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RESEARCH PAPER

ASSOCIATION BETWEEN CIRCULATING CYTOKINES AND PSYCHOSOMATIC SYNDROMES IN PATIENTS WITH MOOD DISORDERS

Mario Altamura, Livia Ficarella, Ivana Leccisotti, Rossana Laurello, Michele Carapellese, Benedetta Vai, Francesco Benedetti, Antonello Bellomo

Abstract

Objective: elevated levels of pro-inflammatory cytokines are frequently observed in mood disorders, but their relationship with psychosomatic symptomatology remains underexplored. This study aimed to examine whether interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are associated with psychosomatic syndromes in patients with major depression (MD) and bipolar depression (BD), and whether these associations are moderated by sex.

Method: seventy-seven outpatients with MD or BD were assessed using the Diagnostic Criteria for Psychosomatic Research-Revised (DCPR-R) and the Patient Health Questionnaire-15 (PHQ-15) to evaluate psychosomatic symptoms. Depression and mania severity were measured with the Beck Depression Inventory-II (BDI-II) and the Mania Rating Scale (MRS). Circulating levels of IL-6 and TNF-α were analyzed. Associations were tested using multivariate regression and mediation analyses, controlling for demographic and health-related variables.

Results: both IL-6 and TNF-α were significantly associated with psychosomatic syndromes (as per DCPR-R) and PHQ-15 scores. IL-6, in particular, showed a strong association with persistent somatization (PS). These relationships remained significant after adjusting for affective-cognitive depressive symptoms and potential confounders. No significant moderating effect of sex was identified. Mediation analyses suggested that psychosomatic syndromes mediate the relationship between inflammatory cytokines and depressive symptomatology.

Conclusions: findings suggest that the link between inflammation and mood disorders is more closely related to psychosomatic syndromes than to mood symptoms alone. Elevated IL-6 levels may reflect somatization processes within depression rather than being directly pro-depressive. Psychosomatic syndromes may thus represent a key clinical and therapeutic target in mood disorders with elevated inflammation.

Key words: diagnostic criteria for psychosomatic research-revised, inflammation, cytokines, somatization, overload, depression

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Introduction

Research has consistently shown that individuals with mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), exhibit a significantly higher prevalence of medically unexplained somatic symptoms compared to general population controls or patients with other psychiatric diagnoses (Bekhuis et al., 2015; Edgcomb et al., 2016; Kapfhammer, 2006; Stubbs et al., 2015; Vaccarino et al., 2008). Earlier studies have shown that the prevalence of somatic symptoms among patients with MDD was in the range of 43%–78% (Vaccarino et al., 2009). Significantly, these medically unexplained somatic complaints, encompassing a broad range of physical discomforts and neurovegetative disturbances such as pain, fatigue, and gastrointestinal or cardiopulmonary symptoms, have emerged as robust predictors of poorer outcomes in major depressive disorder, independently of co-occurring somatic diseases, lifestyle factors, and baseline disability (Bekhuis et al., 2016; Bohman et al., 2018). Compared to non-somatic depression, somatic depression is associated with distinct brain imaging abnormalities, including functional resting-state alterations in regions such as the precentral gyrus, paracentral gyrus, and prefrontal cortex. These findings suggest that depression with somatic symptomatology may represent a distinct subtype of the disorder (Geng et al., 2019; Liu et al., 2021; Zu et al., 2019). The estimated prevalence of somatic symptoms in bipolar spectrum disorders was 47.8% (Edgcomb et al.,

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2016). In BD, medically unexplained symptomatology has been identified as an independent marker of greater disease severity, heightened risk of suicidality, and a rapid-cycling course, irrespective of comorbid anxiety disorders or concurrent somatic conditions (Edgcomb & Kerner, 2018).

While the relevance of somatic symptomatology in mood disorders is well recognized, the underlying mechanisms driving the emergence of medically unexplained somatic symptoms remain largely unexplored and poorly understood. Importantly, in this context, somatic symptoms in patients with depression and other mood disorders are increasingly understood within the framework of psychosomatic medicine (Mewes, 2022). Rather than being seen as mere residuals or epiphenomena of mood disturbances, these symptoms are often regarded as psychosomatic manifestations, where psychological factors and biological mechanisms, such as neuroendocrine and immune dysregulation, contribute to their onset, maintenance, and clinical course (Altamura et al., 2022; Fava et al., 2017; Desai & Chaturvedi, 2016; Majd et al., 2020). Supporting this perspective, heightened pro-inflammatory activity has been implicated in the pathophysiology of psychosomatic conditions such as fibromyalgia and chronic fatigue syndrome (Anderson et al., 2014; Dantzer et al., 2008; Van der Feltz-Cornelis et al., 2020). Nevertheless, the precise psychobiological mechanisms underlying psychosomatic syndromes in mood disorders remain largely elusive, underscoring the need for integrative research to elucidate their etiopathogenesis and guide the development of targeted therapeutic strategies.

