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Eveningness chronotype and depressive affective temperament associated with higher high-sensitivity C-reactive protein in unipolar and bipolar depression

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ABSTRACT

Background: Several studies investigated the role of inflammation in the etiopathogenesis of mood disorders. The aim of our cross-sectional study is evaluating baseline high-sensitivity C-reactive-protein (hsCRP) levels in a cohort of unipolar and bipolar depressive inpatients, in relation with psychopathological, temperamental and chronotype features.

Methods: Among 313 screened inpatients, we retrospectively recruited 133 moderate-to-severe depressive patients who were assessed for hsCRP levels, chronotype with Morningness-Eveningness Questionnaire (MEQ) and affective temperament with Temperament Evaluation of Memphis, Pisa, Paris and San Diego (TEMPS).

Limitations: The cross-sectional and retrospective design of the study, the small sample size, the exclusion of hypomanic, maniac and euthymic bipolar patients.

Results: hsCRP levels were significantly higher among those with previous suicide attempt ($p = 0.05$), death ($p = 0.018$) and self-harm/self-injury thoughts ($p = 0.011$). Linear regression analyses, adjusted for all covariates, demonstrated that higher scores at the TEMPS-M depressive, while lower scores at the hyperthymic and irritable affective temperaments [$F = 88.955$, $R^2 = 0.710$, $p < 0.001$] and lower MEQ scores [$F = 75.456$, $R^2 = 0.405$, $p < 0.001$] statistically significantly predicted higher hsCRP.

Conclusion: Eveningness chronotype and a depressive affective temperament appeared to be associated with higher hsCRP levels during moderate-to-severe unipolar and bipolar depression. Further longitudinal and larger studies should better characterise patients with mood disorders by investigating the influence of chronotype and temperament.

1. Introduction

From an immunological and neuroinflammatory perspective, chronic low-grade inflammation and defective regulatory immune cells (both innate and adaptive) have been consistently described in patients with mood disorders (Teixeira et al., 2016; Colpo et al., 2018; Fries et al., 2019; Teixeira et al., 2019; Bauer and Teixeira, 2021; 26). Several studies documented an immune dysfunction towards a pro-inflammatory profile in the pathophysiology of mood disorders, as demonstrated by the high frequency of comorbid autoimmune conditions in patients with mood disorders (Rosenblat and McIntyre, 2015; Cremaschi et al., 2017; Wang et al., 2018). Moreover, altered peripheral levels of several pro-inflammatory cytokines [e.g., tumor-necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), IL-6, an soluble receptor of TNF-type 1, and so forth], pro-oxidative stress biomarkers and antioxidants (e.g., zinc, vitamin E, glutathione and coenzyme Q10) have been reported in patients affected with mood disorders, particularly during acute mood episodes (Köhler et al., 2017; Sayana et al., 2017; Wigner et al., 2018; Bauer and Teixeira, 2021). Pro-inflammatory cytokines can directly contribute to the development of depressive symptoms (Troubat et al., 2021), by inducing stress-responsive neuroendocrine and neurotransmitter changes similar to those implicated in depression (Machado et al., 2017). Similarly, the induction of oxidative stress pathways accompanied by an immune-inflammatory response may play a pivotal role in the pathogenesis of mood disorders, by modulating the glutamatergic system implicated in the neurobiology of depression (Doser

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and Hoerndli, 2021). In particular, C-Reactive Protein (CRP) is a pentameric acute phase reactive protein, member of the pentraxin family, secreted mainly by hepatocytes in response to the innate humoral system activation (Marnell et al., 2005; Nehring et al., 2021; Sproston and Ashworth, 2018). The main role of CRP is to recognize and eliminate pathogens and damaged cells, by activating several inflammatory-related mechanisms such as the complement system and through binding with the fragment crystallizable (Fc) receptor on B lymphocytes, natural killer cells, macrophages, neutrophils and mast cells (Nehring et al., 2021). CRP could have both proinflammatory and anti-inflammatory properties (Sproston and Ashworth, 2018; Thiele et al., 2014; Wu et al., 2015). It is produced as a native protein (nCRP), which may exert anti-inflammatory activities, and can irreversibly dissociate itself into five separate monomers (mCRP), which, conversely, may increase the cytokine production, promote monocyte chemotaxis and the recruitment of circulants leukocytes (Sproston and Ashworth, 2018; Thiele et al., 2014).

CRP is easily measured through a blood sample, also in its high-sensitivity form (hs-CRP) (Ridker, 2003). In clinical practice, CRP is routinely used as a biomarker of systemic infection, chronic disease state and chronic low-grade inflammation (Joseph et al., 2015). Moreover, it has been well documented that CRP levels are associated with a cardiovascular risk such as stroke, peripheral vascular disease and myocardial infarction (Orsolini et al., 2018).

Indeed, several mechanisms have been hypothesised by which CRP can interact with the central nervous system (CNS) (Felger et al., 2020). In particular, as CNS inflammation has been already documented in several psychiatric disorders, such as depression and schizophrenia, it has been supposed that increased CRP levels and its pro-inflammatory activity could drive CNS inflammation through microglia and astrocytes activation (D'Mello et al., 2009; McKim et al., 2018; Wesselingh et al., 2019). Indeed, CRP usually does not freely cross the blood brain barrier (BBB), except in specific situations, such as severe perceived stressful events and/or after a traumatic brain injury (Menard et al., 2017; Prakash and Carmichael, 2015). In fact, these events may facilitate the access of peripheral CRP into cerebrospinal fluid (CSF) through BBB, by allowing its activity in the CNS (Menard et al., 2017; Jeon et al., 2021; Prakash and Carmichael, 2015; Sulhan et al., 2020). In turns, CRP could induce the BBB disruption, through the binding and activation of some ligands such as Fc receptors, CD16 and CD23 expressed in the microglia, astrocytes and endothelial cells (Horn et al., 2018; Kuhlmann et al., 2009; Woo et al., 2020).

