follow-up. After adjustment for covariates, higher baseline levels of interferon-γ were associated with SI occurrence during follow-up. Higher baseline interferon-γ and lower orexin-A were associated with increased depression severity, and atypical and anxious, but not melancholic, symptoms. There was also a tendency for associations of elevated baseline levels of interferon-γ, interleukin-1β, and lower plasma serotonin levels with SI at the six-month follow-up time point. Meanwhile, reduction in transforming growth factor- β1 (TGF-β1) plasma concentration correlated with atypical symptoms reduction.

Conclusion: We identified interferon-γ and orexin-A as potential predictive biomarkers of SI and depression, whereas TGF-β1 was identified as a possible target of atypical symptoms.

1. Introduction

Mood disorders, encompassing major depressive disorder (MDD) and bipolar disorder (BD), have been linked to a reduced lifespan due to both suicides and medical complications (Zivin et al., 2015). They also pose significant challenges to treatment, with 30–40 % of individuals diagnosed with major depressive episodes not achieving remission with standard interventions (Bo et al., 2019; Rush et al., 2006). Major depressive episodes, characterized by multiple diagnostic criteria including suicidal thoughts and behaviors, are further complicated by residual symptoms even in remission, leading to poorer clinical outcomes (Grover et al., 2021; Heuschen et al., 2022). In addition, the majority of individuals with mood disorders have suicidal ideation (SI) and around 5–6 % will die by suicide (Isometsä, 2014). However, clinical assessments often fall short in predicting disease course, as evidenced by the majority of patients who died by suicide screening negative for SI during their last visit to the Emergency Department (Simpson et al., 2021). This underscores the need to identify reliable biological markers that can offer insights into prospective SI and depression.

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In recent years, peripheral inflammatory markers have drawn attention in the context of mood disorders and suicidal thoughts and behaviors. Elevated concentrations of inflammatory markers, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) have been found in individuals with MDD and BD (Osimo et al., 2020; Solmi et al., 2021; Yuan et al., 2019). These increases in inflammation have been posited as potential transdiagnostic severity indicators, associated with particular symptoms, such as energy-related symptoms, anhedonia, sleep problems, and SI, beyond their association with specific diseases (Byrne et al., 2022; Dolsen et al., 2020; Goldsmith et al., 2023). In addition, increased inflammatory marker levels have been observed in patients with SI and suicide attempt (SA) history among patients with mood disorders, suggesting a "two-hit" model, in which increased peripheral inflammation is associated with mood disorders, with an even more pronounced elevation in patients with current SI and SA history within mood disorder, possibly independently from depression severity (Lengvenyte et al., 2019a; Neupane et al., 2023; Vasupanrajit et al., 2022).

While cross-sectional studies shed light on the underlying pathophysiological processes, longitudinal studies in mood disorders show that baseline increases in inflammatory markers are associated with more severe depressive symptoms and treatment resistance at follow-up (Eswarappa et al., 2019; Huang et al., 2023). Compellingly, the causal hypothesis comes from semi-experimental studies in individuals who received cytokine interferon-alpha (IFN-α) therapy, which showed that approximately 30 % of patients developed a major depressive episode, often several weeks to months after treatment initiation (Capuron et al., 2009; Udina et al., 2012).

Technological advancements, such as multiplexing, have refined our ability to analyze multiple biomarkers concurrently, with some preliminary success in detecting potential prognostic biomarkers in mood disorders (Sandberg et al., 2022; Targum et al., 2022). Furthermore, in addition to peripheral inflammatory markers, increases in nitro-oxidate stress markers and some growth factors have also been associated with SI and SA (Vasupanrajit et al., 2022). Platelet-derived vascular homeostasis factors might also be implicated, as platelets respond to oxidative stress and are an important source of inflammatory proteins, chemokines, and serotonin, bridging hemostasis, oxidative stress, and inflammation (Cognasse et al., 2019). We have previously reported different associations between inflammatory and platelet-related markers and both past SA and subsequent suicidal events during a two-year follow-up, which suggested temporal differences in associations (Lengvenyte et al., 2023).

In this ancillary analysis, we examine the prospective relationship between the baseline concentrations of 32 proteins linked to inflammation, vascular homeostasis, growth, and sleep, with SI over six months, as well as SI and depression severity at a six-month follow-up, in individuals with mood disorders. Additionally, we explored correlations between symptom changes and biological markers in a subset of patients with two blood samples.

2. Methods

2.1. Study design and participants

This is a prospective secondary six-month follow-up analysis of 149 individuals seeking treatment for depression. Participants were enrolled in a larger study investigating factors associated with a lifetime history of SA, current SI and prospective suicidal events. The study was approved by the ethical review committee (CPP Sud Mediterranée IV, clinicaltrials.gov NCT02824081). Results from the primary analyses were published previously (Lengvenyte et al., 2023). This analysis examines self-reported SI during the six-month follow-up, offering a more sensitive measure of prevalence compared to our previous study, which focused on Emergency Department visits and captured more severe cases of SI and SA. Additionally, we employed a different depression severity scale (see details below) to more comprehensively assess various aspects of depressive symptomatology.

Participants were recruited in an academic hospital after a consultation for SI, recent SA or depression between January 2016 and February 2018. Inclusion criteria were age between 18 and 65 years, a psychiatrist-confirmed diagnosis of BD or MDD according to DSM-5 criteria (American Psychiatric Association, 2013), with the last episode being a major depressive episode, and the capacity to comprehend the study design and sign the informed consent. Exclusion criteria were acute inflammatory conditions (either symptomatic or with high sensitivity C-reactive protein (hsCRP) >50 ng/ml), ongoing anti-inflammatory or immunomodulatory treatment, pregnancy or breastfeeding, current psychotic symptomatology, diminished capacity to understand the study's objectives, absence of affiliation to social security, participation in another protocol, refusal to participate, legally incapacitated, or having one's liberty deprived due to judicial or administrative decisions. During the follow-up, all participants received usual care.

Participants provided written informed consent. They received no financial compensation. After the initial evaluation, all participants were invited to a 6-month follow-up visit either face-to-face, providing a second blood sample, or by telephone, only performing the psychometric assessment. See the study flowchart in Fig. 1. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines when reporting (von Elm et al., 2007).

The baseline assessment consisted of an interview with a clinician blinded to the patients' blood test results, questionnaires, and biological measurements. Psychiatric diagnoses were assessed with the Structured Clinical Interview for DSM-5 (American Psychiatric Association, 2013).