A growing body of evidence indicates that both major MDD and BD are linked to elevated levels of inflammatory markers (Altamura et al., 2024; Dowlati et al., 2010; Harsanyi et al., 2022; Min et al., 2023; Modabbernia et al., 2013; Munkholm et al., 2013; Stewart et al., 2009; Ting et al., 2020). Immune dysregulations in mood disorders include abnormal peripheral levels of low-grade inflammation cytokines, chemokines, cell populations, gene expression, and markers of both peripheral and central immune activation, with marked differences between BD and MDD, and alterations common to the two diagnosis which include high pro-inflammatory cytokines such as Interleukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α) (Dowlati et al., 2010; Min et al., 2023; Poletti et al., 2024; Solmi et al., 2021). Over the last decades research involving individuals with depression has shown that somatic symptoms are associated with elevated cytokine levels suggesting that inflammation may play a causal role in the development of somatic distress and neurovegetative disturbances, rather than cognitive-affective symptoms (Altamura et al., 2022; Chu et al., 2019; Duivis et al., 2013; Euteneuer et al., 2012; Hazeltine et al., 2022; Janszky et al., 2005; Li et al., 2017; Maid et al., 2020). Longitudinal studies have suggested that inflammation may contribute to depressive somatic symptomatology, rather than simply serving as a secondary consequence of the disorder (Chu et al., 2019; Ernst et al., 2021). Most importantly, findings obtained with the model of cytokine-induced depression in medically ill patients undergoing cytokine immune therapy have shown that somatic symptoms develop rapidly in the majority of patients who develop depression, while psychological symptoms (e.g., low mood and cognitive symptoms) develop slowly at later stages of treatment (Capuron et al., 2002; Capuron & Castanon, 2017). The biphasic onset of cytokine-induced symptomatology suggests that somatic symptoms may serve as critical mediators in the link between inflammation and depression (Capuron & Castanon, 2017; Chu et al., 2019). However, there is limited research investigating whether the associations between inflammation and depression are mediated by somatic symptomatology. This gap in knowledge highlights the need for studies that specifically examine the role of somatic symptoms as potential mediators in the inflammation-depression link (Song et al., 2022). Regarding sex, both epidemiological and experimental studies have highlighted significant differences in the relationship between depression and inflammation (Derry et al., 2015; Jarkas et al., 2024). Notably, these differences seem to be predominantly influenced by somatic symptoms (Duivis et al., 2013; Niles et al., 2018). Although extensive evidence links inflammatory cytokines to somatic symptoms in mood disorders, no study has yet investigated their association with psychosomatic syndromes, with the aim of elucidating the underlying biological pathways. This knowledge gap likely reflects the challenges in identifying subtle psychosomatic phenomena and capturing patients' complex subjective experiences, which are frequently underrecognized in clinical practice (Duivis et al., 2013; Euteneuer et al., 2011). In this study, we evaluated psychosomatic symptoms using the revised version of the Diagnostic Criteria for Psychosomatic Research-Revised (DCPR-R). The Diagnostic Criteria for Psychosomatic Research (DCPR) provide a structured and clinically oriented framework for identifying and classifying psychosomatic syndromes. In addition, they enable the detection of subsyndromal psychosomatic psychopathology—often overlooked or undetected by conventional diagnostic systems—thereby improving the assessment of patients presenting with unexplained somatic symptoms. The DCPR-R encompasses 14 psychosomatic syndromes categorized into four distinct clusters: stress-related conditions (allostatic load); abnormal illness behaviors (including hypochondriasis, health anxiety, disease phobia, thanatophobia, illness denial, persistent somatization, conversion symptoms, and anniversary reaction); subclinical affective disturbances (such as irritable mood, somatic symptoms secondary to psychiatric disorders, and demoralization); and specific personality traits (type A behaviour and alexithymia) (Fava et al., 2017). Notably, the DCPR include the categories of "Persistent Somatization" and "Functional Somatic Symptoms Secondary to Psychiatric Disorders" (e.g., palpitations, sweating, tremor, flushing), which can be regarded as refined substitutes for traditional notions of somatization. These categories capture somatic complaints that are not merely residual effects of mood disorders but instead represent complex manifestations arising from the interplay of emotional, cognitive, and biological factors (Fava et al., 1994; Sonino et al., 1998; Bellomo et al., 2007). The validity and clinical utility of the DCPR have been well-documented in patients with mood disorders, supporting their potential integration with the DSM-5 to enhance the comprehensiveness of clinical assessments (Altamura et al., 2015; Bellomo et al., 2007; Porcelli & Guidi, 2015; Porcelli & Rafanelli, 2010).

Investigating the association between elevated inflammatory cytokines and DCPR psychosomatic syndromes in mood disorders is crucial for clarifying their psychobiological underpinnings and guiding the refinement of diagnostic frameworks and therapeutic approaches. Such efforts may also enable the stratification of patients into clinically meaningful subgroups, ultimately fostering personalized interventions that address individual profiles and

needs (Fried et al., 2020). The primary objective of this study was to compare levels of proinflammatory cytokines (IL-6 and TNF-α) in patients with mood disorders who either exhibited or did not exhibit DCPR syndromes. Subsequently, we examined potential associations between these inflammatory markers and specific DCPR syndromes. Furthermore, we examined whether psychosomatic syndromes mediate the relationship between inflammation and depressive symptomatology and assessed the potential moderating role of sex in this mediation. Based on previous literature, we hypothesized that patients meeting criteria for DCPR syndromes would exhibit higher levels of proinflammatory cytokines and that these psychosomatic syndromes would partially mediate the association between inflammation and depressive psychopathology.

