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Is there an association between inflammatory/anti-oxidant markers and the presence of psychotic symptoms or severity of illness in mood and psychotic disorders? A multi-centric study on a drug-free sample

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ABSTRACT

The immune and antioxidant systems are intimately connected and their role in the etiology of major psychiatric disorders is currently under study. The aim of this study was to evaluate the potential associations between inflammatory/antioxidant peripheral markers and presence of psychotic symptoms or severity of illness in patients affected by major psychiatric disorders.

One hundred and twenty-six drug-free patients were included. A blood sample was collected to measure total/B/T lymphocytes and plasma levels of albumin, total bilirubin, uric acid, C-reactive protein, and vitamins A and E. Severity of illness was assessed using psychometric scales. Groups of patients divided according to diagnosis were compared in terms of measured markers using multivariate analyses of variance (MANOVAs). Linear and logistic regression analyses were performed to investigate the potential association between markers and severity of illness or presence/absence of psychotic symptoms.

Albumin plasma levels were higher in patients with substance-induced psychotic disorder (SIPD) than subjects affected by schizophrenia ($F = 4.923$; $p = 0.003$). Lower vitamin E ($OR = 0.81$; $p = 0.014$) and T lymphocyte ($OR = 0.99$; $p = 0.048$) plasma levels were predictive of lifetime psychotic symptoms. Lower vitamin A levels were associated with higher Montgomery-Åsberg Depression Rating Scale scores ($\beta = -24.26$; $p = 0.029$), independent of diagnosis.

Patients with SIPD may be less vulnerable to oxidative stress. The severity of depressive symptoms, inversely associated with vitamin A plasma levels, is likely to be modulated by the degree of inflammation. Patients presenting with lifetime psychotic symptoms may be more vulnerable to oxidative stress and may have a higher activation of humoral immunity.

1. Introduction

To date, the pathogenesis of mood and psychotic disorders is largely unclear. Several biological, psychological, and social factors contribute in determining the etiology of such disorders. In terms of biological factors, oxidative stress and inflammation seem to play an important role (Altmura et al., 2014; Bergink et al., 2014).

Oxidative stress is defined by an overproduction of free radicals, such as Reactive Nitrogen Species (RNS) and Reactive Oxygen Species (ROS), generated from cellular metabolism and usually balanced through antioxidant defenses that consist of both enzymatic and non-enzymatic pathways. The enzymatic antioxidant system primarily includes glutathione peroxidase, superoxide dismutase, and catalase. The non-enzymatic system consists of molecules that can be found in plasma

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and cerebrospinal fluid, such as uric acid, albumin, bilirubin, vitamin A and E (Bitanirwe and Woo, 2011). The failure of these systems leads to a persistent oxidative stress resulting in damage of cell membranes and alteration in neurotransmission (Yao and Keshavan, 2011). The impairment of enzymatic antioxidant pathways in schizophrenia was largely investigated, while few studies focused on the non-enzymatic antioxidants, which seem to be weakened in schizophrenia patients with respect to the healthy population (Wu et al., 2013; Lu et al., 2020). A recent paper, investigating non-enzymatic antioxidants in major depression, demonstrated that vitamins A, E, and C blood levels were significantly reduced among depressed patients with respect to healthy subjects (Islam et al., 2020).