2.2. Patient assessment

The outcome of interest was the occurrence of self-reported SI over the 6-month follow-up period, which we assessed with the Columbia-Suicide Severity Rating Scale (C-SSRS): Since Last Visit (Posner et al., 2011) SI subscale, encompassing any instance of SI since inclusion. This scale has been validated and used in prospective studies, capturing SI over extended periods of time (Greist et al., 2014; Madan et al., 2016; Maruani et al., 2023; Thoma et al., 2023). The SI subscale scores range from 0 (no SI) to 5 (active SI with specific plan and intent). To provide a clinically meaningful outcome, we dichotomized these scores into none versus any SI (score ≥1), which has been linked to increased suicide risk (Liu et al., 2020). Given that active SI is frequently used in clinics and epidemiological surveys (WHO, 2020), and to reflect the severity continuum, we also performed a sensitivity analysis with trichotomized SI into none (score 0), passive (scores 1–2), and active SI (scores 3–5).

For a secondary outcome, we used the C-SSRS SI subscale to assess past-week SI at baseline, which has been shown to be predictive of future SI and SA (Brown et al., 2020; Gipson et al., 2015), providing a cross-sectional snapshot. We also employed the 30-item clinician-rated Inventory for Depressive Symptomatology (IDS-30_C) to assess depression severity at baseline and at 6-months follow-up (John Rush et al., 1986). Each item was scored from 0 to 3, with the total score being a sum of scores in 28 out of 30 items, ranging from 0 to 84. To capture current rather than past 6-month SI at follow-up, we also used the SI item (#18), dichotomized into no vs any SI (score ≥1). The IDS-30_C allows to assess melancholic, atypical, and anxious symptom domains that may help address the heterogeneity of depression, which is of particular interest in biomarker research, as different depressive features have been suggested to have different biological underpinnings (Harald and Gordon, 2012; van Haeringen et al., 2022). We selected the symptoms to include in melancholic, anxious, and atypical symptom domain based on DSM-5 criteria and previous studies that used IDS-30_C or it's self-report version QIDS-SR to measure these features (American Psychiatric Association, 2013; Arnow et al., 2015; McClintock et al., 2011; Stewart et al., 2010; Vogelzangs et al., 2016). Melancholic features comprised

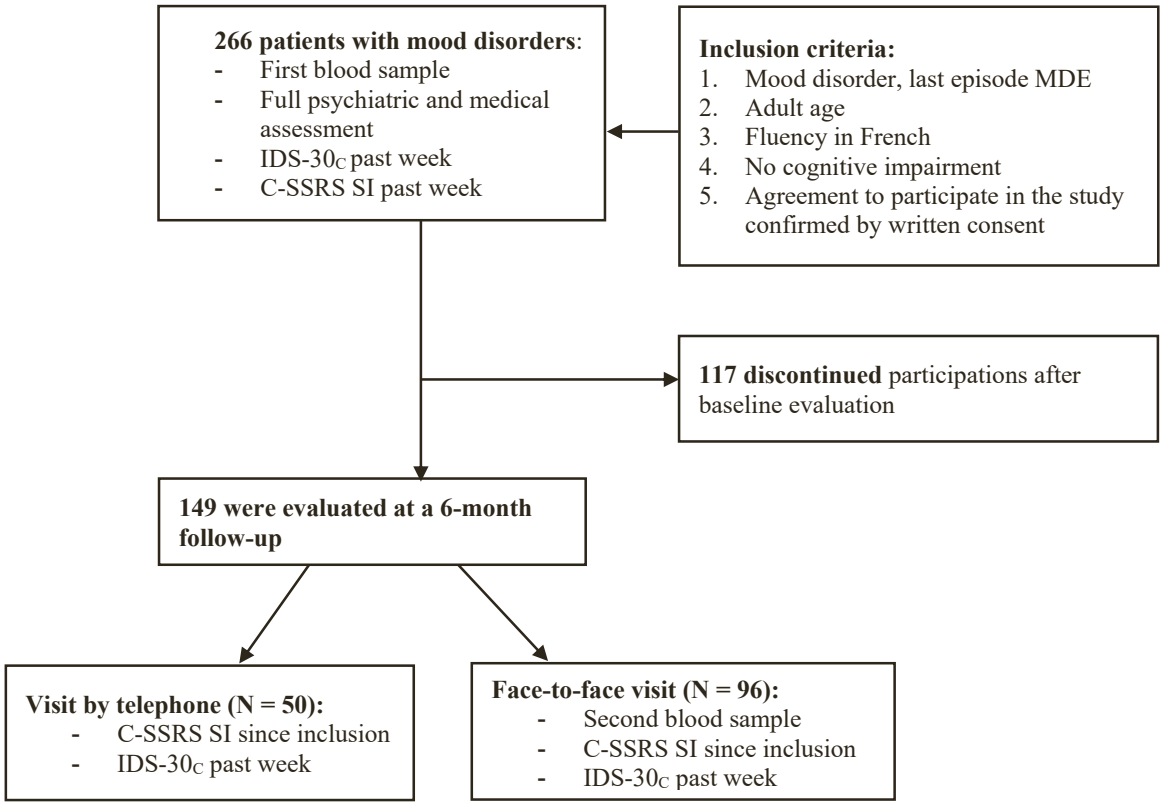

Fig. 1. Patient enrolment and follow-up.

loss of mood reactivity, loss of pleasure, morning insomnia, reduced mood variation, psychomotor retardation or agitation, anorexia, decreased weight, poor self-outlook, and quality of mood [score 0–40] (Arnow et al., 2015; Stewart et al., 2010; Vogelzangs et al., 2016). Atypical symptoms included hypersomnia, increased appetite, increased weight, leaden paralysis, and interpersonal rejection sensitivity [0–20] (Stewart et al., 2010; Vogelzangs et al., 2016). Anxious symptoms encompassed anxious mood, somatic complaints, sympathetic arousal, panic/phobic symptoms, and gastrointestinal symptoms [0–20] (McClintock et al., 2011). We included individuals with all levels of depression severity.

Other measurements included patient age, sex, and body mass index (BMI), lifetime history of SA, baseline psychotropic medications, subdividing them into four categories (antidepressants, antipsychotics, mood stabilizers (including lithium), and Z-drugs/benzodiazepines), nicotine use, educational status, psychiatric comorbidities (based on the MINI questionnaire: alcohol and substance use disorders, post-traumatic stress disorder, eating disorders, anxiety disorders, and obsessive compulsive disorder), and physical health comorbidities (self-report: cardiovascular, neurological, endocrinological diseases, and autoimmune disorders). Since 6-month follow-up evaluation included only C-SSRS SI and IDS-30_C scale administration, data on treatment changes and intermediate clinical events except for SI were not collected.