In this regard, a wide range of studies also investigated the role of immunity dysregulation in psychiatric disorders (Dubois et al., 2018; Horn et al., 2018; Michopoulos et al., 2015; Moylan et al., 2014; Renna et al., 2018; Rosenblat and McIntyre, 2017; Turna et al., 2020), by also evaluating how CRP may exert a pathoplastic and/or psychopathological role in mental disorders (Caldirola et al., 2021; Felger et al., 2020; Orsolini et al., 2022, 2018; Osimo et al., 2020). Increased CRP levels were observed in major depressive disorders (MDD) patients (Mocking et al., 2017; Nobis et al., 2020; Osimo et al., 2020; Wium-Andersen et al., 2013). Moreover, elevated serum CRP levels have been reported in patients with atypical MDD, in MDD patients with predominantly somatic symptomatology and in patients at higher risk of psychiatric hospitalisation (Duivis et al., 2013; Hickman et al., 2014; Wium-Andersen et al., 2013). Furthermore, higher hs-CRP levels were observed in patients with more severe MDD symptoms and in treatment-resistant MDD patients (TRD) (Chamberlain et al., 2019; Köhler-Forsberg et al., 2017). However, just a concomitant chronic low-grade inflammatory state (i.e., CRP ranging from 3 mg/L to 10 mg/L) was found only in a quarter of depressed patients, independently by the age, ethnicity, gender, Body Mass Index (BMI) or concomitant psychopharmacological treatment (Chamberlain et al., 2019; Khandaker et al., 2014; Osimo et al., 2019). For this reason, some researchers also identified a subgroup of depressive patients who more likely display a concomitant low-grade inflammatory status which may be associated with a different illness etiopathogenesis, clinical course, treatment response, prognosis and treatment (Hickman et al., 2014; Köhler-Forsberg et al., 2017; Osimo et al., 2019). Therefore, some authors also argued that the changes in the pattern of CRP levels, depending on the clinical course, would represent a peculiar feature of not all depressive patients, being rather a characteristic within a subgroup of depressive subjects (Orsolini et al., 2022). Similarly, altered levels of inflammatory mediators, including CRP, have been also found in Bipolar Disorder (BD) patients (Jacoby et al., 2016; Munkholm et al., 2015; Solmi et al., 2021). In particular, it has been reported that higher CRP levels were much higher in manic and euthymic BD phases, by suggesting that CRP levels could be probably an early sign for the onset of the manic switch (Becking et al., 2013; Cunha et al., 2008; Dargél et al., 2015; Fernandes et al., 2016; Gorgulu et al., 2021). Moreover, increased CRP levels have been observed in BD patients with a more severe symptomatology (Dickerson et al., 2007; Hamdi et al., 2021; Lee et al., 2013), in those with late-onset BD (Wium-Andersen et al., 2016) and in patients with a longer BD illness history (Solmi et al., 2021). Therefore, similar to MDD, it has been hypothesised a low-grade inflammatory state also in a subgroup of BD patients with a more severe symptomatology and a higher rate of treatment-resistance (Gan et al., 2019; Queissner et al., 2018).

Despite altered CRP levels have been described in a range of psychiatric conditions, by supporting rather the hypothesis that CRP could be rather an aspecific biomarker, which should be part of a larger fingerprint, its role in mood disorders appear widely consistent. However, despite the abovementioned promising findings, only few studies (with contradictory findings) investigated the transdiagnostic inflammatory biomarker role of CRP levels across mood disorders, comparing unipolar and bipolar depression (Caldirola et al., 2021; Cunha et al., 2008; Huang and Lin, 2007; Wysokiński et al., 2016; Zhang et al., 2022). Therefore, the aim of the present retrospective chart review study is evaluating the levels of hs-CRP at baseline (i.e., at the first day of hospitalisation) in a sample of unipolar and bipolar depressed inpatients in order to evaluate whether altered hs-CRP levels were associated with a set of psychopathological, chronotype and/or affective temperamental features, in order to stratify subgroups of unipolar versus bipolar depressed patients according to the neuroinflammatory pattern during their acute illness depressive phase. Moreover, a secondary objective was comparing hs-CRP levels across different diagnostic subgroups of subjects with a current depressive episode in the context of a MDD, a Bipolar Disorder Type I (BD-I) and a Bipolar Disorder Type II (BD-II). Third objective was investigating whether hs-CRP levels may more likely act as a transdiagnostic inflammatory biomarker (independently by the type of mood disorder), a phase-specific inflammatory biomarker or a trait-specific inflammatory biomarker (independently by the type of mood disorder), in order to identify (if any) subgroups of MDD/BD-I/BD-II patients could benefit from a personalised treatment, including an anti-inflammatory therapy.

2. Methods

2.1. Study design and participants

A naturalistic, observational, cross-sectional study was carried out by retrospectively collecting information documented from inpatients' electronic medical records (EMRs) at the Unit of Clinical Psychiatry, Department of Neurosciences/DIMSC, University Hospital "Ospedali-Riuniti" in Ancona, Italy. All patients affected by a mood disorder, consecutively hospitalised at the acute psychiatric ward, during the timeframe from December 1, 2021 to August 25, 2022, were screened for eligibility. Inclusion criteria included the following: a) age $\geq$18 years old at the time of assessment; b) diagnosis of current depressive episode (moderate-to-severe) within the context of a MDD, BD-I or BD-II, according to the DSM-5-TR criteria (APA, 2022); c) absence of psychotic disorders except for psychotic symptoms related to the current depressive episode, in the case of MDD or BD-I inpatients; d) consent to

participate in the study and written informed consent to use their data for research purposes. Exclusion criteria were lack of willingness or capacity to provide informed consent to participate in the study, a diagnosis of autism spectrum disorder (ASD), intellectual disability or mental retardation, a diagnosis of personality disorder, a moderate-to-severe cognitive impairment, current intake of immunosuppressive and/or anti-inflammatory drugs, current intake of corticosteroids, current or recent (during the last 3 months) use of alcohol and/or other psychotropic drugs; concomitant chronic inflammatory diseases and/or systemic neoplastic and/or neurodegenerative disorders, such as Parkinson's Disease and/or Alzheimer's disease. In addition, as our focus was to investigate only the chronic low-grade inflammatory processes, we excluded all inpatients with an acute inflammation (i.e., hsCRP>10 mg/L). All recruited patients were asked to voluntarily provide written consent to use the clinical information collected and rating scales administered during their hospitalisation as standard routinary clinical practice, for research purposes. The study was approved by our local Institutional Review Board. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and according to the guidelines for Good Clinical Practice (GCP).

