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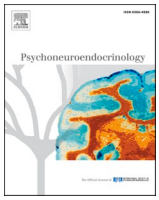

Cortisol and C-reactive protein (CRP) regulation in severe mental disorders

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ABSTRACT

Background: People with schizophrenia (SZ) and bipolar disorder (BD) show abnormalities in the biological stress system and low-grade inflammation. However, whether the hypothalamic-pituitary-adrenal (HPA) axis-immune regulation is disrupted in SZ and BD, is yet to be determined.

Methods: Cortisol and C-reactive protein (CRP) were measured in blood samples collected at or before 10 am in participants with SZ (N = 257), BD (N = 153), and healthy controls (N = 40). Cortisol/CRP ratio was calculated as an indicator of the balance between HPA axis activity and inflammatory activity, called HPA axis-immune regulation. Global functioning and symptom levels were obtained using the Global Assessment of Functioning (GAF) Scale and Positive and Negative Syndrome Scale (PANSS). Standardized neuropsychological tests were used to assess cognitive function. All analyses were adjusted for demographic variables (age and sex) and the time of blood sampling.

Results: Participants with a SZ or BD diagnosis had lower cortisol/CRP ratios (F=5.93, p = 0.003) compared to healthy controls. The difference was no longer statistically significant (p > 0.1) when BMI was added as a co-variate to the model. Within patients, those on psychotropic treatment (n = 337) had lower cortisol/CRP ratio than those not taking psychotropic agents (n = 59) (F=4.72, p = 0.03). Compared to HC, only patients on regular psychotropic agents had lower cortisol/CRP ratio (p = 0.02). Within the SZ group, lower cortisol/CRP ratio was associated with having poorer general functioning as measured by GAF (ß=-0.18, p = 0.01), and more severe negative and general symptomatology as measured by PANSS (ß=0.19, p = 0.007 and ß=0.18, p = 0.01, respectively). In SZ, lower cortisol/CRP ratio was also associated with poorer verbal memory, learning, and processing speed (ß=-0.20 p = 0.007, ß=-0.19 p = 0.01, ß=-0.25, p > 0.001, respectively). No associations were observed between cortisol/CRP ratio and clinical and cognitive functioning in the BD group.

Conclusion: These findings may indicate HPA axis-immune dysregulation in SZ. Our study further indicates that disrupted HPA axis-immune regulation in people with SZ and BD is associated with psychotropic treatment and fat mass, highlighting the clinical importance of weight control and regular psychotropic treatment follow-ups within this group.

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1. Introduction

People with schizophrenia (SZ) or bipolar disorder (BD) often present with an abnormal hypothalamic-pituitary-adrenal (HPA) axis regulation with higher cortisol levels during the day, a blunted awakening response and reactivity to stress (Pruessner et al., 2017). Cortisol, which is released from the adrenal glands in response to stressful stimuli, is a potent anti-inflammatory hormone (Vinson, 2009). However, chronic stress decreases hormonal anti-inflammatory effects (Cohen et al., 2012; Miller et al., 2002, 2008; Cole, 2008) and inflammation stimulates HPA axis activity (Suarez and Sundy, 2017). Systemic levels of C-reactive protein (CRP) may reflect acute and chronic inflammatory conditions (Pepys and Hirschfield, 2003). Low-grade inflammation appears to be central to SZ and BD pathophysiology (Dieset et al., 2019; Leboyer et al., 2016). Previous studies suggest elevated cortisol and low-grade inflammation may manifest as poorer treatment response with more severe clinical presentation, as well as worse somatic health outcomes in patients with severe mental disorders (Mondelli et al., 2015). However, whether the HPA axis-immune regulation is disrupted in SZ and BD, remains to be determined.

The glucocorticoid resistance model by Nikkelslat and colleagues (2020) suggests the coexistence of hypercortisolemia and inflammation in treatment resistant major depressive disorder (MDD), especially in people with a history of early trauma (Nikkheslat et al., 2020). Conversely, the homeostasis model by Suarez and Sundy (2017) suggests cortisol insufficiency in regulating CRP in MDD. The homeostasis model by Suarez and Sundy (2017) uses the ratio between the two factors to measure their reciprocal relationship and any imbalance between the two (i.e., dominant cortisol or dominant CRP). This model is supported by studies showing 'low' cortisol/CRP ratios, reflecting low cortisol and elevated CRP, in depressed women (Miller et al., 2005). To our knowledge, no previous studies have investigated the reciprocal relationship in SZ and BD and how this is associated with clinical and cognitive correlates within these disorders.