2.3. Plasma biomarker analysis

Biological analyses have been previously described elsewhere (Lengvenyte et al., 2023). In the present analyses, we excluded cellular markers that were included in the initial analysis (blood cell counts, mean platelet volume, mean corpuscular volume and anisocytosis coefficient) due to the reduced sample size and overall small effect sizes associated with such markers in psychoneuroimmunology literature (Lengvenyte et al., 2022). We collected morning peripheral blood following an overnight fast and within 24 hours of psychiatric evaluation. High-sensitivity CRP (hsCPR) was analyzed on the same day with the C800 Roche platform. For other analyses, plasma was prepared by centrifugation, aliquoted, and stored at −80°C for batched analyses. Out of 36 inflammatory, vascular homeostasis and plasticity-related soluble proteins, we excluded four (interleukin (IL)-1α, IL-2, interferon-inducible T-cell alpha chemoattractant (CXCL11/I-TAC), and coagulation factor III/tissue factor) due to more than 30 % missing data. All 32 proteins retained proteins passed our quality control.

Markers were chosen based on previous literature and possible pathophysiological pathways implicated in suicidal thoughts and behaviors. Given the previously established role of inflammation in depression and suicidal thoughts and behaviors (Lengvenyte et al., 2019a; Vasupanrajit et al., 2022), and the balance between pro- and anti-inflammatory mediators moderating the overall inflammatory response, we included the following inflammatory and immune response markers: pro-inflammatory cytokines interleukin (IL)-1β, IL-6, monocyte chemoattractant protein-1 (MCP-1), interferon-gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), interferon gamma-induced protein 10 (IP-10), soluble interleukin 2 receptor-alpha (sIL-2ra), soluble CD-14 ligand (sCD40l), soluble TNF receptor I (sTNFRI) and TNF-alpha, and an anti-inflammatory cytokine IL-4. Together, they are responsible for early responses and immune reactions, and have been reported to be altered in suicidal behaviors, depression, or related conditions (Goh et al., 2023; Janelidze et al., 2013; Maes et al., 1995; Ogłodek, 2018; Ohlsson et al., 2019; Pantazatos et al., 2017; Pereira et al., 2018; Romero-Sanchiz et al., 2020; Santos et al., 2015; Vasupanrajit et al., 2022).

Given the role of platelets and vascular health in bridging hemostasis and inflammation, and previously reported associations of platelet counts with SI (Cognasse et al., 2019; Lengvenyte et al., 2022), the following cytokines and chemokines released from platelets upon activation previously implicated in depression and related phenomena were analyzed: platelet factor 4 (Pf4), soluble CD40 ligand (sCD40l), coagulation factor III/tissue factor, platelet-derived growth factor (PDGF)-AB,

PDGF-BB, serpin, macrophage inflammatory protein- (MIP-) 1α and 1β, thrombospondin (TSP)-1, TSP-2, CD31/platelet endothelial cell adhesion molecule (PECAM-1), soluble CD62p, and RANTES (regulated on activation, normal T cell expressed and secreted, also called as CCL5) (Jha et al., 2017; Kittel-Schneider et al., 2020; Leo et al., 2006; Pereira et al., 2018; Serebruany et al., 2003; Wirtz et al., 2009; Yang et al., 2022). Finally, several neural function and growth factors that have a potential interest in suicidal thoughts and behaviours due to their links to brain function and depression were included: neurotensin, orexin-A, substance P, neutrophil-activating peptide 2 (NAP-2), transforming growth factor beta 1 (TGF-β1), stromal cell-derived factor 1 (SDF-1), Fas ligand, and brain-derived neurotrophic factor (BDNF) (Almeida-Montes et al., 2000; Bondy et al., 2003; Brundin et al., 2007; Kim et al., 2019; Lee and Kim, 2010; Vasupanrajit et al., 2022). More details on biological roles and previous psychiatry studies on biomarkers included are presented in Supplemental Table S1.

Merch Millipore (Molsheim, France) (Luminex), Bio-Techne SA (Chatillon sur Seiche, France) (ELISA), and Tecan France (Lyon, France) (ELISA) platforms were used (Supplemental Table S1). All parameters were assayed in duplicate wells. We observed low levels of inter-plate variability for all analytes (coefficient of variation <2). Supplemental Table S2 provides details on biological analyte levels at baseline and follow-up, their change and stability. The left-censored values falling below the lower limit of quantification were substituted with half of the measured minimum values for that analyte. This method was similar to methods used in other studies (Arnold et al., 2012; Barbosa et al., 2020; Wei et al., 2018). Due to the right skew, we then applied a natural log-transformation (ln (x+1)), and standardized to z-scores for easier comparison. After transformation, we detected no significant outliers. For analyses of changes, we used the raw values.

2.4. Statistical analysis

Baseline characteristics were summarized using χ2 and Mann-Whitney-Wilcoxon tests. The homogeneity of variance was checked with Levene's test. Given the non-normal distribution of biological and psychological variables, Spearman's rank partial correlation, adjusted for age, sex, and BMI, assessed associations between plasma proteins and depressive symptoms.

We applied a two-step analytical approach initially involving the selection of informative proteins with feature elimination, followed by the evaluation of their associations with outcomes through logistic regression models. Feature elimination was performed using a 10-fold cross-validated Elastic Net with plasma proteins and covariates as the predictors. These models balanced LASSO and ridge penalizations to address collinearity and led to a sparse selection of variables. The hyperparameter α was set at 0.5. Only variables that were not reduced to zero in at least 75 % of the cross-validation folds were retained for further analysis (Bunea et al., 2011). In the second step, we then used binary logistic regression to assess specific associations between pre-selected proteins and clinical outcomes. No outliers (Cook's distance) and collinearity (Variable Inflation Factor) were detected. In order to explore the impact of covariates on the association between biomarkers and prospective outcomes, estimates were adjusted for age, sex, BMI and primary psychiatric diagnosis (Model 1), additionally adjusted for baseline depression and SA history (Model 2), and for sex, medication groups and tobacco use (due to the possible influence of medications and tobacco on biomarkers, depression and SI) (Model 3). Additionally, we also ran a model adjusting for age, sex, BMI, primary psychiatric diagnosis, SA history and baseline SI, when the outcome was the SI to test the independence from baseline suicidality (Model 4). Adjustments were adapted for cross-sectional outcomes by eliminating adjustments for baseline depression and SI severity.

Additionally, we conducted sensitivity analyses using ordinal and multinomial logistic regression to refine the operationalization of SI as a trinary outcome, thereby enhancing statistical efficiency (Nosek and Errington, 2017). In these analyses, we also adjusted for potential confounders including age, sex, and BMI, baseline SI, depression severity, and SA history, treatment, and tobacco use.

Predictors were normalized before entering into the models, producing standardized regression (β) weights. Model fits were tested with the χ^2, goodness-to-fit tests, and the test of parallel lines for ordinal regression. Corresponding analyses were applied for secondary outcomes, employing multivariate linear regression for continuous outcomes. Shapiro-Wilk Test was used to test data distribution, the homoscendality was evaluated using Residual Plots and Q-Q Plots.