2.2. Study procedures and measures

The study used EMR variables that clinicians collected within standard psychiatric clinical practice during hospitalisation. The assessment was performed during a semi-structured clinical interview (whereas the patient was at his/her first hospitalisation in our psychiatric ward) or through the consultation of previous clinical databases (for patients who were previously hospitalised in our psychiatric ward). An ad hoc case report form (CRF) was developed and filled out for each subject enrolled in the study. The CRF included socio-demographic features (i.e., age [in years], sex, marital status, educational level [in years]), family and personal psychiatry history, illness duration, age of illness onset, previous and current psychotropic medications, current and/or past smoking use (including the average number of cigarettes smoked daily), anthropometric variables (i.e., body mass index [BMI, Kg/m^2], abdominal circumference [cm], body weight [Kg], height [cm], blood pressure [mmHg]); medical comorbidities (including concomitant medications for medical disorders); concomitant cardiovascular risk factors (i.e., hypertension, increased low-density lipids [LDL], reduced high-density lipids [HDL], hypertriglyceridemia, increased HbA1c levels, positive family cardiovascular history). As standard routine clinical practice, to all patients who are hospitalised in our psychiatric ward were administered a set of psychometric scales, as illustrated below, at their first day after hospitalisation (t0), together with a blood sample assessing routinary laboratory test (as illustrated below) including hs-CRP levels. To minimise circadian variations, blood samples are usually collected on the first day after hospitalisation at 08.00 ± 1 h a.m. from the cubital vein and analysed within 3 h using an immunoturbidimetric method (lowest detection limit of 0.02 mg/dL), as a routinary procedure of our psychiatric ward. The following values were also collected and included in the analysed dataset, from the fasting venous blood sample: blood glycated haemoglobin (Hbg%), blood thrombocyte count ($\times 10^9$/l), plasma total cholesterol (mmol/l), plasma high-density lipoprotein (HDL, mmol/l), plasma triglycerides (TGs, mmol/l), fasting glucose (mmol/l).

The psychiatric diagnosis was made through the MINI-5 clinical interview (Mini-International Neuropsychiatric Interview, Italian translation, version 7.0.0.) (Rossi et al., 2004; Sheehan et al., 1998) and only patients who met DSM-5 criteria for current moderate-to-severe MDD, BD-I or BD-II were included in the study. Those individuals who met DSM-5 criteria for Personality Disorders by using the semi-structured clinical interview for DSM-5 (SCID-5-PD) (First et al., 2017) were properly excluded. Furthermore, during the same day of the blood sample, all patients were administered the following psychopathological rating scales to assess general psychopathology (Brief Psychiatric Rating Scale [BPRS]), depressive (Hamilton Depression Rating Scale-21 items, [HAM—D_{21}]), manic/hypomanic (Young Mania Rating Scale [YMRS] and Mood Disorder Questionnaire [MDQ]), affective mixed symptomatology (Mixed States Rating Scale [MSRS]) and clinical global severity (CGI). The BPRS is a 24-item, semi-structured interview, scored on a 7-point severity, filled by the interviewer (Overall and Gorham, 1962; Roncone et al., 1999). Scores below 30 indicate a mild symptomatology, while scores ranging from 31 to 41 a moderate symptomatology and above 42 a severe symptomatology (Burger et al., 2003). The HAM-D_{21} is a 21 item clinician-administered scale (Hamilton, 1960), including the first 17 items measuring the severity of depressive symptoms and the last four items measuring adjunctive factors potentially associated with depression, such as paranoia, obsessive and compulsive symptoms (Sharp, 2015). A score ranging from 8 to 16 indicates a mild depression, from 17 to 23 a moderate depression, a score above 24 a severe depression (Zimmerman et al., 2013). The YMRS is an 11-item clinician-rated scale measuring the (hypo)manic symptomatology severity during the last 48 h and through the clinician's observation during the interview (Young et al., 1978). Four items are on a 8-point scale (irritability, speech, thought content and disruptive/aggressive behavior), while the other seven items are scored on a 4-point scale. The total score ranges from 0 to 60, with higher scores indicating more severe mania (Young et al., 1978). CGI is a standardized assessment scale for measuring global symptoms severity and treatment response for patients with mental disorders (Guy, 1976). The CGI-Severity (CGI—S) is a 7-point scale assessing the patient's severity of illness at the time of the assessment. The CGI-S rates from 1 to 7, with (1) representing the normality (i.e. not at all ill) and (7) patients with the most severely ill (i.e. extremely ill) (Guy, 1976). The MDQ developed by Hirschfeld et al. (2000), is a screening instrument for bipolar disorder. Hirschfeld et al. (2000) suggested a standard cutoff of 7 (i.e., 7 or more symptoms detected in the first part, and those symptoms occurred simultaneously in the second part, and the consequences of those symptoms caused moderate or serious impairment in the third part) as the optimal cutoff value to discriminate between bipolar versus not bipolar patients. The screening accuracy of the MDQ is not influenced by the current mood state (either euthymic state, depressed or manic/hypomanic) (Wang et al., 2020). The MSRS is a self-administered rating scale structured by 11 items. The response to each question would be "yes" or "no". A "yes" answer would score 1 (or 2 if the symptom scored on items 1-2-3-4-8-9-10-11 is present for 50 % of the month), a "no" answer would score zero. Scores can range from 0 to 19, with a higher score meaning a more severe mixed state presentation. If a patient is positive (meaning having a total score equal or >1) on the MSRS, this will suggest a "generic" diagnosis for a mixed state in the bipolar spectrum, based on the Akiskal's full-spectrum scheme (Akiskal and Pinto, 1999). A medium-high level of mixed state is defined with scores ranging from 2 to 6; a medium level of mixed state is defined if the score is 7 to 12; a high level of mixed state is defined if the score ranges 13 to 19.