The glucocorticoid resistance model highlights the experience of trauma as an importance factor in MDD. Patients with a psychotic and bipolar disorder report more social stressful life events in childhood and in adulthood compared to people in general (Etain and Aas, 2021; Pruessner et al., 2017; Varese et al., 2012), however studies investigate the role of trauma on glucocorticoid resistance is less clear in psychosis and in bipolar disorder. In addition to experiencing of more early life stress than the general population, there is evidence that people with psychosis or bipolar disorder may be more vulnerable to trauma experiences due to their genetic makeup (Aas, Alameda, et al., 2023; Aas, Andreassen, et al., 2023). A history of childhood trauma is also associated with more severe clinical expression of both a psychotic disorder and a bipolar disorder (Aas, Ueland, et al., 2023; Alameda et al., 2021; Etain and Aas, 2021), as well as elevated C-reactive protein and body mass index (Aas et al., 2017). Although there is evidence that early life stress may affect brain development as shown by poorer cognitive functioning in people with childhood trauma compared to those with no trauma, this is also evident in the general population, and thus not diagnosis specific (Sideli et al., 2022).

To evaluate the dynamic interplay between the HPA axis and inflammatory activity in SZ and BD, we used a ratio of cortisol to CRP level previously applied by Suarez and Sundy (2017). We hypothesized disruption of the HPA axis and inflammatory activity (i.e. HPA axis-immune dysregulation) in the direction of cortisol insufficiency in influencing the immune system. Secondly, we hypothesize that in people with a severe mental disorder, the HPA axis-immune dysregulation will correlate with having poorer cognitive functioning and more severe symptom severity. Lastly, we also investigate if HPA axis-immune dysregulation in severe mental disorders is associated with childhood trauma experiences.

2. Methods

2.1. Participants

Data were obtained from the ongoing Thematically Organized Psychosis (TOP) study at the Norwegian Center for Mental Disorders Research (NORMENT). Participants were enrolled between 2007 and 2020 from psychiatric units within the major hospitals in Oslo, Norway.

For the current study, we included participants with cortisol sampled between 7:30 am and 10 am and with CRP levels of 10 mg/L or lower. This gave a total of 450 participants (schizophrenia spectrum disorder, SZ [$n = 257$] (schizophrenia, $n = 143$, schizophreniform, $n = 16$, schizoaffective disorder, $n = 30$ other psychosis $n = 68$;) Bipolar disorder, BD [$n = 153$], (bipolar I, $n = 98$, bipolar II, $n = 49$, Bipolar Disorder Not Otherwise Specified BD NOS, $n = 6$), and healthy controls [$n = 40$]). Inclusion criteria for healthy controls were as follows: living in the same city district as the patients, age between 18 and 65 years, having no lifetime diagnosis of a severe mental disorder and absence of severe mental disorders in close relatives. Exclusion criteria for both patients and controls were intellectual disability (IQ under 70), organic- or substance induced affective or psychotic disorder, neurological disorder, autoimmune diseases or cancer, or a medical condition interfering with brain function. Patients with an acute infection (CRP above 10) were excluded. Controls were also excluded if they had any severe psychiatric disorder or substance abuse or dependency. The Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate approved the study.

2.2. Clinical assessment

Participants were assessed using the Structured Clinical Interview for DSM-IV (Axis I disorders (SCID-I), chapters A-E; Spitzer, Williams, Gibbon & First, 1992). Trained medical doctors and psychologists carried out the clinical assessments. A good inter-rater reliability for diagnostic assessments at the TOP study was indicated, with an overall kappa score between 0.92 and 0.99 (Hoegh et al., 2020). Ninety (41.2) of the bipolar patients had at least one psychotic episode but the psychotic episode was secondary to their primary affective illness. Current positive and negative psychotic symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Current general functioning was rated using a split version of the Global Assessment of Functioning Scale (GAF) assessing current functioning (GAF-F) and symptom level (GAF-S) (Pedersen et al., 2007). Patients gave information on Daily defined dose (DDD) and type of medication (yes/no use). Although other studies have been published in overlapping datasets (Aas et al., 2017, 2012, 2014; Aas, Dieset, et al., 2019; Aas, Elvsashagen, et al., 2019; Aas, Pizzagalli, et al., 2019), this is the first study investigating the bidirectional relationship between cortisol and CRP levels within this context. We have previously published a paper on C-reactive protein and childhood trauma (Aas et al., 2017) and hair cortisol and childhood trauma (Aas et al., 2019), but not blood cortisol or the cortisol/C-reactive-protein ratio.

2.3. Cognitive assessment

Trained personnel completed cognitive assessment of both patients and controls. Cognitive and clinical assessments were completed within the same timeframe, no more than two weeks apart. Two cognitive batteries were implemented. Participants included before 2012 were assessed with a standardized battery previously described by Simonsen and colleagues (2011) (Simonsen et al., 2011), while participants included between 2012 and 2018 were assessed with a battery based on the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008). Analogous tests in the two batteries were combined to represent the following four domains: 1) Verbal learning was assessed with the California Verbal Learning Test (CVLT-II) (Delis et al., 2004) or the

Hopkins Verbal Learning Test (HVLT-R) (Benedict et al., 1998), 2) Verbal memory was assessed with the CVLT-II, long delay free recall, or the HVLT-R, long delay free recall, 3) Processing speed was assessed with digit symbol coding from WAIS-III (or Brief Assessment of Cognition in Schizophrenia (Keefe et al., 2004) and 4) Working memory was assessed with letter-number sequencing from WAIS-III or letter-number sequencing from the MCCB.