We used SPSS Statistics 28.0.1.0 for Mac (IBM Corporation) and JASP 0.16.4 software. The statistical significance threshold was set at $p < 0.05$, two-sided, with Bonferroni correction for family-wise final regression analyses with selected markers, and $p < 0.01$ for correlation analyses due to their exploratory nature and the involvement of continuous variables, which can yield significant results more easily. 95 % confidence intervals [95 %CI] were obtained with non-parametric 1000-step bootstrapping (Abram et al., 2016).

The analysis presented in this manuscript was exploratory and no statistical method was used to predetermine sample size, but the post-hoc sensitivity analysis indicated that the present analysis achieved a power of 0.85 based on a sample of 139 individuals, and was able to detect small effect sizes (Chen et al., 2010).

3. Results

3.1. Participant characteristics

Out of 266 individuals initially enrolled, 149 (56 %) individuals with mood disorders returned for a six-month follow-up. Participants were predominantly female (70.5 %) with a median age of 46 years (IQR 35–52). Half of the patients had mild-to-moderate depression severity and reported SI or a lifetime history of SA. Detailed baseline characteristics are presented in Table 1. Individuals with follow-up were generally older, had a BD diagnosis more frequently, were more likely to be on mood stabilizers, and had lower baseline depression severity and less SI (Supplemental Table S3).

3.2. Cross-sectional associations

Numerous protein concentrations were positively correlated with each other. Notable pairwise correlations between proteins and clinical variables were negative correlations between plasma serotonin and depression severity (rho = −0.249, 95 % CI −0.394 – (-0.095), p = 0.002), SI severity (last week) (rho = −0.247, 95 % CI −0.383 – (-0.102), p = 0.004), and atypical symptoms (rho = −0.224 (95 % CI −0.384 – (-0.066), p = 0.009). See the heatmap in Supplemental Figure S1.

In the Elastic Net, plasma levels of TNF-α, lIP-10, and serotonin were selected as associated with baseline depression severity, with the latter association being statistically significant in separate multivariate linear regression models adjusted for age, sex, BMI, diagnosis, and SA history. This association did not withstand Bonferroni correction nor additional adjustments for treatment (Supplemental Table S4). No analytes correlated with baseline SI score.

At follow-up, we did not replicate the baseline association between low serotonin and depression (Supplemental Figure S2). Notably, the required sample size for the largest observed baseline correlation was higher than the number of observations at the follow-up. However, at 6 months follow-up, we found correlations between IFN-γ levels and atypical symptoms (p = 0.009), and SI (last week) (p = 0.015). These correlations lost their significance after additional adjustment for tobacco and antidepressant use.

Table 1
Baseline sociodemographic and clinical characteristics of the sample.

	Mean (SD), median (IQR) or n (%), n = 149	Missing, n (%)
Demographics	.	.
Age in years, median (IQR)	46 (35–52)	.
Sex, n (%), males	44 (29.5 %)	.
Body mass index (kg/m^2), median (IQR)	23.74 (20.48 – 27.12)	.
Mean (SD)	24.56 (5.70)	
Clinical characteristics	.	.
Type of mood disorder:		.
Bipolar disorder, n (%)	76 (51.0 %)	
Major depressive disorder, n (%)	73 (49.0 %)	
History of suicide attempt, n (%)	69 (46.3 %)	.
Current nicotine use, n (%)	70 (47.0 %)	.
Comorbidity		
Substance or alcohol use disorder, n (%)	48 (32.4 %)	1 (0.7 %)
Eating disorder, n (%)	25 (16.8 %)	.
Anxiety disorder, current, n (%)	85 (57.4 %)	1 (0.7 %)
Obsessive compulsive disorder, n (%)	24 (16.2 %)	1 (0.7 %)
Post-traumatic stress disorder, n (%)	21 (14.2 %)	1 (0.7 %)
History of psychosis, n (%)	18 (12.1 %)	.
Non-inflammatory chronic somatic comorbidity, n (%)	36 (35.3 %)	47 (31.5 %)
Psychotropic medication, current use	.	.
Antipsychotics, n (%)	62 (41.6 %)	.
Antidepressants, n (%)	80 (53.7 %)	.
Mood stabilizers, n (%)	60 (40.3 %)	.
Benzodiazepines/Z-drugs, n (%)	75 (50.3 %)	.
Depression severity, mean (SD); median (IQR)	25.54 (14.51); 27 (14 – 37)	9 (6.0 %)
Melancholic symptoms, median (IQR)	7 (2–11)	6 (4.0 %)
Atypical symptoms, median (IQR)	2 (1 – 4)	8 (5.4 %)
Anxious symptoms, median (IQR)	3 (2 – 5)	8 (5.4 %)
Suicidal ideation (IDS-C30), median (IQR)	1.08 (1.15); 1 (0–2)	6 (4.0 %)
0, n (%)	65 (45.5 %)	
1, n (%)	25 (17.4 %)	
2, n (%)	29 (20.3 %)	
3, n (%)	24 (16.8 %)	
Suicidal ideation (IDC-C30), binary	78 (54.5 %)	6 (4.0 %)
CTQ total score, median (IQR)	47.00 (35.25 – 62.75)	21 (14.1 %)
Suicidal ideation (C-SSRS), mean (SD); median (IQR)	1.71 (1.95); 1 (0 – 3)	10 (6.7 %)
Suicidal ideation (C-SSRS), binary	75 (54.0 %)	10 (6.7 %)

Abbreviations: C-SSRS, Columbia Suicide Severity Rating Scale; IDS-C30, 30-item Inventory of Depressive Symptomatology – Clinician rating IQR interquartile range, SD, standard deviation;
Depressive symptom severity was measured with the IDS-C30 [range 0–84], which measured depressive symptoms in past week at inclusion at six-months follow-up. Atypical symptoms: hypersomnia, increased appetite, increased weight, leaden paralysis, and interpersonal rejection sensitivity [0–15]. Melancholic symptoms: loss of mood reactivity, loss of pleasure, morning insomnia, mood variation, psychomotor retardation, psychomotor agitation, anorexia or weight decrease, self-outlook, and quality of mood [0–30]. Anxious symptoms: anxious mood, somatic complaints, sympathetic arousal, panic/phobic symptoms, and gastrointestinal symptoms [0–15] (Arnow et al., 2015). Psychiatric diagnosis and comorbidities were assessed with the Mini-International Neuropsychiatric Interview for Diagnostic and Statistical Manual 5 (DSM-5).

3.3. Baseline analytes associated with suicidal ideation over the 6-months follow-up (since last visit), and with depression severity and suicidal ideation (last week) after 6 months

Over the follow-up, 51.4 % (N = 71) of individuals reported SI. In the Elastic Net, IFN-γ and MIP-1 α were selected as predictors of SI during follow-up. However, only the association with baseline IFN-γ was robust after adjusting for age, sex, BMI, diagnosis, SA history, baseline SI, and treatment, and a Bonferroni correction. This association did not survive Bonferroni correction when adjusted for baseline depression severity (Table 2). In a sensitivity analysis with patients without baseline SI (N = 59), the baseline plasma IFN-γ, but not MIP-1 α, concentration was associated with SI during the follow-up (N = 19; 32.2 %) after adjustment for age or SA history (only the former significant after the Bonferroni correction), but not for baseline depression severity (Supplemental Table S5).