Furthermore, all patients filled the Italian validated short version of the Temperament Evaluation of the Memphis, Pisa, Paris and San Diego (short TEMPS-M) (Fico et al., 2020), a 35 items questionnaire used to assess affective temperaments described by Akiskal (depressive, anxious, hyperthymic, cyclothymic and irritable) using a dimensional approach with a five-point Likert type scale ranging from 1 to 5 (1 = "not at all"; 2 = "a little"; 3 = "moderately"; 4 = "much"; 5 "very much"). TEMPS-M displays a good internal consistency (Cronbach α ranging from 0.69 to 0.84) (Fico et al., 2020), also in our study (Cronbach α = 0.783). Chronotype was assessed using the 19-item Morningness-Eveningness Questionnaire (MEQ) by Horne and Östberg (Horne and Ostberg, 1976). Analyses were performed with the continuous total score of the MEQ, with higher values reflecting a morningness tendency and lower values reflecting an eveningness tendency. In addition, we also performed analyses by categorising MEQ scores in three groups: morning-type chronotype (MEQ ranges from 59 to 86), intermediate-type chronotype (MEQ ranges from 42 to 58) and eveningness-type

chronotype (MEQ ranges from 16 to 41). In our study, MEQ displays a good internal reliability (Cronbach α = 0.874).

2.3. Statistical analyses

Clinical and socio-demographic categorical characteristics were summarised using frequency (N) and percentage (%). After analysing the continuous variables for skewness, kurtosis, normality distribution through the Shapiro-Wilk test, and the equality of variances by Levene test, parametric or non-parametric statistical tests were used, when appropriate. Normally distributed continuous variables were represented using the average mean and standard deviation (SD), whether normally distributed, or the median and 95 % Confidence Interval (95% CI) when not normally distributed. CRP was logarithmically transformed (lnhsCRP) in order to obtain an approximated normally distributed variable, following an approach also used in previous studies (Jokela et al., 2016; Uher et al., 2014). The Analysis of Variance (ANOVA) was performed to compare the primary outcome (i.e., hs-CRP levels) with categorical socio-demographic variables (i.e., sex, ethnia, occupational status, marital status, BMI category, intensity of physical activity, smoke habits, level of smoking) and clinical variables (i.e., family and personal psychiatry history, type of hospitalisation, type of mood disorder, severity of current depressive episode, specifier of current depressive episode, presence/absence of psychotic symptoms, type of predominant affective temperament, type of predominant chronotype, previous history of suicidal attempt, internal comorbidity, presence/absence of hypertension, presence/absence of hypertrigiceridemia, presence/absence of hypercolesterolemia, level of at-risk diabetic level). The Analysis of Variance (ANOVA) or not parametric Kruskal-Wallis test were performed, when appropriate, to compare other continuous variables (i.e., age, number of illness years, age of illness onset, number of previous suicidal attempts, number of previous psychiatric hospitalisation, etc.) with all abovementioned categorical socio-demographic and clinical variables. Bivariate Pearson's correlations have been used to investigate potential relationships between the lnhsCRP scores and other secondary continuous variables. Linear regression analyses with a Bonferroni's adjustment for multiple comparison tests, were performed between the lnCRP (as dependent variable) and all independent psychopathological variables (i.e., HAM—D_{21}, BPRS, YMRS, MSRS, MEQ, TEMPS-M total and subscales). All analyses were adjusted for the following baseline covariates possibly affecting hsCRP levels: age, sex, smoking status, BMI, blood pressure and glycemic profile at baseline. Data analysis was performed using the Statistical Package for Social Science for MacOS (SPSS) Software, version 27.0 (IBM Corp., Armonk NY). All the analyses were two-sided with α of 0.05.

3. Results

3.1. Socio-demographic and clinical characteristics of the sample

Demographic and clinical characteristics across mood disorders are summarised in Table 1. Among 313 inpatients hospitalised and screened during the timeframe from December 2021 to August 2022, a final sample of 113 patients were recruited in the study. In the final sample, most participants are females (N = 66; 58.6 %), Caucasian (N = 105; 92.9 %), single (N = 65; 57.5 %) and in the normal weight range (N = 70; 61.9 %). The mean age was 44.0 (SD = 17.4), without significant differences across sexes (p = 0.465). The average educational level was 12.7 (SD = 3.6). The average median BMI was 22.2 (95 % CI = 22.6–25.0), without significant differences across sexes (p = 0.172). Regarding the average physical activity, most of the patients did not declare a regular physical activity (N = 55; 48.7 %) while 46.9 % (N = 53) declared to be regular tobacco smokers. The average number of daily cigarettes was 17.4 (SD = 9.3). Most of the participants declared a family history of cardiovascular diseases (N = 68; 60.2 %).

Most of the sample had a previous psychiatric history (N = 93; 82.3

Table 1
Demographic and clinical characteristics of the sample.