Brain cells are particularly vulnerable to the toxic effects of free radicals. In response to oxidative stress, microglia and astrocytes release inflammatory mediators, which, in turn, exacerbate the imbalance between antioxidants and oxidative status (Hsieh and Yang, 2013). A large cohort study demonstrated that inflammatory markers (white blood cell count and C-Reactive Protein – CRP) are related to both positive and negative symptoms (Liemburg et al., 2018), as also reported in the conclusions of a systematic review by Orsolini and colleagues (Orsolini et al., 2018). These findings were replicated in a recent study supporting the immune hypothesis of psychotic disorders (Steiner et al., 2020). T-cell aberrancies were identified in psychotic patients as well as a reduced number of circulating lymphocytes (Bergink et al., 2014). In addition, a reduction of T lymphocytes with an increase of B lymphocytes was observed during the acute phase of schizophrenia, with a return to normal levels after treatment (Maino et al., 2007; Steiner et al., 2010). Similarly, mood disorders seem to be characterized by over-inflammation (Bauer and Teixeira, 2019), over-activation of innate and cell-mediated immunity (Maes, 2011), and a significant imbalance between oxidative stress and antioxidant mechanisms (Maes et al., 2019; Orlovska-Waast et al., 2019). In contrast, symptoms of Substance-Induced Psychotic Disorder are hypothesized to be triggered by the effects of the different substances on the immune system, particularly in subjects with genetic predisposition (Aas et al., 2018).

In clinical practice, it is well known that the presence of severe psychotic symptoms is associated with diminished social functioning (Oorschot et al., 2017), lower treatment response (Ahn et al., 2017), and remission rates, and a less favorable global clinical outcome (Jääskeläinen et al., 2018). In this sense, the identification of potential biological markers associated with psychotic symptoms may be useful to early recognition of patients with more severe forms of illness (Buoli et al., 2016; Altamura et al., 2019).

In this framework, aims of the present study were: (1) to compare groups of patients divided according to diagnosis and the presence/absence of psychotic symptoms in relation to inflammatory/antioxidant peripheral markers; (2) to investigate the potential association between biomarker blood levels and the severity of illness measured by psychometric scales.

2. Materials and methods

2.1. Patients

A total of 126 patients were recruited from the Inpatient Clinics of two Italian psychiatric departments: Desio Hospital (Monza) and Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico (Milan). Study procedures were approved by the accredited Medical Ethics Review Committee (Area 2 Ethics Committee) of Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico. The research project is in accordance with the provisions of the Declaration of Helsinki.

Inclusion criteria were: (1) age 18–65 years, (2) able and willing to provide informed consent, (3) drug-free for at least two weeks (as reported by the patients and their relatives), (4) diagnosis of schizophrenia, bipolar disorder with or without psychotic symptoms, major depressive disorder with or without psychotic symptoms or substance-induced

psychotic disorder (SIPD) according to the criteria of the Diagnostic and Statistical Manual of Mental Disorder, 5th edition (DSM-5) (DSM-5®, 2013; First et al., 2016). Patients were diagnosed by a structured clinical interview administered by psychiatrists.

Exclusion criteria were: (1) the presence of a medical or neurological chronic illness, (2) intellectual disability, (3) other DSM-5 diagnoses (DSM-5®, 2013), and (4) severe acute alcohol or substance intoxication in the four weeks prior.

The following demographic and clinical variables were collected: age, gender, age at onset, diagnosis, duration of illness, duration of untreated illness (DUI), presence of lifetime psychotic symptoms, substance abuse, type of substance abuse, and family history of psychiatric disorders. The lifetime presence of psychotic symptoms was defined as the presence of hallucinations or delusions at any time prior to the current episode. Severity of illness was measured by the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), Young Mania Rating Scale (YMRS) (Young et al., 1978), Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960), and Montgomery and Åsberg Depression Rating Scale (MADRS). (Montgomery and Åsberg, 1979).

Blood samples were collected in the morning in fasting condition at the beginning of hospitalization to measure the levels of parameters routinely assessed in clinical practice. Specifically, we measured total bilirubin, albumin, uric acid, and vitamin A and E as non-enzymatic markers of oxidative stress, while CRP and the number of B and T lymphocytes were collected as inflammatory markers. The number of B and T lymphocytes was determined by cytofluorometry, while the other biological parameters were measured by enzyme-linked immunosorbent assay (ELISA) kits.