Table 2
Associations between baseline markers and suicidal ideation during the follow-up.

Predictor variable	IFN-γ			MIP-1 α		
Elastic Net	β (95 % CI)	.	VIP, %	β (95 % CI)	.	VIP, %
	0.090 (0.084 – 0.096)	.	96.0 %	0.061 (0.055 – 0.068)	.	75.3 %
Binary regression	OR (95 % CI)	Wald	p-value	OR (95 % CI)	Wald	p-value
Model 1	**1.736 (1.193 – 2.526)**	**8.321**	**<0.001** **	1.278 (0.897 – 1.819)	1.849	0.164
Model 2	**2.102 (1.286 – 3.437)**	**8.783**	**0.009***	1.380 (0.893 – 2.133)	2.100	0.175
Model 3	**1.714 (1.168 – 2.514)**	**7.584**	**0.004** **	1.293 (0.896 – 1.867)	1.889	0.187
Model 4	**2.778 (1.608 – 4.802)**	**13.400**	**0.002** **	1.278 (0.841 – 1.943)	1.319	0.265

Abbreviations: CI, confidence interval; IFN-γ, Interferon-gamma; MIP-1 α, Macrophage Inflammatory Protein-1 alpha; OR, odds ratio.
Suicidal ideation was based on the Columbia Suicide Severity Rating Scale (C-SSRS) questionnaire suicidal ideation part, administered at 6-months follow-up, which asked about suicidal ideation since the initial evaluation. The outcome dichotomized into no suicidal ideation (score 0) versus any suicidal ideation (scores 1–5) was used in all cases. Biological analyte values were naturally log-transformed and z-normalized.
In the Elastic Net, which included all biological analytes, sex, age, and body mass index, the variable inclusion probability (VIP) was set at 75 %.
Model 1: adjusted for sex, age, body mass index (BMI), and primary psychiatric diagnosis (bipolar disorder versus major depressive disorder)
Model 2: adjusted for sex, age, BMI, primary psychiatric diagnosis, SA history, and baseline depression severity
Model 3: adjusted for sex, treatment groups (antidepressant, antipsychotic, mood stabilizer, and benzodiazepine/Z-drug) and tobacco use
Model 4: adjusted for sex, age, BMI, primary psychiatric diagnosis, suicide attempt (SA) history, and baseline C-SSCRS suicidal ideation score
* p<0.05,
** p<0.006 (Bonferroni-corrected, **bold),** two-sided. P-values were obtained by bootstrapping with 1000 permutations.

In the ordinal regression of SI trichotomized into none, passive, and active (Fig. 2), only the associations between baseline IFN-γ plasma concentration and follow-up SI survived adjustments for sex, SA history, baseline SI or depression severity, treatment, with the Bonferroni correction (Supplemental Table S6). A multinomial regression (Supplemental Table S7) showed that the differences were primary driven by the differences between no SI versus active SI during the follow-up.

When the outcome was the SI at the 6-month follow-up (last week) 28 % (N = 40) of individuals scored positive). Baseline plasma levels of IFN-γ, serotonin, IL-1β, RANTES, and MIP-1 α levels were selected as potentially associated with this outcome (VIP >75 %, Supplemental Table S8). In separate adjusted models, only low plasma serotonin remained significant after adjusting for age, sex, and BMI (OR 0.577, 95 % CI 0.378 – 0.881, p = 0.007), but this did not survive Bonferroni correction nor further adjustments for baseline depression, SI and SA history, and treatment. High baseline concentrations of IFN-γ and IL-1β were associated with SI at six-month follow-up in models adjusted for baseline depression severity (OR 1.729, 95 %CI 1.081 – 2.764, p = 0.026 and OR 1.597, 95 % CI 1.054 – 2.420, p = 0.020, respectively), and for

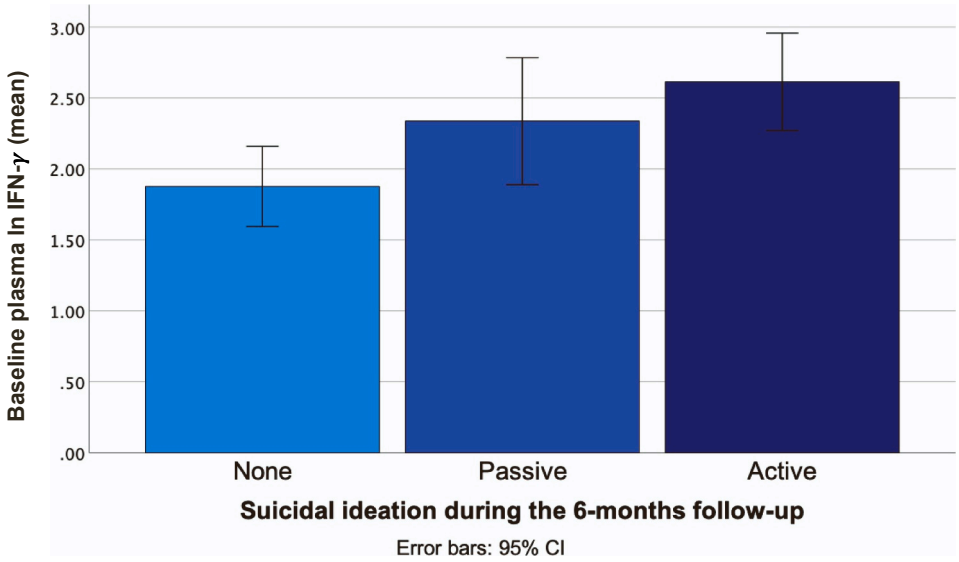

Fig. 2. Baseline ln IFN-γ levels according levels of suicidal ideation severity during the follow-up. Suicidal ideation was measured with the Columbia Suicide Severity Rating Scale (C-SSRS) suicidal ideation score, based on the six-month follow-up self-report.

SI and SA history (OR 1.706, 95 % CI 1.058 – 2.751, p = 0.048, and OR 1.663, 95 % CI 1.089 – 2.539, p = 0.016, respectively), but these associations did not survive Bonferroni correction.