Socio-demographic characteristics	
Females, N (%)	66 (58.4)
Males, N (%)	47 (41.6)
Age, years, mean (SD)	44.0 (17.4)
Educational level, years, mean (SD)	12.7 (3.6)
Abdominal circumference, cm, mean (SD)	79.9 (18.2)
Body weight, kg, mean (SD)	66.3 (20.1)
Body height, cm, mean (SD)	166.5 (8.5)
Etnia, N (%)	
Caucasian	105 (92.9)
Asiatic	1 (0.9)
African	2 (1.8)
South American	2 (1.8)
Other etnies	3 (2.7)
Marital status, N (%)	
Single	65 (57.5)
Married/in a Stable relationship	38 (33.6)
Separated/divorced	8 (7.1)
Widowed	2 (1.8)
Occupational status, N (%)	
Full-time employer	29 (34.5)
Part-time employer/occasional employer	14 (12.4)
Unemployer	23 (20.4)
Student	14 (12.4)
Retired	22 (19.5)
Disability/inability	1 (0.9)
BMI, N (%)	
Underweight (<18.5 Kg/m^2)	10 (8.9)
Normal Weight (18.5–24.9 Kg/m^2)	70 (61.9)
Overweight (25–29.9 Kg/m^2)	22 (19.5)
Obese range I (30–34.9 Kg/m^2)	6 (5.3)
Obese range II (35–39.9 Kg/m^2)	3 (2.7)
Obese range III (>40 Kg/m^2)	2 (1.8)
Physical activity, N (%)	
Inactivity	55 (48.7)
Mild intensity	32 (28.3)
Moderate intensity	21 (18.6)
Moderate-to-severe intensity	3 (2.7)
Severe intensity	1 (0.9)
Tobacco use, N (%), *yes*	53 (46.9 %)
Smoking Habit, N (%)	
Current smoker	53 (46.9)
Occasional smoker	2 (1.8)
Ex-smoker	6 (5.3)
Not smoker at all	52 (46)
Medical comorbidity, N (%), *yes*	42 (37.2)
Concomitant hypertension, N (%), *yes*	12 (10.6)
Concomitant hypercholesterolemia, N (%), *yes*	19 (16.8)
Concomitant dyslipidemia, N (%), *yes*	18 (15.9)
Medical therapy, N (%), *yes*	34 (30.1)
Cardiovascular family history, N (%), *yes*	68 (60.2)
Previous personal psychiatry history, N (%), *yes*	93 (82.3)
MDD	48 (51.6)
BD-I	28 (30.1)
BD-II	17 (18.3)
Family psychiatry history, N (%), *yes*	61 (54 %)
Lifetime suicidal attempt, N (%), *yes*	34 (30.1)
Last month, suicidal attempt, N (%), *yes*	37 (32.7)
First hospitalisation, N (%), *yes*	55 (48.7)
Current psychiatric diagnosis, N (%)	
MDD	57 (50.4)
BD-I	32 (28.3)
BD-II	24 (21.2)
Current depressive episode severity, N (%)	
Moderate	51 (45.1)
Severe	62 (54.9)
Current depressive episode specifier, N (%)	
With anxiety	27 (23.9)
With mixed features	18 (15.9)
With melancholic features	12 (10.6)
With atypical features	26 (23.0)
With psychotic features	23 (20.4)
With seasonal course	7 (6.2)
Psychopharmacological therapy, before hospitalisation, N (%)	
Naive	36 (31.9)
Previous therapy, not current	51 (45.1)
Previous therapy, current	26 (23.0)

N: number; %: percentage; SD: standard deviation; BMI: Body Mass Index (Kg/m^2); MDD: Major Depressive Disorder; BD-I: Bipolar Disorder type I; BD-II: Bipolar Disorder type II.

%), mainly MDD ($N = 48$; 51.6 %), and a previous psychiatric hospitalisation ($N = 58$; 51.3 %). The final sample is constituted by inpatients with a current moderate-to-severe depressive episode and with a current diagnosis of MDD ($N = 57$; 50.4 %) or BD ($N = 56$; 49,6 %), of which 57.1 % ($N = 32$) affected by BD-I (Table 1). One-third of the sample had a medical comorbidity ($N = 42$; 37.2 %) and 30.1 % ($N = 34$) of the entire sample took a concomitant medical (not psychiatric) therapy. The median age of illness onset was 28 (95%CI = 28.2–33.7), without sex-based differences ($p = 0.930$). The median number of illness years was 9 (95%CI = 10.4–14.9), without differences across sexes ($p = 0.328$). The median number of illness episodes was 2 (95%CI = 2.7–4.1), without differences across sexes ($p = 0.091$). While the median number of psychiatric hospitalisations was 2 (95%CI = 1.6–2.6), without sex-based differences ($p = 0.374$). The median number of suicidal attempts was 2 (95%CI = 1.7–3.1), without significant differences across sexes ($p = 0.804$).

3.2. Patients' characteristics and hs-CRP concentrations

The median lnhsCRP was 0,491 (95%CI = 0,201-0,417), without significant differences across sexes ($p = 0.531$), ethnicity ($p = 0.459$), occupational status ($p = 0.268$), marital status ($p = 0.965$), smoker versus not-smokers ($p = 0.160$), level of smoker status ($p = 0.487$), and level of physical activity ($p = 0.119$), the presence/absence of a medical comorbidity ($p = 0.439$), the presence/absence of a concomitant medical (not psychiatric) therapy ($p = 0.165$), the presence/absence of a family cardiovascular history ($p = 0.254$). While lnhsCRP levels were significantly lower among patients with an underweight BMI ($N = 10$), compared to normal weight, overweight and obese inpatients [$F(3,109) = 3.875$, $p = 0.011$]. No significant differences in lnhsCRP levels were found between other BMI groups. In addition, lnhsCRP levels were significantly higher among patients with hypertension [$F(1,111) = 5.587$; $p = 0.020$] and dyslipidemia [$F(1,111) = 6.447$; $p = 0.013$]. No significant differences were found based on the presence/absence of hypercholesterolemia ($p = 0.336$) and the level of glycated haemoglobin ($p = 0.160$).

No significant differences in lnhsCRP levels were found depending on the presence/absence of a previous psychiatric history ($p = 0.971$), present/absent history of a psychiatric hospitalisation ($p = 0.301$). No significant differences in lnhsCRP levels were found based on the presence/absence of a previous psychopharmacological therapy before hospitalisation ($p = 0.160$), even though it was observed an increasing lnhsCRP levels trend among those drug-naive subjects compared to patients who were taking a psychopharmacological therapy at the day of hospitalisation ($p = 0.066$). While an increasing lnhsCRP level trend was observed in those subjects with a positive family psychiatry history, compared to those without a family psychiatry history ($p = 0.064$). No significant differences in lnhsCRP levels were found across different diagnostic subgroups [$F(2,110) = 0.855$; $p = 0.428$), either based on the type of depressive specifier (as assessed by MINI) [$F(5,107) = 0.679$; $p = 0.640$), the depressive severity (as assessed by MINI) [$F(1,111) = 0.634$; $p = 0.428$] or the presence/absence of psychotic symptoms associated with depressive episode [$F(1,111) = 1.036$; $p = 0.311$]. While those patients who declared a previous lifetime suicidal attempt [$F(1,111) = 3.929$; $p = 0.05$], to have had death (not suicidal) thoughts during the last month [$F(1,111) = 5.764$; $p = 0.018$], and self-harm and/or self-injury thoughts during the last month [$F(1,111) = 6.638$; $p = 0.011$] reported significantly higher lnhsCRP levels. Moreover, positive correlations were found between lnhsCRP levels and the number of illness years ($r = 0.563$; $p < 0.001$) and the age of illness onset ($r = 0.702$; $p < 0.001$).