2.2. Statistical analyses

Descriptive analyses on the total sample were performed. Quantitative (including biomarker values) and qualitative variables were compared between the groups identified according to the diagnosis (schizophrenia, psychotic mood disorders, non-psychotic mood disorders, SIPD) respectively by multivariate analyses of variance (MANOVAs) and chi-square tests (Table 1). The same analyses were performed to compare the two groups identified by the presence or absence of lifetime psychotic symptoms. Biological markers that were statistically significant ($p < 0.05$) in the univariate analyses functioned as independent variables in a logistic regression analysis in which presence or absence of psychotic symptoms was the dependent variable. Finally, linear regression analyses were performed with peripheral blood markers as independent variables and BPRS, YMRS, HAM-D, or MADRS scores as dependent ones.

Statistical Package for Social Sciences (SPSS) for Windows (version 26.0) was used to perform the aforementioned analyses.

3. Results

3.1. Descriptive analyses and diagnostic group comparisons

A total of 151 individuals were eligible to be included in the study. Twelve individuals refused to participate, and 13 were lost arriving at the emergency department during the weekend. The final sample ($N = 126$) included 66 males and 60 females (15.8% of patients were affected by schizophrenia, 54.8% by psychotic mood disorders, 15.1% by non-psychotic mood disorders and 14.3% by SIPD). The mean age was 38.20 ± 13.80 years. 80.2% of the total sample had presented lifetime psychotic symptoms (Table 1).

Demographic and clinical data and differences among groups are summarized in Table 1. Patients affected by psychotic mood disorders were more frequently females ($p < 0.05$) while those with SIPD were more frequently males ($p < 0.05$); schizophrenia patients reported more frequent lifetime psychotic symptoms with respect to the other diagnostic groups ($p < 0.05$) and presented with a longer duration of illness when compared to patients affected by SIPD ($p = 0.04$); the SIPD group

Table 1
Significant differences between diagnostic groups in terms of demographic and clinical variables.

Variables		SKZ n = 20	Psychotic mood disorders n = 69	Non-psychotic mood disorders n = 19	SIPD n = 18	TOTAL SAMPLE N = 126	F or χ^2	p value
Age (years)		37.2 (±15.2)	39.7 (±13.8)	40.9 (±13.2)	30.7 (±10.9)	38.2 (±13.8)	1.91	0.132
Gender	Male	13 (65.0%)	30 (43.5%)	7 (36.8%)	16 (88.9%)	66 (52.4%)	14.93	0.002
	Female	7 (35.0%)	39 (56.5%)	12 (63.2%)	2 (11.1%)	60 (47.6%)		
Age at onset (years)		22.0 (±5.4)	26.9 (±10.6)	31.6 (±14.8)	26.2 (±14.5)	26.8 (±11.3)	1.89	0.135
Lifetime psychotic symptoms	Yes	16 (80.0%)	67 (97.1%)	0 (0.0%)	18 (100.0%)	101 (80.1%)	59.25	<0.001
	No	4 (20.0%)	2 (2.9%)	19 (100.0%)	0 (0.0%)	25 (19.9%)		
Duration of illness (years)		14.3 (±14.9)	13.0 (±11.8)	10.0 (±10.1)	4.6 (±4.6)	11.5 (±11.7)	2.93	0.037
DUI (years)		3.3 (±4.3)	2.8 (±5.6)	2.8 (±5.8)	1.6 (±1.6)	2.7 (±5.0)	0.36	0.783
Substance abuse	Yes	4 (20.0%)	8 (11.6%)	3 (15.8%)	11 (61.1%)	26 (20.6%)	21.73	0.001
	No	16 (80.0%)	61 (88.4%)	16 (84.2%)	7 (38.9%)	100 (79.4%)		
Type of abuse	No	16 (80.0%)	60 (86.9%)	15 (78.9%)	7 (38.9%)	98 (77.8%)	37.58	0.001
	Alcohol	2 (10.0%)	0 (0.0%)	3 (15.8%)	1 (5.6%)	6 (4.8%)		
	Cannabis	1 (5.0%)	7 (10.2%)	0 (0.0%)	4 (22.1%)	12 (9.5%)		
	Cocaine	1 (5.0%)	2 (2.9%)	1 (5.3%)	5 (27.8%)	9 (7.1%)		
	Methadone	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (0.8%)		
	None	12 (60.0%)	27 (43.5%)	6 (33.3%)	9 (52.9%)	54 (46.2%)		
Family history of psychiatric disorders	SKZ	0 (0.0%)	3 (4.8%)	1 (5.5%)	1 (5.9%)	5 (4.3%)	12.25	0.660
	BD	2 (10.0%)	12 (19.4%)	5 (27.8%)	0 (0.0%)	19 (16.2%)		
	MDD	3 (15.0%)	13 (21.0%)	3 (16.7%)	3 (17.6%)	22 (18.8%)		
	Anxiety disorders	1 (5.0%)	1 (1.6%)	1 (5.6%)	0 (0.0%)	3 (2.6%)		
	Others	2 (10.0%)	6 (9.7%)	2 (11.1%)	4 (23.6%)	14 (11.9%)		
	Missing	–	7	1	1	9		
	Family history of more than one psychiatric disorders	Yes	7 (35.0%)	20 (32.8%)	8 (44.4%)	4 (22.2%)		
No	13 (65.0%)	41 (67.2%)	10 (55.6%)	14 (77.8%)	78 (66.7%)			
Missing	–	8	1	–	9			