2.4. Inflammatory and cortisol markers

Serum CRP and morning serum total cortisol ("serum cortisol") were measured with standard methods at the Department of Medical Biochemistry, Oslo University Hospital. CRP and cortisol and were analyzed by validated methods at the central hospital laboratory at our institution. They report coefficients of variation of 5 %, 4 % and 4 % for low, medium and high levels of cortisol, respectively. The CV% given for CRP is 15 % for levels < 5 mg/L and 6 % for levels ≥ 5 mg/L. Serum levels of CRP was measured by particle-enhanced immunoturbidimetric method (Cobas Integra 800 – Cobas 8000 from Roche Diagnostics, Mannheim, Germany). CRP and cortisol were measured in the same blood sample. Individuals with CRP values above 10 mg/L were excluded to avoid effects of ongoing infections (Nikkheslat et al., 2020). Serum cortisol was measured with a competitive luminescence immunoassay (Immulite 2000xpi, Siemens Healthineers, Erlangen, Germany), obtaining cortisol levels in the range 3,0 −1750 nmol/L. Only participants with blood samples measured between 7:30 and 10 am were included in the analysis to avoid confounding from diurnal variation. 98.7 % were fasting at the time of the blood sampling.

2.5. Statistical analyses

Data were analyzed with IBM Statistics SPSS, version 26. For comparison of demographic data, analysis of variance (ANOVA) was performed with post hoc Bonferroni adjusted follow up analyses. Chi square tests were performed for dichotomous variables. Data that were non-normally distributed (GAF-scores, PANSS-scores, cortisol/CRP ratio) were log transformed before entered into the parametric analyses.

Analysis of covariance (ANCOVA) was used to investigate if patients differed from healthy controls on cortisol/CRP ratio. An overall ANCOVA was conducted to compare all 3 groups with post hoc Bonferroni adjusted follow up analyses. We adjusted all analyses for age and sex, and performed adjustments for time of blood sampling, BMI and medication (current vs. no current psychotropic medication). We used a ratio of cortisol to CRP level to determine the dynamic interplay between HPA axis function and inflammatory activity, see Suarez and Sundy (2017). The clinical and cognitive variables were added as the dependent variable one at a time, adjusted for confounders (see description above). Assumptions for linear regression was checked and found satisfactory. The main analyses were adjusted for False Discovery Rate (FDR). Alpha level was set at < 0.05 with FDR corrections. Standardized effect sizes were calculated by hand using the Cohen's *d* equation for any significant group differences (Cohen, 1988; Durlak, 2009): $d = \frac{M_1 - M_2}{\text{Sample SD pooled}}$

This effect size measure can be interpreted using Cohen's rule of thumb, where.20 represents a small effect,.50 a medium effect, and.80 a large effect size (Durlak, 2009). Standardized coefficient beta will be presented for the regression analysis. The standardized beta coefficient can be interpreted using similar guidelines to that of Cohen's *d* (Durlak, 2009).

As SZ and BD are usually viewed as part of the same continuum with shared neural, genetic and psychological mechanisms (Smeland et al., 2020; Sorella et al., 2019) analysis was performed in the total sample prior to dividing into diagnosis (SZ and BD).

3. Results

3.1. Demographics and clinical characteristics

The mean age of the participants was 32.42 ± 10.85 years (see Table 1 for a full descriptive overview). The BD group was older and more likely female compared to the SZ group and healthy controls. The mean age of the BD group was 35.14 ± 12.35 compared to 30.75 ± 9.96 in the SZ group). Patients had higher BMI than healthy controls (F=5.67, p = .04). The rate of daily use of psychotropic medication use was 88.3 % in SZ and 80.4 % in BD. The majority of the SZ and BD total sample were taking regular antipsychotics (85.5 %), whilst 30.0 % were taking mood stabilizers and 42.1 % antidepressants. Sixty percent of the patients reported daily tobacco smoking. No association was observed between daily smoking and Cort/CRP ratio (F=.05 p = .82). Both SZ and BD had higher CRP levels than healthy controls, but there were no significant differences between the patient groups. No significant differences were observed for cortisol levels between groups. An earlier age at onset of a psychiatric disorder was associated with lower Cort/CRP ratio (Spearman's correlation, r = -.12, p = .01). No significant association was observed between sex and Cort/CRP levels (t = .21, p = .42). For a full overview of demographic and clinical characteristics, see Table 1.