Finally, baseline levels of IFN-γ and orexin-A were selected as possibly associated with the follow-up depression severity (VIP > 75 % in the Elastic Net with all biological analytes, age, sex, and BMI). The associations of high IFN-γ and low orexin-A with depression severity were robust for adjustments for sex, age, BMI, primary diagnosis, SA history, baseline depression severity, baseline treatment and tobacco use (except for the treatment and tobacco adjusted association between baseline IFN-γ and future typical symptoms). However, only the association between low orexin-A and follow-up depression severity, adjusted for age, sex, BMI, and diagnosis, survived the Bonferroni correction. In analyses examining depression symptom dimensions, the association of low orexin-A and high IFN-γ with the atypical and anxious symptom scores survived adjustments for confounders, including baseline depression severity. However, only the association between high IFN-γ and anxious symptoms, adjusted for age, sex, BMI, and diagnosis, survived the Bonferroni correction. The association between low orexin-A and atypical symptoms at follow-up approached Bonferroni-corrected significance in a parallel model (p = 0.009) (Table 3). None of the biomarkers were associated with the melancholic features.

3.4. Associations between changes in protein levels, depressive symptoms, and suicidal ideation during the 6-months follow-up

We observed an overall symptomatic improvement during the follow-up. Symptom changes are presented in Fig. 2 and reported in more detail in Supplemental Table S9. We also observed significant changes in biomarker levels in a subset of individuals (N = 96) who had a follow-up blood draw (Supplemental Table S2).

The only significant correlations observed between changes in symptoms and plasma protein levels, after adjustment for age, sex, BMI, and diagnosis, were as follows: a positive correlation between reduction in atypical symptoms and decrease in TGF-β1 plasma levels (rho = 0.282 (95 % CI 0.053 – 0.476, p = 0.008), and a negative correlation between change in serpin plasma concentration and reduction in melancholic symptoms (rho = −0.312 (95 % CI −0.518 – (-0.098), p = 0.002). See the heatmap in Supplemental Figure S2. The positive association between changes in TGF-β1 and atypical symptoms was robust to further adjustment for antidepressant use, tobacco use, and baseline depression severity (rho = 0.339 (95 % CI 0.155 – 0.523, p = 0.002). However, the negative correlation between serpin level changes and melancholic symptoms was diminished in significance (rho = −0.236 (95 % CI −0.451 – 0.015), p = 0.031). Finally, in the Elastic Net including all biological analytes, age, sex, and BMI, no changes in biological analytes were associated with the presence of SI at follow-up in more than 75 % of cases. Conversely, changes in IFN-γ and IL-4 were initially associated with depression severity at follow-up, as detailed in Supplemental Table S10; however, these associations did not withstand additional adjustments for covariates and multiple testing corrections.

4. Discussion

In this prospective analysis in individuals seeking treatment for mood disorders, we utilized Elastic Net, and regression analyses to evaluate relationships of 32 plasma markers with SI over a six-month follow-up period, as well as with SI and depression severity at 6-month follow-up and at baseline. The main finding was that baseline plasma IFN-γ concentration was associated with the self-reported SI over the 6 months follow-up period, independently of baseline SI, depression severity, and history of SA. We also observed associations between high baseline IL-1β and SI (last week) at 6-months follow-up, and between high baseline IFN-γ and low baseline orexin-A and follow-up depression severity, with specific associations with depressive symptom profiles.

We found no cross-sectional associations between plasma biomarkers and either depression severity or SI, a finding that aligns with previous small-to-moderate size studies (Fernandes et al., 2016; Zalli et al., 2016). Notably, effect sizes in cross-sectional studies between symptom severity and inflammatory markers tend to be small (Köhler-Forsberg et al., 2017; Lengvenyte et al., 2022). However, longitudinal studies, primarily conducted in community samples, suggest that higher baseline levels of inflammatory markers may be associated with future depressive symptoms (Toenders et al., 2022). Furthermore, patients with mood disorders displaying elevated proinflammatory markers, related gene polymorphisms or proinflammatory gene expression profiles tend to respond poorly to antidepressants and are more prone to relapse (Baune et al., 2010; Strawbridge et al., 2015). Conversely, classic and novel antidepressants and other medications, including mood stabilizers and antipsychotics, have anti-inflammatory properties (Al-Amin et al., 2013; Lengvenyte et al., 2019b; Leu et al., 2017; Tynan et al., 2012).

An important finding our study is the association of baseline plasma IFN-γ concentration with the SI over the 6-months follow-up, and