Mean (±standard deviation) for continuous variables; frequencies (percentage) for dichotomous variables. In bold statistically significant differences.

Abbreviations: BD, bipolar disorder; DUI, duration of untreated illness; MDD, major depressive disorder; SKZ, schizophrenia; SIPD, substance-induced psychotic disorder.

included more current substance abusers than non-abusers ($p < 0.05$) (as expected), while patients affected by psychotic mood disorders were more frequently non abusers ($p < 0.05$). Finally, among substance abusers, SIPD patients used cocaine more frequently than other substances ($p < 0.05$), while patients affected by psychotic mood disorders used cannabis more frequently than cocaine or alcohol ($p < 0.05$).

Regarding peripheral biomarkers, the four groups significantly differed with respect to albumin mean plasma levels ($F = 4.923$; $p = 0.003$). Post-hoc analyses revealed that albumin was significantly higher in the SIPD group compared to patients affected by schizophrenia ($p =$

0.010), psychotic mood disorders ($p = 0.008$), and non-psychotic mood disorders ($p = 0.013$) (Fig. 1). When adjusted for gender, only the differences with schizophrenia patients remained statistically significant ($p = 0.040$).

No statistically significant differences were found between the diagnostic groups for total lymphocytes ($F = 1.865$; $p = 0.140$), B lymphocytes ($F = 1.409$; $p = 0.245$), T lymphocytes ($F = 1.508$; $p = 0.218$), CRP ($F = 0.725$; $p = 0.539$), total bilirubin ($F = 0.231$; $p = 0.875$), uric acid ($F = 0.691$; $p = 0.560$), vitamin A ($F = 0.965$; $p = 0.412$), and vitamin E ($F = 0.598$; $p = 0.618$).