3.2. Cortisol/CRP ratio in patients compared to controls

Patients had higher levels of CRP than healthy controls, HC (F=6.49, p = 0.002, Cohen's *d*=.60), but no significant differences between groups were found for cortisol levels (F=1.17, p = 0.31). Further, the patient group had a lower cortisol/CRP ratio than controls (F=5.93, p = .003, Cohen's *d*=.61; see Fig. 1). No difference in CRP, cortisol or cortisol/CRP ratio levels were observed in patients with SZ compared to patients with a BD diagnosis. Analyses above were adjusted for time of blood sample, age, and sex. As shown in Fig. 2. BMI was positively associated with lower cortisol/CRP ratio (ß=-.43, p < .001, see Fig. 2). Differences in cortisol/CRP ratio in patients compared to controls disappeared when BMI was added into the model (p > .1). Patients on regular psychotropic agents (n = 337) had lower cortisol/CRP ratios than those without current use of psychotropics (n = 59, F=4.72, p = .03, Cohen's *d*=.36; see Fig. 3). Dividing into medication type, this was specifically evident for antipsychotic medication (t = -1.36, p = .09). A difference on the threshold of statistical significance was also observed between antipsychotic medication and BMI levels (t = 1.59, p = .06). A correlation matrix between cortisol/CRP ratios, cortisol, CRP, BMI and regular psychotropic medication (DDD) are found in Supplementary Material Table S1. Compared to HC, only patients on regular psychotropic agents had lower cortisol/CRP ratio (p = 0.02). No significant difference in BMI was observed in patients on regular psychotropic agents compared to those not taking psychotropic agents (t = -.36, p = .72). No statistically significant association was observed between cortisol/CRP ratio and tobacco use (F=.03, p = .47). No association was observed between cortisol/CRP ratio and reports of childhood trauma from the CTQ in patients (ß=-.01, p = .82), or controls (ß=.13, p = .47). No association was observed between cortisol and clinical or cognitive variables, while higher CRP levels were associated with more severe negative and general psychopathology on the PANSS, more symptoms on the GAF-S and poorer performance on processing speed (see Supplementary Material Table S2).

3.3. Cortisol/CRP ratio and clinical features

Within the patient population, a lower cortisol/CRP ratio was associated with more severe negative symptoms (ß=.11, p = .027) as well as more general psychopathology symptoms from the PANSS (ß=.11, p = .016, see Table 2). Analyzing diagnoses separately showed that, within SZ, a lower cortisol/CRP ratio was associated with having more severe negative symptoms and general psychopathology (ß=.18, p = .01

Table 1
Demographics of the sample.

	Schizophrenia spectrum diag. SZ, N = 257	Bipolar disorder BD, N = 153	Controls HC, N = 40	Statistics	Post hoc test
Age, median, mean±SD	30.75 ± 9.96	35.14 ± 12.35	32.72 ± 7.94	F= 8.10, df= 2, p < .001	BD>SZ
Sex, N (%) Males	160 (62.26)	60 (39.21)	25 (57.50)	X^2= 21.68, df= 2, p < .001	BD<HC, SZ
Years in education, mean±SD	13.17 ± 2.90	14.15 ± 2.85	14.88 ± 2.32	F= 9.77, df= 2, p < .001	SZ<HC, BD
CRP mg/l, mean±SD	3.52 ± 2.86	3.07 ± 2.80	1.87 ± 1.85	F= 6.49, df= 2, p = .002	SZ>HC, BD>HC
Cortisol nmol/l, mean±SD	449.07 ± 145.00	435.92 ± 166.05	477.43 ± 180.68	F= 1.17, df= 2, p = .31	
Cortisol_CRP ratio, median, mean±SD	5.23 ± 1.12	5.36 ± 1.18	5.94 ± .94	F= 6.96 df= 2, p = .001	SZ, BD<HC
Ethnicity N (%) European ancestry	205 (79.8)	139 (90.8)	39 (97.5)	X^2= 6.61, df= 2, p = .04	
BMI, median, mean±SD	26.30 ± 4.90	25.34 ± 4.43	23.88 ± 2.27	F= 5.67, df= 2, p = .004	SZ>HC
Age at onset of psychiatric disorder, mean±SD	24.97 ± 8.42	22.37 ± 10.53	—	F= 6.88, df= 1, p = .009	BD<SZ
Medication, psychotropic agents, Yes N (%)*	227 (88.3)	123 (80.4)	—	X^2= 2.12, df= 1, p = .15	
PANSS Positive, median, mean±SD	15, 14.71 ± 5.04	9, 10.29 ± 3.85	—	F= 87.23, df= 1, p < .001	SZ< BD
PANSS Negative, median, mean±SD	15, 15.41 ± 6.66	9, 9.47 ± 2.91	—	F= 108.55, df= 1, p < .001	SZ<BD
PANSS General, median, mean±SD	32, 32.12 ± 8.76	24, 25.19 ± 5.80	—	F= 75.69, df= 1, p < .001	SZ<BD
GAF-S, median, mean±SD	40, 43.27 ± 11.69	56, 56.30 ± 11.84	—	F= 118.05, df= 1, p < .001	BD>SZ
GAF-F, median, mean±SD	41, 44.62 ± 11.96	51, 53.37 ± 13.20	—	F= 47.52, df= 1, p < .001	BD>SZ
CTQ total score, median, mean±SD	42, 45.92 ± 15.56	39, 41.85 ± 14.90	29, 30.16 ± 5.39	F= 17.92, df= 2, p < .001	SZ, BD>HC
Verbal learning, mean±SD	−.59 ± 1.21	.11 ± 1.53	.20 ± 1.01	F= 19.60, df= 2, p < .001	SZ<HC, BD
Verbal memory, mean±SD	−.56 ± 1.25	−.05 ± 1.15	.26 ± 1.05	F= 12.59, df= 2, p < .001	SZ<HC, BD
Processing speed, mean±SD	−1.39 ± 1.60	−.66 ± 1.56	.05 ± 1.00	F= 20.35, df= 2, p < .001	SZ, BD<HC; SZ< BD
Working memory, mean±SD	−.77 ± 1.25	−.47 ± 1.15	.14 ± .97	F= 10.77, df= 2, p < .001	SZ, BD<HC