Methods

Adult patients with confirmed diagnoses of MDD or BD Type I-II were consecutively recruited from the community mental health services in Foggia, Italy, between March 2023 and February 2024. All testing procedures were completed in a single day. Baseline data were gathered for each patient, covering demographic factors, personal health habits, medication usage, and medical history. Inclusion criteria required a diagnosis of either MDD or BD according to DSM-5 guidelines, which was verified using the Structured Clinical Interview for DSM-5 (SCID-5-CV) (First et al., 2015). Exclusion criteria for participants included the following: the presence of major medical or neurological conditions; a history of drug or alcohol abuse or dependency; symptoms related to inflammation, such as fever or infectious or inflammatory diseases; uncontrolled systemic or metabolic disorders, or other significant physical conditions known to influence mood; and the use of medications known to impact mood or the immune system, including corticosteroids, non-steroidal anti-inflammatory drugs, and statins. The severity of depressive symptoms was assessed using the Beck Depression Inventory (BDI), a standardized tool designed to measure the intensity of depressive states (Beck et al., 1996). The Beck Depression Inventory II (BDI-II) is a 21-item self-report tool designed to measure the severity of depressive symptoms. Each item is rated on a 4-point scale, ranging from 0 (symptom not present) to 3 (severe symptom), yielding a total score between 0 and 63. Depression severity is categorized as follows: minimal depression (scores 0–13), mild depression (14–19), moderate depression (20–28), and severe depression (29–63). Most studies examining the factorial structure of the BDI-II support a two-factor model comprising cognitive-affective and somatic-vegetative dimensions (Wang & Gorenstein, 2013). In our study, we utilized these dimensions by categorizing BDI-II items accordingly: items 1–14 (e.g., sadness, pessimism, past failure, loss of pleasure, guilt, self-dislike, suicidal ideation, indecisiveness, worthlessness) were summed to define the cognitive-affective subscale. Items 15–21 (e.g., loss of energy, sleep disturbances, irritability, appetite changes, fatigue, and loss of interest in sex) were combined to calculate the somatic subscale (Stapel et al., 2022). This approach allows for a nuanced evaluation of depressive symptoms across these two domains. To ensure recovery from manic symptoms, BD patients were included only if they scored ≤8 on the Young Mania Rating Scale (YMRS) (Young et al., 1978). Psychosomatic factors assessed with the Diagnostic Criteria for Psychosomatic Research – Revised version (DCPR-R) and the Patient Health Questionnaire (PHQ-15). The DCPR-R is administered through a face-to-face interview, which typically requires 15 to 30 minutes to complete. It includes questions scored in a yes/no format to evaluate the presence of 14 distinct psychosomatic syndromes. A patient can be diagnosed with more than one syndrome simultaneously, reflecting the complex and overlapping nature of psychosomatic psychopathology (Fava et al., 2017). The PHQ-15 (Patient Health Questionnaire-15) is a widely utilized screening tool for assessing somatic symptoms in patients, especially in clinical settings for mental health and psychosomatic evaluations. It includes 15 items that focus on common physical symptoms such as pain, gastrointestinal distress, and fatigue, which are rated by the patient on a 3-point scale: 0 ("not bothered at all"), 1 ("bothered a little"), and 2 ("bothered a lot") (Kroenke et al., 2002). Blood samples were collected from participants' antecubital veins using a vacutainer during outpatient clinic hours, which spanned from 8 a.m. to 5 p.m. (Kupper et al., 2012). Immediately after collection, the samples were placed on ice and centrifuged within 30 minutes. The resulting serum was stored at -80°C until further analysis. Inflammatory markers, specifically TNF-alpha and IL-6, were quantified using enzyme-linked immunosorbent assay (ELISA) kits. The sensitivity for TNF-alpha was 0.75 pg/ml (RayBiotech, Inc.), and for IL-6, it was 0.81 pg/ml (Abcam). Each sample was analyzed in duplicate, with the average value being calculated (Altamura et al., 2022). All participants provided informed consent in accordance with the Declaration of Helsinki, and the study was approved by the local ethics committee (9/CE/2016).