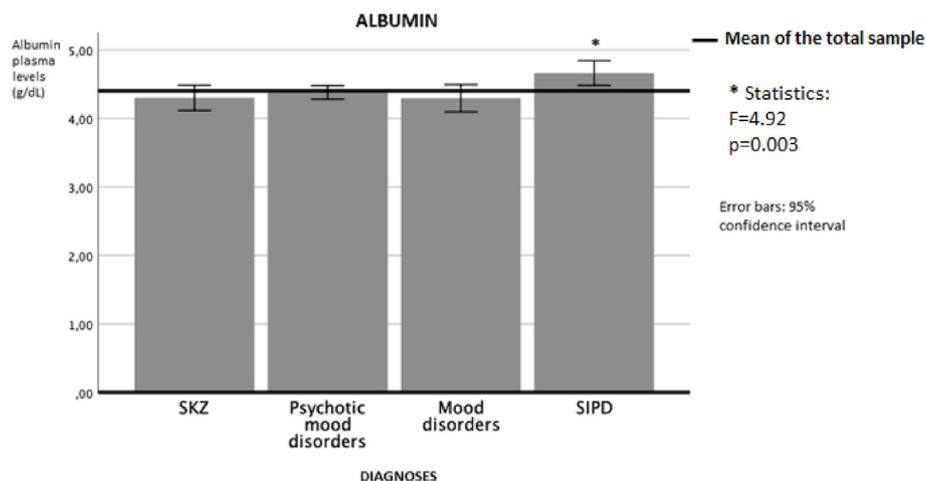


Fig. 1. Statistically significant difference of mean albumin plasma levels between diagnostic groups. SKZ, schizophrenia; SIPD, substance-induced psychotic disorder.