Abbreviations: SZ=Schizophrenia spectrum diagnosis (schizophrenia, $n = 143$, schizophreniform, $n = 16$, schizoaffective disorder, $n = 30$ other psychosis $n = 68$; BD=Bipolar disorder (bipolar I, $n = 98$, bipolar II, $n = 49$, Bipolar Disorder Not Otherwise Specified BD NOS, $n = 6$; Regular medication: 85.5 % were taking antipsychotics, 30.0 % mood stabilizers and 42.1 % antidepressants. Total Daily Defined dose was mean SD.87 ± .92. BMI=Body mass index; CRP=C-reactive protein; GAF-F=Global assessment of functioning - function; GAF-S=Global assessment of functioning - symptoms; HC=Healthy controls; IDS=Inventory of depressive symptoms; PANSS=Positive and negative syndrome scale; SD=Standard deviation; CTQ=Childhood trauma questionnaire. Cortisol, CRP and cortisol/CRP ratio is adjusted for age, sex and time of the blood sample (all taken between 07.30 and 10 am). Missing data: Number of years in education was available for 99.3 % of the sample (N = 447). BMI was available for 96,4 % of the sample (N = 434). Working memory was available for 86,67 of the sample (N = 390). CTQ total score available for 59,3 % of the sample (N = 267). PANSS-scores were available for 99,5 % of the patient group (N = 408). Processing speed was available for 93.6 % of the sample (N = 421). Verbal learning was available for 93,1 % of the sample (N = 419). Verbal memory was available for 90 % of the sample (N = 405).

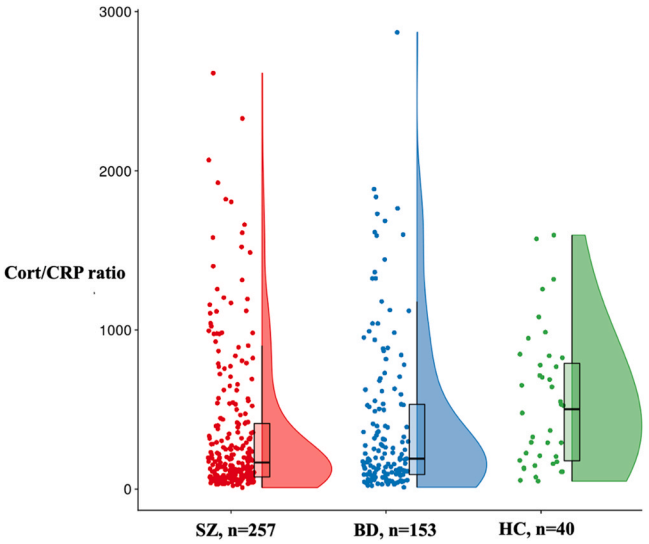

Fig. 1. Cortisol/CRP ratio in patients compared to healthy controls. ANCOVA, F= 5.93, p = 0.003. Analysis adjusted for time of blood sample, age, and sex. Abbreviations: SZ=Schizophrenia; BD=Bipolar disorders; HC=Healthy controls.

and ß=0.19, p = .007, respectively). Within SZ, a lower cortisol/CRP ratio was also associated with poorer functioning (GAF-F) (ß=.18 p = .01). All analyses above were adjusted for age, sex, time of blood sample, BMI, and regular psychotropic agents (yes/no). Within BD, no association was observed between clinical features and cortisol/CRP ratio (see Table 3).