3.3. hsCRP levels and psychopathological symptomatology

The mean HAM-D_{21} score was 24.5 (SD = 4.1), without differences across sexes ($p = 0.892$). The mean YMRS score was 5.3 (SD = 4.7), without differences across sexes ($p = 0.077$). The mean MSRS score was 8.3 (SD = 4.4), without differences across sexes ($p = 0.803$). The average BPRS score was 57.6 (SD = 17.3), without differences across sexes ($p = 0.324$). Significant positive correlations were found between lnhsCRP levels and YMRS total score ($r = 0.193$; $p = 0.040$) and BPRS total score ($r = 0.192$; $p = 0.041$).

Regarding each subscales at the TEMPS-M, the mean score at the depressive subscale was 21.1 (SD = 8.5), at the cyclothymic subscale was 21.7 (SD = 7.9), at the hyperthymic was 20.3 (SD = 9.5), at the irritable was 15.1 (SD = 4.8) and anxious affective temperament subscale was 13.7 (SD = 4.6). No significant sex-based differences were found depending on the type of affective temperament, except for the irritable subscale in which males reported higher scores compared to females ($p = 0.018$). Significant positive correlations were found between lnhsCRP levels and depressive ($r = 0.738$; $p < 0.001$) and cyclothymic ($r = 0.486$; $p < 0.001$) affective temperaments; while negative correlations were reported between lnhsCRP levels and hyperthymic ($r = -0.805$; $p < 0.001$) and irritable ($r = -0.206$; $p = 0.029$) affective temperaments. In the MDD sample, lnhsCRP levels were found significantly higher in individuals with depressive compared to hyperthymic affective temperament and lower in individuals with hyperthymic compared to cyclothymic affective temperament ($F(2,54) = 70.016$; $p < 0.001$). In the BD sample, lnhsCRP levels were found significantly lower in individuals with hyperthymic compared to depressive and cyclothymic affective temperaments and significantly higher in individuals with depressive versus cyclothymic affective temperament ($F(2,53) = 66.458$; $p < 0.001$).

A multinomial stepwise linear regression model, adjusted for all covariates, demonstrated that higher scores at the TEMPS-M depressive, while lower scores at the TEMPS-M hyperthymic and irritable affective temperament subscales [$F(3,109) = 88.955$, $R^2 = 0.710$, $p < 0.001$] statistically significantly predicted higher lnhsCRP levels (Table 2).

The average mean MEQ total score was 45.3 (SD = 16.6), without any sex-based significant differences ($p = 0.365$). Significant differences in lnhsCRP levels were found across different chronotypes when categorised in three subgroups [$F(2,110) = 44.517$; $p < 0.001$], being subjects with an eveningness-type chronotype those who displayed more higher lnhsCRP levels, compared to intermediate-type and morningness-type chronotypes (both with $p < 0.001$]. In the MDD sample, lnhsCRP levels were found significantly higher in eveningness-type individuals compared to morning-type and intermediate-type ($F(2,54) = 30.480$; $p < 0.001$). In the BD sample, lnhsCRP levels were found significantly higher in eveningness-type individuals compared to morning-type and intermediate-type ($F(2,53) = 15.840$; $p < 0.001$). Moreover, a negative significant correlation was found between lnhsCRP levels and MEQ total scores ($r = -0.636$; $p < 0.001$). The linear regression analysis

Table 2
Multinomial linear regression model across affective temperaments (Outcome = lnhsCRP).

	B	SE	ß	t	*p*-value (two-tailed)
(constant)	0.553	0.192		2.877	0.005
Depressive temperament score	0.023	0.005	0.331	4.424	**<0.001**
Hyperthymic temperament score	−0.037	0.005	−0.608	−7.895	**<0.001**
Irritable temperament score	0.014	0.007	0.116	2.082	**0.040**

hsCRP: high-sensitivity C-Reactive Protein; B: regression coefficient; SE: standard error. Significant values are in bold.

demonstrated that lower MEQ scores [$F(1,11) = 75.456$, $R^2 = 0.405$, $p < 0.001$] statistically significantly predicted higher lnhsCRP levels (Table 3).