Statistical analyses

Statistical analyses were conducted using IBM SPSS Statistics software, version 26.0. Descriptive analysis was employed to assess patient characteristics. Chi-square tests were used for categorical data, while t-tests were applied for continuous data. To determine the normality of each dataset, kurtosis and skewness were calculated. To examine the relationship between inflammatory cytokines (independent variables) and dependent variables (DCPR syndromes, PHQ-15), both univariate and multivariable logistic and linear regression models were used. Only DCPR syndromes present in over 10% of participants were included as dependent variables (Altamura et al., 2018). To minimize overfitting and comply with recommended participants-to-predictors ratios (Harrell, 2015; Peduzzi et al., 1996), we adopted a two-step modelling strategy. First, univariate regression analyses were conducted for each inflammatory marker (IL-6, TNF-α) and each psychosomatic outcome (DCPR syndromes, PHQ-15) (Altamura et al., 2022). For each predictor–outcome association, age, sex, illness duration, education level, body mass index (BMI), smoking habits, chronic medical conditions, depressive symptoms (BDI scores), and psychotropic medication use (antidepressants, antipsychotics, mood stabilizers) were evaluated as potential confounders, based on their established associations with inflammatory markers (Fried et al., 2020). Gender, smoking status (never/past vs current), chronic disease, and psychotropic medication use were recoded as dichotomous variables. Covariates that altered the strength of the association by >10% were classified as confounders and retained in the final models, following established epidemiologic guidelines (Maldonado & Greenland, 1993; Rothman et

al., 2008). Second, multivariable regression models were performed for each biomarker, including only the subset of covariates identified as true confounders. To address the issue of multiple comparisons, Bonferroni correction was applied to adjust the significance threshold.

Mediational model

To explore the mediating effect of psychosomatic conditions, we summed the number of syndromes for each patient. The relationship between pro-inflammatory cytokines (IL-6 and TNF-α) and depressive symptomatology (BDI total score and its subdomains) was examined, with psychosomatic syndromes (measured by the sum of DCPR syndromes – DCPR sum – and PHQ-15) considered as potential mediators in this relationship. This analysis involved evaluating key assumptions, including the significant predictive relationships between inflammatory markers and depressive symptoms, between psychosomatic dimensions and depressive symptoms, and between inflammatory markers and psychosomatic dimensions. Further models were also created to assess the moderative effect of sex on mediation, considering its potential effects on these relationships. Mediation and moderated mediation analyses were performed by using a nonparametric resampling procedure implemented in a SPSS macro-PROCESS, with respectively model 4 and 59 (Preacher & Hayes, 2009) (http://www.processmacro.org/index.html). 5.000 bootstrap resamples were used to generate 95% confidence percentile intervals. Standardised indirect effects were used to evaluate the effect size of the indirect effect (Preacher & Kelley, 2011; Fairchild et al., 2009).

Results

A total of 98 outpatients were invited to participate in the study, with 21 (21.4%) declining. The most frequently cited reason for refusal was a lack of time. Consequently, the sample included 77 patients with established diagnoses of MDD or BD. A small number of cytokine concentrations were undetectable (N = 4), with TNF-α being undetectable in three individuals and IL-6 in one individual. These values were substituted with the minimum detectable value (sensitivity threshold) in accordance with standard procedures for handling such cases (Horesh & Iancu, 2010). The cytokine values were log-transformed to achieve a normal distribution for statistical analysis. Despite this transformation, the cytokine data are presented as the mean ± SD of the original (untransformed) values to facilitate comparison with results from other studies (Tab.1). The results for demographic and clinical variables are shown in **table 1**. No significant differences were observed between the participants and those who declined to participate, in terms of demographic characteristics. All patients were receiving appropriate pharmacological treatment, including antidepressants, mood stabilizers, and atypical antipsychotics, either as monotherapy or in various combinations. Based on BDI-II cut-off scores that categorize depression severity, 21 participants (27.3%) reported minimal depressive symptoms, 22 (28.6%) experienced mild depressive symptoms, 23 (29.8%) had moderate symptoms, and 11 (14.3%) scored in the severe depressive symptom range. The duration of illness varied from 5 to 20 years, with a median of 9 years. Thirty-seven patients (37%) had at least one co-occurring medical condition, most commonly cardiovascular (41%), endocrine (32%), and metabolic (11%) disorders. 52 patients (67.5%) met the criteria for at least one DCPR diagnosis (DCPR+), with 18.1% having a single diagnosis (DCPR=1) and 49.3% having more than one (DCPR >1). The most commonly observed DCPR syndromes in the study were Allostatic Overload Syndrome (AOS) (41%, N=32), Persistent Somatization (PS) (35%, N=27), Demoralization (30%, N=23), and Functional Somatic Symptoms Secondary to a Psychiatric Disorder (FSS) (14%). Patient characteristics based on their DCPR status are summarized in **table 2**. No significant differences were found between patients who received at least one DCPR diagnosis (DCPR+) and those without a DCPR diagnosis (DCPR-) in terms of age, gender, BMI, BDI-II cognitive/affective scores, and YMRS scores. DCPR distress associated with a higher severity of depressive psychopathology, and with raised levels of cytokines. Patients with at least one DCPR diagnosis scored significantly higher on both the total and somatic subscale of the BDI-II, as well as on the PHQ-15. Additionally, these patients exhibited significantly higher levels of the pro-inflammatory cytokines IL-6 and TNF-alpha compared to those without DCPR diagnoses. **Table 3** and **4** summarize the regression analyses of the association between inflammatory markers and dependent variables (DCPR syndromes, PHQ-15). In the multivariable analyses, the association between IL-6 and DCPR syndromes (i.e., Persistent Somatization and Functional Somatic Symptoms Secondary to Psychiatric Disorders) was adjusted for covariates including age, smoking status, depressive symptoms (BDI), and comorbidity, as only these were identified as confounders. The association between TNF-α and DCPR syndromes (i.e., Demoralization, Allostatic Overload, and Functional Somatic Symptoms Secondary to Psychiatric Disorders) was adjusted for gender, age, smoking status, and depressive symptoms (BDI). After applying the Bonferroni correction, the association between IL-6 and Persistent Somatization (PS) remained statistically significant, while other tested associations did not reach the adjusted significance threshold and were therefore excluded from further interpretation.