3.4. Cortisol/CRP ratio and cognitive functioning

Within the total patient sample, lower cortisol/CRP ratio was associated with poorer processing speed (ß=-.10, p = .045, see Table 4). Analyzing the diagnoses separately showed that, within SZ, a lower cortisol/CRP ratio was associated with poorer performance on tests of verbal learning (ß=-.19 p = .01), verbal memory (ß=-.20 p = .007), and processing speed (ß=-.25 p > .001). Analyses were adjusted for age, sex, time of blood sample, BMI, and psychotropic agent use (yes/no). No association was observed for working memory and cortisol/CRP ratio in the SZ group (p > .1). Within BD, no association was observed between any cognitive domain and cortisol/CRP ratio (see Table 5).

4. Discussion

Our study suggests a HPA axis-immune dysregulation in patients with a severe mental illness. Separate analyses of SZ and BD showed that lower cortisol/CRP ratio was related to more severe current symptoms and poorer cognition in SZ but not in BD, suggesting that lower cortisol/CRP ratio might be specifically related to the underlying pathophysiology of SZ. Our study further indicates that HPA axis-immune dysregulation in patients is linked to having high BMI as well as use antipsychotic regular psychotropic agents, highlighting the clinical importance of weight control and treatment follow-ups within these disorders.

Only recently have studies begun to employ multisystem approaches to explore the complex biological underpinnings of severe mental disorders. A study in patients with MDD demonstrated that those with more severe depressive symptoms also had insufficient cortisol release relative to increased CRP levels. Lower cortisol/CRP ratios were associated with higher levels of stress-induced negative affect (Suarez and Sundy, 2017). Our study is the first to suggest a HPA axis -immune dysregulation in psychotic and bipolar disorder indicating insufficient cortisol release relative to increased CRP levels. In SZ, this disruption was associated with more severe clinical and cognitive characteristics.

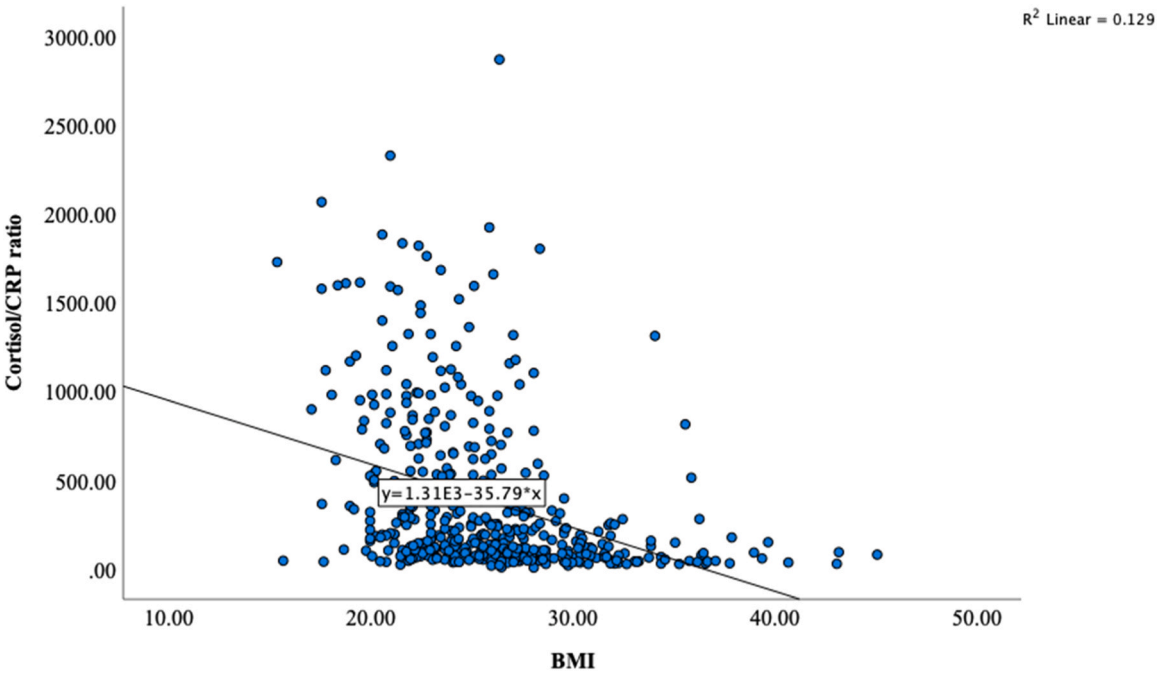

Fig. 2. Cortisol/CRP ratio and BMI. Linear regression, ß= -0.43, p < 0.001. Adjusted for time of blood sample, age, and sex, and regular psychotropic agents (yes/no). Abbreviations: BMI=Body mass index.