4. Discussion

The present retrospective study investigated whether hsCRP levels were associated with overall depression severity and/or a specific trait-based features (e.g., predominant affective temperament and chronotype) within a specific mood disorder diagnosis (MDD vs BD-I vs BD-II). Our study was carried out in a real-world setting by retrospectively recruiting a cohort of MDD, BD-I and BD-II patients hospitalised due to a current moderate-to-severe depressive episode, and with a baseline measurement of the neuroinflammatory biomarker hsCRP. Our sample is mainly constituted by subjects with a previous psychiatric history, homogeneous regarding the diagnosis of MDD vs BD and other socio-demographic features, including sex and age. However, considering the potential role of concomitant confounding factors, often overexpressed in psychiatric population and associated with increased pro-inflammatory biomarkers, such as obesity, metabolic syndrome, cardiovascular disorders, smoking, voluptuous conduct and unhealthy lifestyle, we properly adjusted all statistical analyses considering these potential confounders, as suggested by previous authors (Delgado et al., 2018; Dixon et al., 2008; Hiles et al., 2015; Huang et al., 2021; Orsolini et al., 2022, 2018; Thaker et al., 2020). Overall, in our study, only significant lower lnhsCRP levels were found among patients with an underweight BMI, compared to other BMI groups. Indeed, published literature documented a direct and interchangeable association between CRP levels and BMI indicative of an overweight and obesity condition (Ambrósio et al., 2018; Berk et al., 2013; Bi et al., 2019; Choi et al., 2013; Han et al., 2019; Visser et al., 1999). However, our findings did not confirm this association within the group of overweight and obese patients. Interestingly, some studies clearly described how CRP levels were indeed associated with a depressive symptomatology, even after correction for the BMI, suggesting that the low-grade inflammatory status observed in depressive symptomatology could be found independently by the BMI (Osimo et al., 2019; Song et al., 2015; Tabata-baeizadeh et al., 2018). Contrarily, other studies suggested the need to adjust the findings for the BMI (Fried et al., 2020; Kappelmann et al., 2021; Pitharouli et al., 2021). For these reasons, our findings have been adequately adjusted considering the BMI. Moreover, our findings also documented higher lnhsCRP levels among patients affected with hypertension and/or dyslipidemia, independently by the type of mood disorder and/or severity of depressive symptomatology. These results are consistent with the literature already published (Bisaria et al., 2020; Koziarska-Rościszewska et al., 2021; Krzesiński et al., 2015). In fact, a recent study showed a statistically significant association between hsCRP and cardiovascular disease (CVD), hypertension, dyslipidemia and the number of the metabolic syndrome elements (Koziarska-Rościszewska et al., 2021). Moreover, patients with CVD, hypertension, diabetes or visceral obesity displayed higher hsCRP levels than in the subgroup without CVD (Koziarska-Rościszewska et al., 2021). Although the mechanism has not been clearly investigated, it seems that CRP may cause the remodelling of the vasculature, causing arterial stiffness and leading to the progression of hypertension (Bisaria et al., 2020). However, most of the published studies investigating the association between CRP levels and CVD, hypertension and dyslipidemia have not been carried out by recruiting a sample of individuals affected by mood disorders, thereby limiting the comparison with our findings. However, to avoid potential confounding biases, our findings have been also adjusted considering these CVD-related variables.

Our findings also reported a significant positive correlation between lnhsCRP levels, number of illness years and age of illness onset. Moreover, even though not significant, an increasing trend in lnhsCRP levels was observed among those drug-naive subjects at the day of hospitalisation and those with a positive family psychiatric history for mood disorders. No significant differences were found across different mood disorders, either on the type of depressive specifier, the presence/absence of psychotic symptoms associated with the depressive episode or other mood disorder-related variables. Indeed, a very recent study comparing CRP levels among patients affected by BD and MDD versus healthy controls, found higher CRP levels in BD compared to MDD and healthy controls (Zhang et al., 2022). BD patients in their maniac phase displayed higher CRP levels of CRP compared to healthy controls, while BD patients in their depressive or mixed episode had CRP levels comparable to the healthy group (Zhang et al., 2022). Previous studies reported higher hsCRP levels both in MDD and BD-I (Huang and Lin, 2007), while higher CRP levels in BD-II compared to MDD patients in their depressive phases (Chang et al., 2017). Further studies documented higher CRP levels mainly in BD, by suggesting a more severe inflammatory dysregulation in BD compared to MDD patients (Bai et al., 2015). Our findings appeared to be more in line with other studies which did not find any significant differences across mood diagnoses (Caldirola et al., 2021; Lu et al., 2019; Wysokiński et al., 2016). However, further larger studies evaluating hsCRP levels should be carried out in order to compare our findings which are mainly based on hsCRP levels, only more recently used in studies recruiting patients affected with psychiatric disorders.

In our study we also found a significant association between lnhsCRP levels and a previous lifetime suicidal attempt, the presence during the last month of death (not suicidal) thoughts and self-harm and/or self-injury thoughts. These results are in line with previous literature which reported a significant association between CRP levels and history of suicidal attempt in depressed patients, a greater risk of suicide after 9 years of follow-up and suicidal ideation (Batty et al., 2016; Chen et al., 2020; Courtet et al., 2015; Park and Kim, 2017). In addition, from a psychopathological perspective, we found only a significant positive association between BPRS and YMRS at baseline and lnhsCRP levels while our findings did not report any significant differences regarding the severity of depression or the mixed symptoms, by indeed confirming previous studies which documented an association between a more severe morbidity and increased hsCRP levels depending on the hypomanic/manic trend (Bai et al., 2015; Dickerson et al., 2007; Hamdi et al., 2021; Zhang et al., 2022).

Finally, our findings highlighted significant positive correlations between hsCRP levels and depressive and cyclothymic affective temperaments, while negative correlations were reported between hsCRP levels, hyperthymic and irritable affective temperaments. Indeed, the linear regression model confirmed that only higher depressive affective temperament levels and lower hyperthymic and irritable affective temperaments statistically predicted higher hsCRP levels. Indeed, there are no studies investigating the relationship between CRP levels (or other inflammatory markers) and the predominant affective temperament in mood disorders, therefore, our findings could not be compared with other literature. However, there is a growing literature investigating the relationship between the type of affective temperament and the chronotype in mood disorders (Chrobak et al., 2017; Lee et al., 2017; Mokros et al., 2017), a relationship that could be extremely significant to be investigated for assessing the vulnerability risk for affective disorders but also to guide diagnosis and treatment (Park et al., 2015). Accordingly, we also assessed the chronotype in our sample, by

Table 3
Linear Regression Model considering chronotype (Outcome = lnhsCRP).

	B	SE	ß	t	p-value (two-tailed)
(constant)	1.319	0.124		10.660	<0.001
MEQ total score	−0.022	0.003	−0.636	−8.687	**<0.001**

MEQ: Morningness-Eveningness Questionnaire; hsCRP: high-sensitivity C-Reactive Protein; B: regression coefficient; SE: standard error. Significant values are in bold.