Furthermore, the effect of IL-6 on depression was mediated by the sum of DCPR syndromes (DCPR-sum) (ab = 2.98, BootSE = 1.24, 95% CI = [0.58, 5.50]) (**figure 1**). IL-6 significantly positively predicted DCPR-sum (a = 2.47, SE = 0.65, t = 3.81, p = 0.0003), which in turn predicted higher depressive symptoms (b = 1.21, SE = 0.57, t = 2.11, p = 0.038). The total effect of IL-6 on depressive symptoms was significant (c = 8.24, SE = 3.29, t = 2.51, p = 0.014). After accounting for the mediating role of DCPR-sum, the direct effect of IL-6 on BDI became non-significant (c' = 5.26, SE = 3.51, t = 1.50, p = 0.138), indicating that the relationship between IL-6 and depression is explained by a full mediation of DCPR-sum. The full mediation of the DCPR-sum for IL-6 was also confirmed for the BDI subdimension of somatic symptoms (ab = 1.57, BootSE = 0.67, 95% CI = [0.211, 2.861]) (**figure 1**). IL-6 significantly positively predicted DCPR-sum (a = 2.47, SE = 0.65, t = 3.81, p = 0.0003), which in turn significantly predicted higher somatic depressive symptoms (b = 0.64, SE = 0.30, t = 2.13, p = 0.036). The total effect of IL-6 on BDI-sum was significant (c = 4.52, SE = 1.71, t = 2.64, p = 0.010), while the direct effect became non-significant (c' = 2.95, SE = 1.83, t = 1.61, p = 0.111). The effect of TNF-alpha on depression was also mediated by PHQ-15 (ab = 3.32, BootSE = 1.44, 95% CI = [0.80, 6.44]) (**figure 1**). Higher TNF-alpha predicted higher PHQ-15 (a = 3.71, SE = 1.31, t = 2.84, p = 0.006), and higher PHQ-15 predicted higher depressive symptoms (b = 0.90, SE = 0.13, t = 7.11, p

Table 1. *Demographic and clinical characteristic of patients (n=77)*

Demographic	
Age (mean (yrs) ± SD	57.41 ± 16.07
Gender, M/F (%)	45/32 (58.5/41.5)
Education (mean (yrs) ± SD)	9.8 ± 3.6
Employed, N (%)	16 (20.7)
Unemployed, N (%)	23 (29.8)
Housewife, N (%)	12 (15.5)
Retired, N (%)	22 (28.5)
Clinical	
MDD, N (%)	57 (81)
BD type I-II, N (%)	13 (19)
Duration of illness (yrs) ± SD	9.01 ± 4.03
Depression symptoms	
BDI-II (total score) (mean ± SD)	20.5 ± 9.01
Somatic dimension (mean ± SD)	8.4 ± 4.1
Cognitive-affective dimension (mean ± SD)	12.1 ± 6.8
DCPR (+)	52 (67.5)
DCPR =1, N (%)	14 (18.1)
DCPR ≥ 2, N (%)	38 (49.3)
PHQ-15 (mean ± SD)	11.3 ± 6.1
IL-6 pg/ml (mean ± SD)	6.013 ± 4.664
IL-6 Log transformed (mean ± SD)	0.649 ± 0.3496
TNF-α pg/ml (mean ± SD)	19.19 ± 34.29
TNF-α Log transformed (mean ± SD)	0.843 ± 0.604
Body mass index (mean ± SD)	24.2 ± 4.7
Comorbidity, N (%)	37 (42)
Smoking habits, N (%)	24 (31)
Medication	
Antidepressants, N (%)	40 (52)
Lithium, N (%)	20 (26)
Valproate, N (%)	13 (17)
Atypical antipsychotics, N (%)	21 (27)
Classical antipsychotics, N (%)	2 (2.5)

Table 2. *Between-group comparison of sociodemographic, psychopathological measures, and inflammatory markers. Mean (SD)*