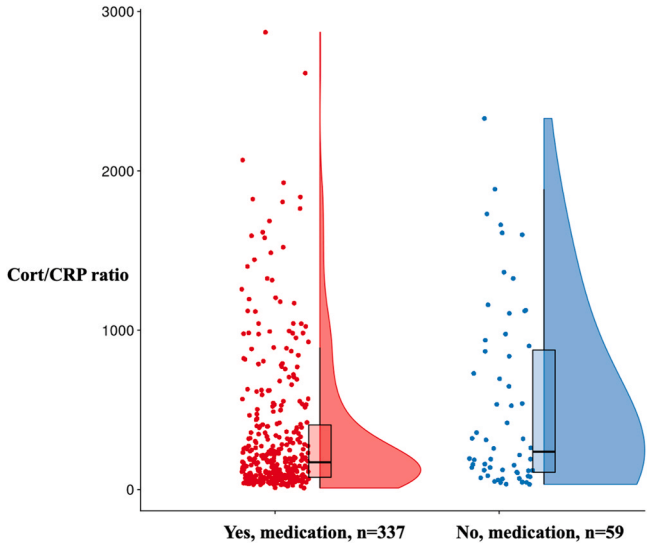

Fig. 3. Cortisol/CRP ratio in patients with and without psychotropic agents. ANCOVA, F= 4.72, p = 0.03. Analysis adjusted for diagnosis (schizophrenia, bipolar disorder), time of blood sample, age, sex and BMI. Abbreviations: BMI=Body mass index.

Table 2
Cortisol/CRP ratio and clinical characteristics in all patients (n = 410).

	ß	SE	t	p
PANSS Negative	−.11	.01	−2.22	.027
PANSS General	−.11	.001	−2.43	.016
PANSS Positive	−.01	.01	−.25	.80
GAF-F	.05	.004	1.17	.24
GAF-S	.04	.004	.95	.34
IDS	−.003	.005	−.06	.96

Analysis adjusted for age, sex, time of blood sampling, BMI, and regular psychotropic agents (yes/no). Abbreviations: BMI=Body mass index; CRP=C-reactive protein; GAF-F=Global assessment of functioning - function; GAF-S=Global assessment of functioning - symptoms; IDS=Inventory of depressive symptoms; PANSS=Positive and negative syndrome scale.

Table 3
Cortisol/CRP ratio and clinical characteristics stratified by diagnosis Schizophrenia spectrum disorder (n = 257) Bipolar disorder (n = 153).

	ß	SE	t	p	ß	SE	t	p
PANSS Negative	−.19	.43	−2.70	.007	−.01	.22	−.05	.96
PANSS General	−.18	.56	−2.50	.013	−.02	.44	−.27	.79
PANSS Positive	−.03	.33	−.42	.68	.02	.29	.22	.82
GAF-F	.18	.75	2.47	.014	−.06	1.03	−.67	.51
GAF-S	.13	.73	1.85	.065	−.06	.92	−.69	.49
IDS	−.07	.90	−.89	.38	.09	.78	1.02	.31

Analysis adjusted for age, sex, time of blood sampling, BMI, and regular psychotropic agents (yes/no). Abbreviations: BMI=Body mass index; CRP=C-reactive protein; GAF-F=Global assessment of functioning - function; GAF-S=Global assessment of functioning - symptoms; IDS=Inventory of depressive symptoms; PANSS=Positive and negative syndrome scale.

Cytokines stimulate not only CRP but also the HPA axis to enable the secretion of glucocorticoid to preserve the body from the potentially harmful effects of long-term immune activation (Suarez and Sundy, 2017). Our study suggests that this process is disrupted in patients with SZ. However, as shown in Fig. 1, large variation in cortisol/CRP ratio was observed in our study and findings should thus be interpreted with caution until replicated in independent samples.

A previous review article suggests that blunted morning cortisol combined with higher cortisol levels during the day is observed in patients with psychosis (Pruessner et al., 2017). While our findings represent the interplay of morning cortisol (all taken between 7:30 am and 10 am) and CRP levels, the Nikkheslat and colleages study (2020) illustrate the interplay of HPA axis and inflammatory activity throughout the day. Nikkheslat and colleages (2020) showed the coexistence of hypercortisolemia during the day and inflammation in treatment resistant MDD, while our study demonstrates lower morning cortisol to CRP levels in SZ. Hence, the relationhip between CRP and cortisol may vary depending on time of day cortisol is measured.

In addition to time of the day cortisol is measured, evidence suggests

Table 4
Cortisol/CRP ratio and cognitive function in all patients (n = 410).

	ß	SE	t	p
Verbal learning	.07	.05	1.39	p = .17
Verbal memory	.07	.05	1.43	p = .16
Processing speed	.10	.03	2.01	p = .045
Working memory	−.003	.05	−.05	p = .96

Analysis adjusted for age, sex, time of blood sampling, BMI, and regular psychotropic agents (yes/no). Abbreviations: BMI=Body mass index; CRP=C-reactive protein.