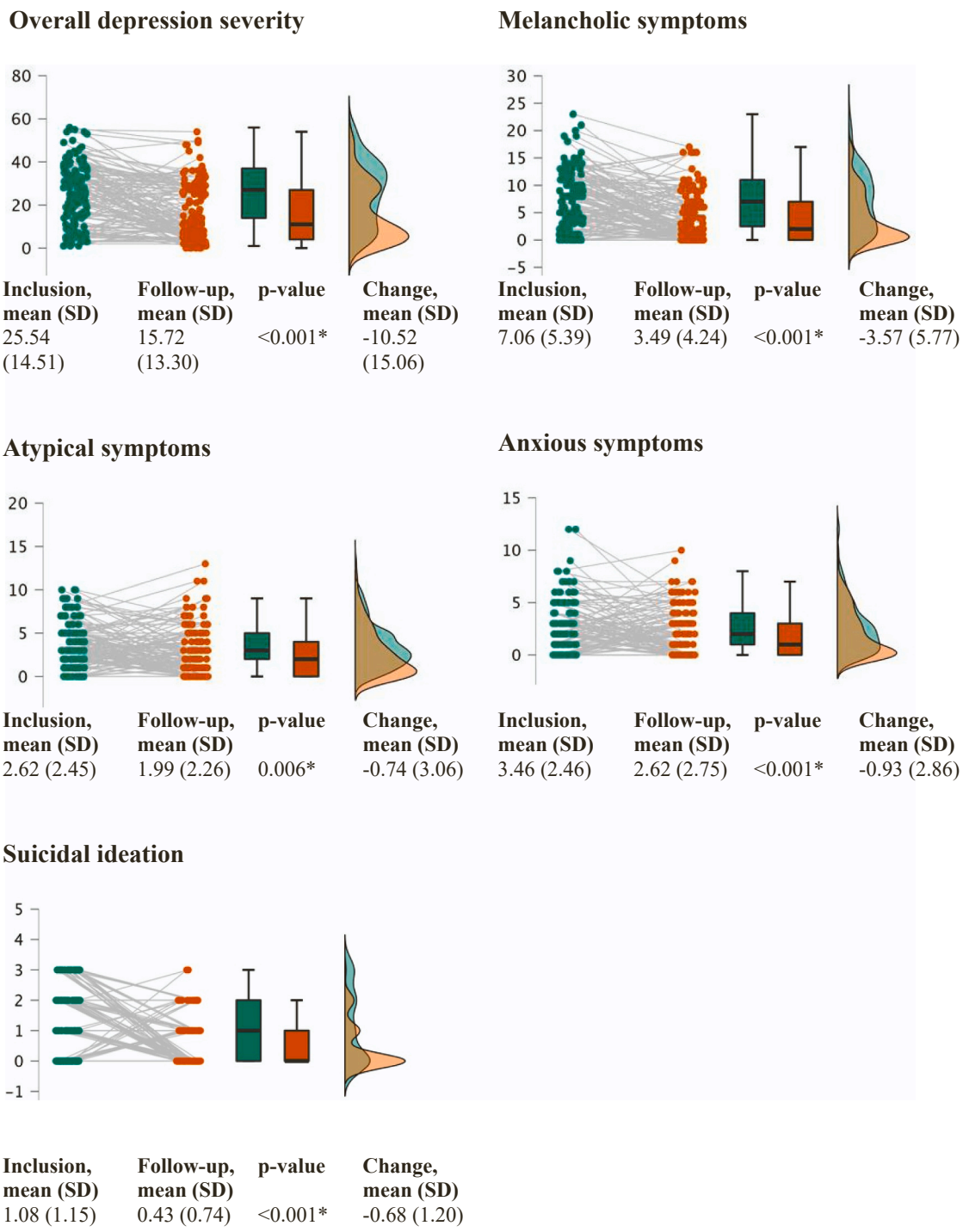

Fig. 3. Symptom change between the baseline and 6-month follow-up. Baseline measurements are depicted in green, and follow-up measurements are depicted in peach. Depressive symptom severity was measured with the IDS-C30 [score range 0–84], which measured depressive symptoms in past week at inclusion at six-months follow-up. Atypical symptoms: hypersomnia, increased appetite, increased weight, leaden paralysis, and interpersonal rejection sensitivity [0–15]. Melancholic symptoms: loss of mood reactivity, loss of pleasure, morning insomnia, mood variation, psychomotor retardation, psychomotor agitation, anorexia or weight decrease, self-outlook, and quality of mood [0–30]. Anxious symptoms: anxious mood, somatic complaints, sympathetic arousal, panic/phobic symptoms, and gastrointestinal symptoms [0–15] (Arnow et al., 2015). Suicidal ideation was the IDS-C30 suicidal ideation item score [0–3]. *Related samples Wilcoxon signed rank test, two-sided tests.

depression severity, especially anxious symptoms, at the follow-up, associations absent at baseline. Importantly, these associations were observed despite our sample excluding individuals with acute inflammatory conditions or those on anti-inflammatory treatments. Moreover, the link between IFN-γ and SI during the follow-up remained robust after adjusting for baseline SI and depression severity, and among those without baseline SI, alluding to a potential pathophysiological link. While there are no studies with IFN-γ treatment, our findings mirror previous research involving individuals receiving IFN-α and IFN-β treatment (Udina et al., 2012). For instance, a third of individuals under IFN-α therapy meet DSM-5 criteria for a major depressive episode several weeks to months post-treatment initiation (Davies et al., 2021),

Table 3
Associations between baseline markers and depression severity at six-months follow-up.

Predictor:	IFN- γ			Orexin-A		
	B (95 % CI)	β	p-value or VIP%	B (95 % CI)	β	p-value or VIP%
Outcome: depression total score						
Elastic Net	0.105 (0.097 – 0.111)	.	96.3 %	-0.070 (-0.076 – (-0.065)	.	85.2 %
Model 1	2.619 (0.464 – 4.884)	0.205	0.025*	**-3.134 (-5.224 – (-1.023)**	**-0.248**	**0.007****
Model 2	2.074 (0.085 – 4.077)	0.166	0.042*	-2.701 (-5.049 – (-0.403)	-0.211	0.025*
Model 3	2.364 (0.188 – 4.436)	0.185	0.034*	-2.825 (-5.283 – (-0.431)	-0.223	0.030*
Outcome: atypical symptom score						
Model 1	0.377 (0.039 – 0.719)	0.174	0.027*	-0.545 (-0.951 – (-0.163)	-0.244	0.009**
Model 2	0.325 (-0.001 – 0.662)	0.151	0.048*	-0.470 (-0.841 – (-0.066)	-0.210	0.016*
Model 3	0.330 (-0.011 – 0.685)	0.152	0.065	-0.554 (-0.971 – (-0.137)	-0.248	0.010*
Outcome: melancholic symptom score						
Model 1	0.405 (-0.307 – 1.110)	0.096	0.266	-0.575 (-1.417 – 0.246)	-0.141	0.165
Model 2	0.221 (-0.459 – 0.914)	0.055	0.512	-0.510 (-1.351 – 0.297)	-0.123	0.237
Model 3	0.348 (-0.417 – 1.100)	0.083	0.358	-0.469 (-1.244 – 0.323)	-0.115	0.244
Outcome: anxious symptom score						
Model 1	**0.683 (0.198 – 1.160)**	**0.244**	**0.005****	-0.609 (-1.166 – (-0.061)	-0.215	0.041*
Model 2	0.587 (0.084 – 1.001)	0.210	0.016*	-0.552 (-1.070 – (-0.020)	-0.192	0.038*
Model 3	0.610 (0.147 – 1.036)	0.218	0.015*	-0.643 (-1.206 – (-0.115)	-0.227	0.031*

Abbreviations: CI, confidence interval; IFN-γ, Interferon alpha.
Biological analyte values were naturally ln-transformed and z-normalized.
Depression severity is measured with the 30-item Inventory of Depressive Symptomatology – Clinician rating (IDS-C30). Atypical symptoms: hypersomnia, increased appetite, increased weight, leaden paralysis, and interpersonal rejection sensitivity [0–20]. Melancholic symptoms: loss of mood reactivity, loss of pleasure, morning insomnia, mood variation, psychomotor retardation, psychomotor agitation, anorexia or weight decrease, self-outlook, and quality of mood [0–40]. Anxious symptoms: anxious mood, somatic complaints, sympathetic arousal, panic/phobic symptoms, and gastrointestinal symptoms [0–20] (Arnow et al., 2015)
Model 1: adjusted for sex, age, and body mass index (BMI), and primary psychiatric diagnosis (bipolar disorder versus major depressive disorder)
Model 2: adjusted for sex, age, BMI, primary psychiatric diagnosis, suicide attempt history, and baseline depression severity
Model 3: adjusted for sex, treatment groups (antidepressant, antipsychotic, mood stabilizer, and benzodiazepine/Z-drug) and tobacco use
* $p<0.05$
** $p<0.008$ (Bonferroni-corrected, **bold**), two-sided. 95 % CI and p-values were obtained by 1000-bootstrapping.

with SI and SA also reported (Sockalingam et al., 2011). Recurrences of depression and SI have been observed even 6 months post-antiviral treatment termination (Chiu et al., 2017).