	DCPR-R (+) N= 52	DCPR-R (-) N= 25	t-test/ χ2	P-values
Age (years)	56.09 (16.20)	55.56 (11.86)	t=-0.14	0.88
Gender (F/M)	24/28	8/17	χ2 = 1.39	0.23
Level of education (years)	10.34 (3.66)	8.92 (3.46)	t=-1.62	0.10
Illness Duration (years)	9.34 (4.46)	8.32 (2.89)	t=-1.04	0.29
BMI (kg/m2)	24.50 (4.69)	23.84 (4.93)	t=-0.56	0.57
Smoking status (N, %)	18 (34)	13 (52)	χ2 = 2.12	0.14
BDI-II total score	22.19 (9.51)	16.96 (6.94)	t=-2.45	0.01
BDI-II somatic	9.63 (3.78)	6.08 (4.03)	t=-3.77	0.003
BDI-II cognitive/affective	12.55 (7.59)	10.88 (5.10)	t=-0.99	0.32
PHQ-15	13.55 (5.56)	6.64 (4.28)	t=-5.41	0.001
IL-6 *	0.47 (0.33)	0.31 (0.29)	t=-2.14	0.03
TNF-alpha *	2.20 (1.08)	1.62 (1.33)	t=-2.00	0.04

DCPR-R (+) = with least one DCPR-R syndrome; DCPR-R (-) = without DCPR-R diagnoses. BMI =Body Mass Index; BDI-II = Beck Depression Inventory– II; PHQ-15 = Patient Health. Questionnaire-15; *log transformed.

Table 3. *Univariate regression analyses for each inflammatory marker (IL-6, TNF-α) and each psychosomatic outcome DCPR syndromes, PHQ-15)*

	IL-6				TNF-α			
	β	OR/t	95%CL	P value	β	OR/t	95%CL	P value
Persistent Somatization	0.440	23.70	4.15/135	**< 0.001**	0.130	1.560	0.71/3.84	0.260
Demoralization	0.063	1.062	0.27/4.14	0.931	0.023	2.330	1.02/5.29	**0.043**
FSS	0.232	6.106	1.00/37.3	**0.050**	0.168	3.310	1.23/8.84	**0.017**
AOS	0.216	3.864	0.93/15.9	0.061	0.232	2.339	1.03/5.27	**0.040**
PHQ-15	0.231	2.055	0.14/9.36	**0.043**	0.312	2.840	1.10/6.31	**0.006**

AOS = Allostatic Overload Syndrome; FSS = Functional Somatic Symptoms secondary to a psychiatric disorder; PHQ-15 = Patient Health Questionnaire-15; β = standardized regression coefficient; OR= odd ratio; 95%CL = Confidence Limits.

Table 4. *Multivariable regression examining associations between IL-6 and persistent somatization*

	IL-6			
	β	OR/t	95%CL	P value
Persistent Somatization	0.305	74.06	8.03/682	**0.001***

Adjusted for covariates: age, smoking status, medical comorbidity and symptom of depression. β = standardized regression coefficient; OR= odd ratio; 95%CL = Confidence Limits. *Bonferroni correction.

< 0.001). The total effect of TNF-alpha on depressive symptoms was significant (c = 6.32, SE = 1.84, t = 3.44, p = 0.001), when controlling for PHQ-15, the direct effect remained marginally significant (c' = 2.99, SE = 1.50, t = 1.99, p = 0.049), suggesting a partial mediation of PHQ-15 (**figure 2**). No significant other mediations or moderations of sex emerged.

Discussion

This exploratory study provides preliminary evidence of a potential psychoneuroimmune link between psychosomatic syndromes and inflammation in mood disorders. To our knowledge, this is the first study to demonstrate that patients with mood disorders who received at least one DCPR diagnosis exhibited significantly elevated levels of proinflammatory cytokines (i.e., IL-6, TNF-α) compared to those without any DCPR diagnoses. Furthermore, proinflammatory cytokines remained significantly associated with psychosomatic syndromes even after adjusting for concurrent depressive symptoms. In addition, psychosomatic psychopathology mediated the association between inflammation and depressive symptomatology. Our findings align with previous research investigating the relationship between cytokines and the somatic symptoms of depression (Hazeltine et al., 2022; Jokela et al., 2016; Fried et al., 2020). Notably, numerous studies have highlighted a strong association between somatic/neurovegetative symptoms and inflammation, with elevated cytokine levels implicated in the manifestation of medically unexplained somatic symptoms in patients with depression (Majd et al., 2020). Building upon these observations, our study provides novel evidence that elevated cytokine levels are associated with psychosomatic syndromes in both unipolar and bipolar depression, independent of the affective and cognitive depressive symptoms (Capuron

Figure 1. *Mediation model testing the mediator effect of the psychosomatic syndromes on the influence of IL-6 on depression*