Table 5
Cortisol/CRP ratio and cognitive function stratified by diagnosis Schizophrenia spectrum disorder (n = 257) Bipolar disorder (n = 153).

	ß	SE	t	p	ß	SE	t	p
Verbal learning	.19	.07	3.67	P = .01	−.01	.08	−.02	.98
Verbal memory	.20	.07	4.24	P = .007	.01	.08	.23	.82
Processing speed	.25	.09	4.63	p < .001	−.02	.10	−.29	.77
Working memory	.07	.08	.96	.34	−.05	.09	−.52	.60

Analysis adjusted for age, sex, time of blood sample, BMI, and regular psychotropic agents (yes/no). Abbreviations: BMI=Body mass index; CRP=C-reactive protein.

that age also influences cortisol with an increase in late childhood and adolescence followed by a drop after adulthood (Coulon et al., 2016). All participants in our study were adults with a mean age of early 30 to mid 30ths which is important for the interpretation of the findings.

Acute and time-limited stressors lead to an adaptive change in the immune system as it prepares for potential injury or infection (Segerstrom and Miller, 2004). However, chronic stressors may influence the immune system's ability to adapt leading to sustained low-grade non-resolving systemic inflammation. Another important mechanism in our study is BMI levels. Higher BMI levels in the patients were associated with lower cortisol/CRP ratio. Higher BMI may contribute to the systemic inflammation through increased adipose tissue (Festa et al., 2001). Our study highlights the importance of monitoring weight gain in psychotic disorders emphasizing a healthy lifestyle. We also found that the patients on regular psychotropic agents had lower cortisol/CRP ratio, however as our study is a cross-sectional study, we can only show associations and not the direction of the relationship. One might speculate that medication is an epiphenomenon and not a cause of the lower ratio since patients with more severe clinical characteristics are also more likely to be prescribed medication. Lastly, in contrast to prior work by Nikkheslat and colleages (2020) we did not find an association between childhood trauma, cortisol and immune system in morning blood samples. We have previously showed that childhood trauma is associated with elevated hair cortisol (as a mean of cortisol relerase over time) and more severe symptoms in a subset of people with psychosis (Aas et al., 2019). It could be that the morning blood cortisol sample taken in the current study was not sensitive enough to capture such an effect.

Study strengths: To our knowledge, this is the first study to investigate Cort/CRP ratio in patients with a psychotic or bipolar disorder. The cohort is also a well described clinical cohort with detailed clinical characteristic as well as biological markers.

Study limitations: A history of childhood trauma events was reported retrospectively, with a recent meta-analysis study showing low overlap between retrospective and prospective data on childhood trauma (Baldwin et al., 2019). Only individuals with a morning blood sample (taken between 07:30 and 10 am) were included. We excluded participants with blood collected outside this window to account for diurnal variation and adjusted for time of sampling. Consequently, we cannot rule out that the method used may have influenced the results. Cortisol levels measured in blood is subject to large variations throughout the day and can be influenced by factors such as stress, diurnal rhythm, activity, and smoking (Pruessner et al., 2017). Repeated measures can capture stress reactivity, or the awakening response, as a marker of the dynamic HPA response to a naturalistic stressor (Mondelli et al., 2010). In our study, we only used a one-time measure. Due to large temporal fluctuations, the traditional methods of blood, saliva, and urine sampling are not well-suited for evaluation of chronic stress (Stalder and Kirschbaum, 2012). To advance our understanding of the cortisol/CRP interplay in severe mental disorders, further studies may use a multisystem approach together with more stable measures of cortisol, including hair cortisol or additionally longitudinal sampling of saliva, blood, or urine for cortisol analysis. Finally, although our hypotheses were consistent with prior research, they were not pre-registered before data analysis. The preregistration of future work in this area will help increase the reproducibility of research findings.

To conclude, our study supports an HPA axis-immune dysregulation in psychosis. Specifically, our study may suggest cortisol insufficiency in regulating CRP levels in psychotic disorders important for future research on pathophysiological pathways and treatment.

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CRediT authorship contribution statement

Viktoria Birkenæs: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Amina Inova:** Writing – original draft, Investigation, Formal analysis. **Monica Aas:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Nils Eiel Steen:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Ole Andreassen:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Srdjan Djurovic:** Writing – review & editing, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition. **Thor Ueland:** Writing – review & editing, Methodology, Conceptualization. **Torill Ueland:** Writing – review & editing, Resources, Methodology, Conceptualization. **Monica B. E. G. Ormerod:** Writing – review & editing, Resources, Methodology, Conceptualization. **Daniel S. Quintana:** Writing – review & editing, Visualization, Methodology.

Declaration of Competing Interest

Nothing to declare.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2024.107272.

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