Although less well studied, the IFN-γ, a T-helper type 1 pro-inflammatory cytokine, has also been implicated in psychopathology. An indirect evidence comes from observational studies on *T. gondii* infection, which elicits release of IFN-γ primarily by cells of the innate immune system (Miller et al., 2009), and has been associated with mental health problems and SA (Sutterland et al., 2019). In support, preclinical studies have suggested that acute infection with an IFN-γ adenovector provoked long-lasting anhedonia-like behavioral changes in mice (Kwant and Sakic, 2004). While prospective clinical studies are lacking, conflicting evidence exists regarding the cross-sectional link between MDD and IFN- γ levels, pointing to both increase and decrease in MDD patients compared to healthy controls (Chen et al., 2021; Köhler et al., 2017). Increased IFN-γ levels have also been linked to experienced intimate partner violence and PTSD symptoms (Woods et al., 2005). With this study the evidence grows, revealing that plasma concentration of IFN-γ could potentially help identify individuals at risk of unfavorable mood disorder progression rather than identifying cross-sectional differences between healthy individuals and those with mood disorders. Meanwhile, antidepressants have been shown to suppress IFN-γ production (Kubera et al., 2001), and depression improvement has been linked to IFN-γ reduction in plasma (Dahl et al., 2014). In our study, associations between baseline IFN-γ and future symptoms were independent from antidepressant use, but antidepressants may have mitigated the observed effects. Future research might explore anti-inflammatory strategies showing initial promise in mood disorders, specifically when stratifying on elevated IFN-γ levels.

We found a possible association between baseline concentration of a pro-inflammatory cytokine IL-1β, and past-week SI at 6-months follow-up, in models adjusted for depression and SI. While this association did not survive a strict Bonferroni correction or adjustments for medications and remains to be confirmed, this finding is in line with a previous study highlighting the link between IL-1β reactivity and one-year follow-up depression severity (Aschbacher et al., 2012). IL-1β predominantly interacts with inflammasome complex, oxidative stress, and neurodegeneration (Cattaneo et al., 2016). Such associations might reflect inflammation-associated cognitive processes potentially disrupting a favorable course of illness. Increased IL-1β levels have been linked to passive coping (Wood et al., 2015), which may obstruct cognitive bias shifts and behavioral changes associated with an antidepressant response (Harmer et al., 2017). Numerous studies have linked elevated IL-1β levels and related genetic variants with treatment resistance in mood disorders (Baune et al., 2010; Murata et al., 2020). Interestingly, both IFN-γ and IL-1β induce the enzyme indoleamine 2,3-dioxygenase (IDO), causing impaired serotonin metabolism (Taylor and Feng, 1991).

A notable finding was the association of low baseline orexin-A with follow-up depression severity. Orexin-A, a hypothalamic neuropeptide, modulates appetite, sleep-wake cycle, stress response, and reward processing (Ji et al., 2019). Chronic antagonism of orexin receptors mitigates depressive-like behaviors in rodents (Mirbolouk et al., 2023). In humans, orexin receptor antagonists improve sleep outcomes in individuals with insomnia (Savitz et al., 2021). Yet, low orexin-A levels have been associated with MDD, BD, and narcolepsy (Brundin et al., 2007; Nishino et al., 2000; Tsuchimine et al., 2019). We found that low baseline orexin-A levels were associated with severity of atypical and to a lesser degree anxious, but not melancholic, symptoms at follow-up, though these associations were not robust to Bonferroni corrections and need confirmation. If confirmed, these associations could suggest that while orexin antagonists may be beneficial for insomnia, low orexin-A concentration might increase the risk of developing atypical symptoms like hypersomnia and increased appetite, paving the way for a personalized approach in depression treatment.

Finally, we observed clinical improvements in symptoms and changes in biomarker levels. Among the biomarkers, only the correla-

tion between the reduction in TGF-β1, a primarily anti-inflammatory cytokine, and a reduction in atypical (but not melancholic or anxious) symptoms was robust to adjustments for covariates. Notably, increased levels of TGF-β1 have been consistently linked to chronic fatigue syndrome and its severity (Strawbridge et al., 2019), which has a significant symptomatic overlap with atypical depression. Although these findings are exploratory, they suggest that markers like IFN-γ may serve more as 'predictors' to identify individuals at risk of unfavorable progression, whereas changes in TGF-β1 plasma concentration may serve as a possible 'target' reflecting the change in atypical symptoms.

5. Limitations

Several limitations are worth acknowledging. Firstly, although rigorous statistical methods were employed to mitigate the risk of false positive findings, this study was secondary in nature, and therefore reported results should be considered as exploratory. The modest sample size may have prevented the detection of more nuanced associations. High attrition rates, particularly among participants with more severe baseline SI and depression, could have introduced bias, potentially underestimating the strength of reported associations. Moreover, the health trajectories of individuals lost to follow-up remain unknown.

Due to the single evaluation of the presence of SI over a six-month follow-up period, the reporting of SI may be subject to recall bias. Additionally, evaluating depressive symptoms solely at the six-month follow-up did not permit an assessment of the ongoing symptom burden and dynamics throughout the period. Future research should consider repeated, fine-grained assessments to capture the evolution of symptoms over time more accurately. Changes in medications, diagnoses, or mood states between assessments were not documented, precluding analysis of their impact on the study outcomes. Although we adjusted our analyses for baseline treatment by major psychiatric medication groups, we could not perform more detailed analyses, and treatment changes during follow-up were not documented. Future studies should investigate the role of medications, including their duration and changes, as these factors are known to affect both symptomatology and biological markers (Gupta et al., 2016; Näslund et al., 2018). We also included only patients with mood disorders from a tertiary care center, thus limiting generalizability and comparison with healthy controls. Since many people did not return for follow-up blood draw, temporal dynamics in biomarkers are to be further explored. While our analysis included both BD and MDD patients and controlled for diagnosis, we could not perform disease-specific analyses due to limited sample size. Lastly, there was no separate validation set.

6. Conclusions

In conclusion, this exploratory study suggests a potential association between baseline plasma levels of IFN-γ and the occurrence of SI during a six-month follow-up in individuals seeking treatment for mood disorders. Furthermore, symptom-specific associations were observed between baseline levels of IFN-γ, IL-1β, and orexin-A with depressive symptoms at the six-month follow-up. A reduction of TGF-β1 plasma concentration was positively correlated with a reduction in atypical symptoms. These findings highlight the potential utility of peripheral blood biomarkers in identifying individuals at risk of unfavourable depression outcomes. Given the exploratory nature of the study, further research is needed to confirm these associations. If such associations were to be confirmed, potential clinical implications include development of clinical prediction models and more targeted treatment strategies.

CRediT authorship contribution statement

Robertas Strumila: Writing – review & editing. **Maude Sénèque:** Project administration. **Philippe Courtet:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Emilie Olié:** Writing – review & editing, Project administration, Investigation. **Hind Hamzeh-Cognasse:** Writing – review & editing, Validation, Methodology. **Fabrice Cognasse:** Writing – review & editing, Validation, Methodology. **Aiste Lengvenyte:** Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2024.107119.

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