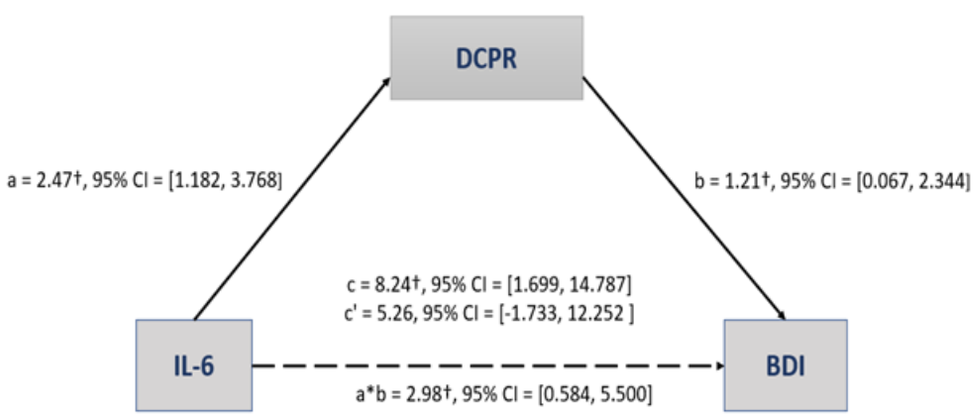
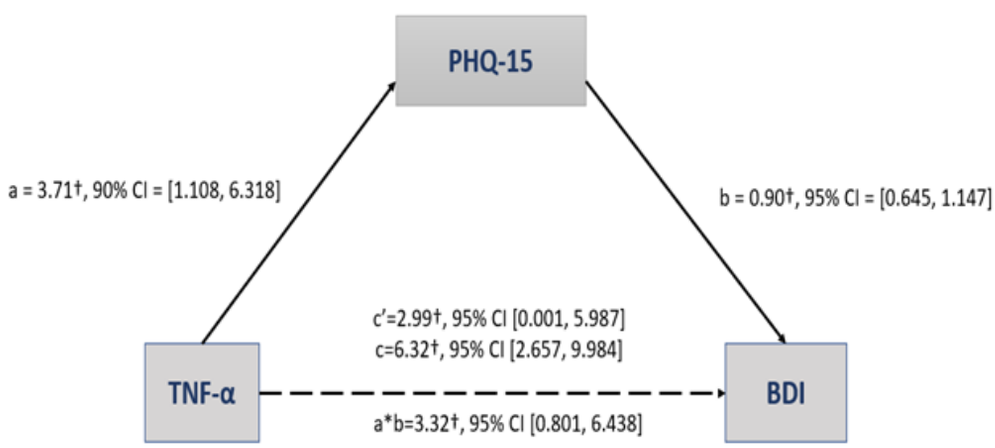


Figure 2. *Mediation model testing the mediator effect of the psychosomatic symptoms on the influence of TNF-α on depression*



& Castanon, 2017). Particular attention should be given to Persistent Somatization (PS), which was identified in 35% of the sample. PS is characterized by functional medical disorders persisting for more than six months and includes symptoms of autonomic arousal affecting multiple organ systems, as well as heightened sensitivity to the side effects of medical treatments (Porcelli & Rafanelli, 2010). The proinflammatory cytokine IL-6 exhibited the strongest association with PS, strongly suggesting that elevated peripheral IL-6 levels play a crucial role in the pathophysiology of psychosomatic symptomatology in both major depressive disorder and bipolar depression (Dantzer, 2009). Several studies support this hypothesis, revealing strong associations between IL-6 levels and the somatic symptoms of depression, regardless of cognitive-affective depressive components or coexisting medical conditions (Duivis et al., 2013; Hazeltine et al., 2022).

In this context, it is well established that cytokines are responsible for the selective activation of specific enzymes which play a crucial role in serotoninergic, glutamatergic, and dopaminergic neurotransmission. Particularly, the prolonged activation of indoleamine 2,3-dioxygenase (IDO) in the brain drives increased tryptophan catabolism, leading to reduced serotonin synthesis and the production of neurotoxic glutamatergic compounds, such as quinolinic acid, which exert neurotoxic effects by overstimulating NMDA receptors. Recently, Maes et al. (2011) and Maes & Rief (2012) demonstrated that the activation of IDO by inflammatory processes, leading to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), may play a significant role in the development of somatization but not in depression. More importantly, recent studies have demonstrated that IL-6 can significantly activate and upregulate the expression of IDO, thereby playing a key role in the comorbidity of somatic symptoms and depression (Anderson et al., 2013; De Jongh et al., 2003; Kim et al., 2012; Xie et al., 2023). Therefore, it is plausible that IL-6 contributes to the manifestation and development of somatization symptoms through its effects on IDO activity and serotonergic neurotransmission. Our findings indicate that psychosomatic symptomatology mediates the relationship between inflammation and depressive symptoms, with psychosomatic DCPR-sum fully accounting for the association between IL-6 and symptoms of depression. These findings align with previous research indicating that somatic and neurovegetative depressive symptoms may act as "bridge" symptoms, linking inflammatory processes to the onset of full-blown depressive episodes (Case & Stewart, 2014; Kapfhammer, 2006). A possible explanation of this is that the somatic symptoms may be more likely to be a consequence of systemic inflammation than the non-somatic symptoms. The idea that inflammation contributes to the development of medically unexplained somatic/neurovegetative symptoms stems from studies on cytokine-induced depression. Research on patients treated with interferon-α (IFN-α) has identified two distinct symptom clusters with different phenomenological profiles. The first cluster is characterized by neurovegetative symptoms, often referred to as "sickness behavior" which include symptoms (e.g., fatigue and lack of energy) that closely resemble the psychosomatic aspects of depression. The second cluster encompasses mood-related symptoms, such as low mood and cognitive impairments, highlighting the intricate relationship between inflammation, mood regulation, and cognitive function. Notably, clinical studies have demonstrated that somatic and neurovegetative symptoms emerge rapidly in most patients undergoing cytokine immune therapy, whereas mood and cognitive symptoms typically develop only in vulnerable individuals following prolonged exposure to proinflammatory cytokines (Capuron et al., 2002; Raison et al., 2006). Therefore, it is plausible that somatic symptoms precede and contribute to the strengthening of the relationship between depression and inflammation.