interestingly finding a significant association between higher hsCRP levels and an eveningness-type chronotype. Considering the CRP levels have been demonstrated to be not related to diurnal/circadian variations (Meier-Ewert et al., 2001), we could hypothesise that the association found between depressive affective temperaments and eveningness chronotype could reflect the association already documented between these two characteristics (Chrobak et al., 2018, 2017). Indeed, eveningness traits have been associated with bipolarity (Chrobak et al., 2018; Dopierala et al., 2016; Jeong Jeong et al., 2015; Robillard et al., 2013), depression (Antypa et al., 2016; Robillard et al., 2013), greater emotional-anger attitude (Jankowski and Linke, 2020), a less emotional control, lower coping strategies, volition and caution, and more affective instability and externalisation (de Punder et al., 2019). Furthermore, evening chronotype is associated with higher risk for developing poor health outcomes, including higher BMI, metabolic syndrome, diabetes type 2 and asthma (de Punder et al., 2019). Conversely, morningness tendency has been identified as a protective factor against depression (Randler et al., 2015). Moreover, a significant association was documented between eveningness chronotype, cyclothymic and depressive affective temperaments, while morningness was more likely associated with a hyperthymic affective temperament (Park et al., 2015). However, very few studies investigated the possible association between chronotype, CRP levels and psychiatric disorders with contradictory and inconclusive results (Dolsen and Harvey, 2021). Literature so far published reported that a shorter sleep duration and a delayed circadian rhythm is associated with high CRP levels (de Punder et al., 2019; Nimitphong et al., 2018; Park et al., 2016). Evening chronotype, also, seems to be related with high CRP levels (Ngo-Nkondjock et al., 2021). Dolsen and Harvey (2021) investigated inflammation markers and sleep in a sample of adolescents with eveningness chronotype, by showing that higher CRP levels and shorter sleep were associated with more emotional and mood instability risk at baseline. A recent study reported that a sample of young adults with lower MEQ scores (i.e. eveningness tendency) significantly reported higher BMI scores, elevated CRP levels and higher cortisol response to acute stress (de Punder et al., 2019). Furthermore, the same authors also reported that the relationship between MEQ score and BMI was mediated by CRP levels, by suggesting that an evening chronotype could increase the risk of adverse metabolic health outcomes (de Punder et al., 2019).

However, despite our interesting and novel findings, our study should be understood considering a series of limitations which should be carefully discussed before considering our results generalizable to the sample of patients affected by unipolar and bipolar depression. Firstly, as our study aimed to preliminarily evaluate whether there is some interesting research direction to be deepened in the field of neuroinflammatory hypothesis in the unipolar and bipolar depression, we performed only a cross-sectional investigation and with a relatively modest sample size. Therefore, further longitudinal (comparison) and larger studies investigating how hsCRP levels, dependent by the predominant affective temperament and/or predominant chronotype, could vary depending on depressive levels (but also depending on the euthymic phase), should be carried out. Secondly, the real-world exploratory design of the study, even though it could allow exploring the association between hsCRP levels and trait-specific characteristics in a setting coming from the real-world, does not guarantee controlling all other potential confounding biases, in spite of our restrictive exclusion criteria and our adjustments for each of the above described potential confounders. Thirdly, another limitation of the study is that we measured chronotype by using a self-rated questionnaire, without including an objective measure of the circadian phase, like the dim light melatonin onset. Fourthly, in order to compare unipolar versus bipolar depression, our study recruited only subjects with a current moderate-to-severe depressive episode, even though we included MDD, BD-I and BD-II diagnosis, but we excluded subjects with a current hypomanic and/or manic episode or in a euthymic phase. Therefore, it would be interesting to evaluate whether the hsCRP levels could be more a trait-specific inflammatory biomarker, independently by the type of acute episode or rather this pattern would be observed in subjects affected with a mood disorder with a specific pattern of affective temperament and/or chronotype only during a depressive episode. Fifthly, we used a cross-diagnostic approach, based on the exploration of mood symptoms, according to the spectrum approach within a cohort of patients admitted with current unipolar and bipolar disorder, with the intent to deconstruct disease complexity and support tailored clinical and treatment approaches, which could be in contrast with the current concept of bipolar versus unipolar disorders as distincts disorders. However, despite the above mentioned limitations, we were able to adjust for important factors potentially affecting hsCRP levels such as smoking, BMI, physical activity and we excluded potential confounders such as subjects with concomitant somatic inflammatory disease and/or an acute inflammatory status (i.e., hsCRP>10 mg/L). Moreover, all laboratory measurements from blood samples were performed at the same time and at the same department with a high-sensitivity immunoturbidimetry assay blinded to depression scores, minimising the risk for differential test results due to different assays or other confounding factors. Furthermore, our cross-diagnostic approach may be extremely useful for improving staging, subtyping and proposing a more tailored and individualised diagnostic and treatment approach to mood spectrum disorders, as also supported by previous literature (Cassano et al., 2004; Corponi et al., 2020; Mineo et al., 2022). Overall, identifying reliable inflammatory biomarkers, such as hsCRP, and associated clinical features could help in potentially predicting clinical course and response to treatments. Further inflammatory biomarkers are currently under investigation for diagnosis, outcome prediction, staging and stratification of interventions, despite research is still needed before they could be widely used for routine clinical care (Serretti, 2022). However, the future potentialities are promising with the possibility of profiling depressed patients about outcome and clinical course prediction and specific indications about preferred treatments.

4.1. Conclusion

Overall, the current findings advance our understanding of the underlying role of the immune system and the HPA-axis in the relationship between chronobiology, affective temperament and depressive symptomatology among patients affected by a mood disorder. Our findings could pose the promises for developing a stratifying model to classify those subjects with a higher trend risk to develop a low-grade inflammatory pattern associated with an acute illness phase who could potentially benefit from a combined anti-inflammatory treatment strategy, beyond the psychopharmacological strategy. Furthermore, it seems reasonable that a neuroinflammatory approach could furtherly help in staging and subtyping depressed patients in more homogeneous samples sharing the same neuroinflammatory pattern and in investigating the clinical and treatment short- and long-term implications as well as in predicting clinical course and prognosis. Further research studies should be carried out by also considering all illness phases and how a specific predominant affective temperament and chronotype may influence the treatment response, illness course and outcomes.

Disclosure statement

The authors have nothing to disclose.

CRediT authorship contribution statement

Laura Orsolini: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Leonardo Ricci:** Data curation. **Simone Pompili:** Data curation, Investigation, Methodology, Writing – original draft. **Angelica Cicolini:** Data curation, Investigation. **Umberto Volpe:** Conceptualization, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare no conflict of interest.

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