We found no gender effects in the link between inflammatory markers and depression. Prior research has yielded mixed results regarding gender differences in the relationship between inflammation and depression. For instance, several cross-sectional studies investigating gender differences in the relationship between inflammation and depression have reported no significant gender effects (Case & Stewart, 2014; Duivis et al., 2013; Euteneuer et al., 2011). Conversely, other studies have suggested that women may be more susceptible to mood and behavioral changes triggered by inflammation (Derry et al., 2015; Köhler-Forsberg et al., 2017). A longitudinal study reported that inflammation (C-Reactive Protein) specifically predicted somatic depressive symptoms in women, but not in men, suggesting that the relationship between the somatic dimension of depression and inflammation may differ by gender (Niles et al., 2018). Future prospective studies are needed to further clarify the biological and psychosocial mechanisms that underlie gender differences in the relationship between inflammation and specific dimensions of depression. Psychiatric pharmacotherapies, including antidepressants, antipsychotics, and mood stabilizers, are increasingly recognized for their anti-inflammatory properties. Evidence across various mental health disorders indicates that these agents reduce pro-inflammatory cytokines, particularly IL-6 and TNF-α (Patel et al., 2023). In our sample, however, we did not observe significant correlations between inflammatory biomarkers and psychiatric medications. One possible explanation is the relatively heterogeneous use of psychotropic agents (e.g., varying combinations of antidepressants, antipsychotics, mood stabilizers), which may exert distinct and potentially opposing effects on inflammatory pathways, thereby diluting detectable associations at a group level. Furthermore, dosage, treatment duration, and individual pharmacodynamic responses—variables we were unable to fully control—may have contributed to this lack of correlation. Although the use of psychotropic medications was included as a covariate in our regression models to mitigate confounding, residual confounding cannot be entirely excluded. Future investigations incorporating more granular pharmacological data (e.g., cumulative exposure, treatment class stratification) are warranted to elucidate the impact of psychiatric treatments on inflammatory profiles in mood disorders.

The results of our study should be considered in the light of several limitations. First, it would increase the value of this research if the study group was more numerous and adverse life events (e.g., childhood maltreatment) associated with inflammation, potentially contributing to the incidence and severity of somatic depressive symptoms, were taken into consideration. Second, its cross-sectional design limits the ability to examine bidirectional influences between depressive symptoms and systemic inflammation. Additionally, it does not allow for a longitudinal assessment of the stability of psychosomatic diagnoses and their relationship with inflammation. Third, the lack of association between cognitive-affective dimensions

of depression and inflammatory markers could be attributed to our method measuring depression, and we cannot rule out the possibility that using other questionnaires than the BDI-II would lead to different results. Fourth, although comparable to other studies in literature the association between inflammatory markers and psychosomatic syndrome found in our study may be related to other potentially clinically relevant mediating or moderating factors (e.g., hypothalamic–pituitary–adrenal [HPA] abnormalities, cognitive style, negative affectivity, serotonin-transporter-linked polymorphic region [5-HTTLPR] gene). Fifth, evidence suggests potential gender differences in the relationship between inflammatory biomarkers and depression (Jarkas et al., 2024). However, our study lacks sufficient statistical power to determine whether the association between inflammatory biomarkers and specific depressive symptom dimensions differs between males and females. Notwithstanding these limitations, results strongly suggest a possible link between increased inflammatory cytokines and psychosomatic psychopathology in patients with mood disorder. Further studies are recommended to replicate these findings and to study the relationship between psychosomatic dimensions and inflammation in patients with mood disorder. Our study confirms the clinical utility of the Diagnostic Criteria for Psychosomatic Research in offering psychiatrists a more nuanced and comprehensive framework than traditional psychiatric classifications for assessing psychosomatic psychopathology in patients with psychiatric disorders. By applying the DCPR, clinicians can better capture the complexity of somatic symptom presentations that often accompany mood disorders. Importantly, our findings indicate that IL-6 does not act as a general pro-depressive cytokine but appears to have a more specific role in the modulation of persistent somatization. Mediation analyses further revealed that psychosomatic syndromes partially mediate the relationship between inflammatory cytokines and depressive symptomatology, suggesting that the link between systemic inflammation and depression may be largely driven by the presence of somatic symptoms rather than depressive symptoms per se. While additional research is necessary to clarify the precise biological and psychological mechanisms, as well as the temporal sequence underlying these associations, the current results have important clinical implications. They highlight the relevance of identifying distinct patient subgroups characterized by psychosomatic syndromes who may be at increased risk for poorer clinical outcomes and who might benefit from tailored, integrative treatment strategies addressing both inflammatory and psychosomatic dimensions.

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