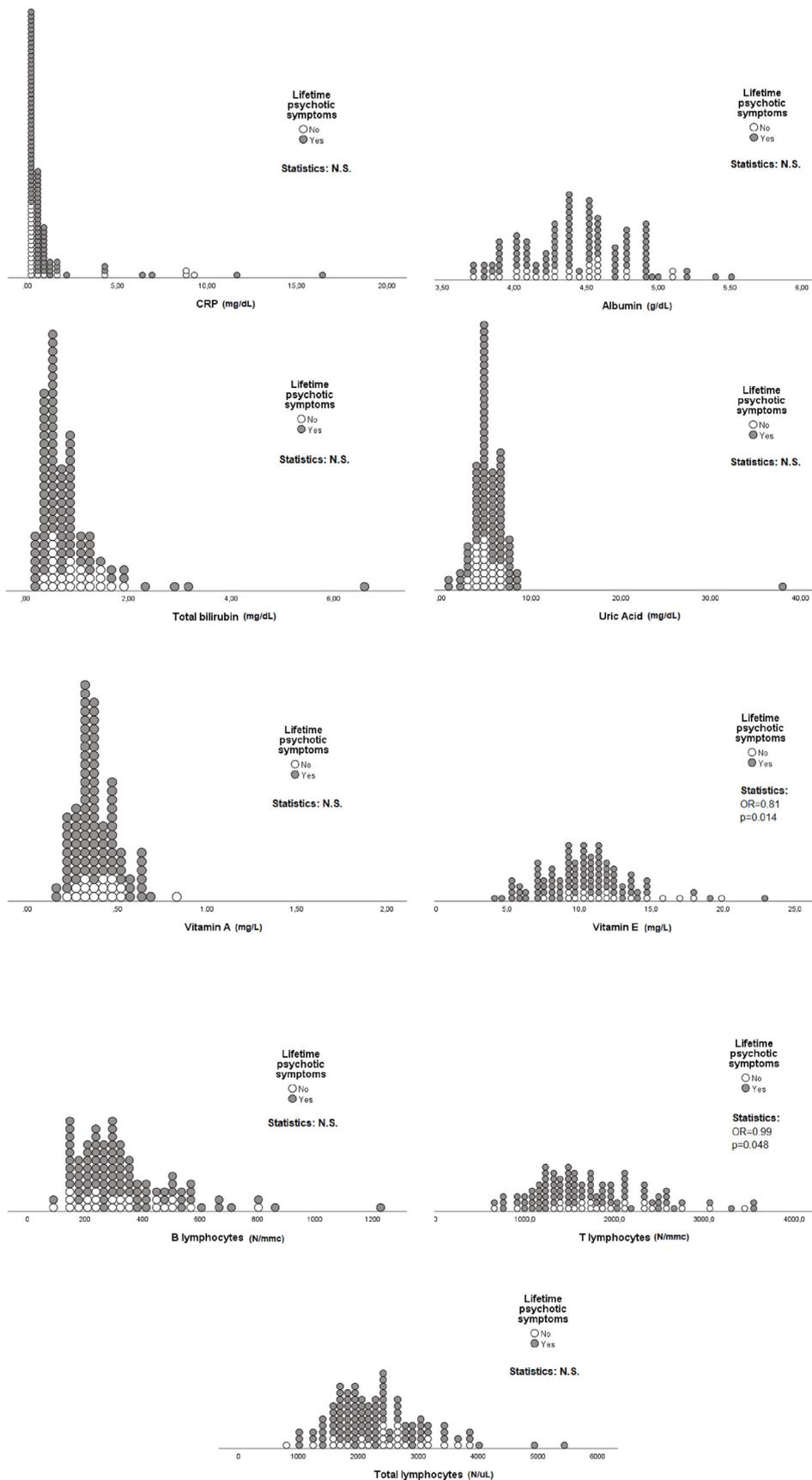


Fig. 2. Peripheral biomarkers according to the lifetime presence of psychotic symptoms. CRP, C-Reactive Protein; N.S., not significant.

3.2. Peripheral markers and psychotic dimension

The two groups (presence/absence of lifetime psychotic symptoms) did not differ for age ($F = 0.062$; $p = 0.803$), gender ($\chi^2 = 1.917$; $df = 1$; $p = 0.166$), age at onset ($F = 2.600$; $p = 0.110$), duration of illness ($F = 3.510$; $p = 0.064$), DUI ($F = 0.258$; $p = 0.612$), substance abuse ($\chi^2 = 3.040$; $df = 1$; $p = 0.081$), family history of psychiatric disorders ($\chi^2 = 4.975$; $df = 5$; $p = 0.419$), family history of more than one psychiatric disorder ($\chi^2 = 1.326$; $df = 1$; $p = 0.250$). However, the type of abuse showed a trend towards a statistically significant difference ($\chi^2 = 9.296$; $df = 4$; $p = 0.054$).

Mean number of T lymphocytes ($F = 5.201$; $p = 0.025$) and vitamin E ($F = 4.646$; $p = 0.034$) plasma levels were significantly lower in patients with lifetime psychotic symptoms compared to subjects without lifetime psychotic symptoms (Fig. 2).

The goodness-of-fit test (Hosmer and Lemeshow Test: $\chi^2 = 6.115$; $df = 8$; $p = 0.634$) showed that the model including the peripheral blood markers as possible predictors of lifetime psychotic symptoms was reliable, allowing for a correct classification of 84.5% of the cases. In addition, the model was significant overall (Omnibus test: $\chi^2 = 10.934$; $df = 2$; $p = 0.004$). Lower T lymphocytes (OR = 0.99; $p = 0.048$) and vitamin E (OR = 0.81; $p = 0.014$) plasma levels were associated with the presence of lifetime psychotic symptoms.

3.3. Peripheral markers and severity of illness

All the four models with peripheral markers (total/B/T lymphocytes, CRP, albumin, total bilirubin, uric acid, vitamins A and E) as independent variables and rating scale scores (BPRS, YMRS, HAM-D or MADRS) as dependent variable could be considered as appropriate (Durbin-Watson's test for autocorrelation: > 1.5 and < 2.5).

The association between every single peripheral marker and psychometric scales scores was not statistically significant ($p > 0.05$), with the exception of vitamin A and MADRS scores. In particular, lower vitamin A plasma levels were significantly associated with higher MADRS scores ($\beta = -24.26$; $p = 0.029$) (Fig. 3).

4. Discussion

The main results of our analyses were as follows:

- (1) SIPD subjects had higher albumin plasma levels than schizophrenia patients on average;
- (2) lower T cell/lower vitamin E plasma levels were associated with the presence of lifetime psychotic symptoms;
- (3) lower vitamin A plasma levels were associated with higher MADRS scores.

The differences between groups regarding demographic and clinical data are similar to those noted in previous studies. Of note, as reported in related, published manuscripts, patients with SIPD are more often males (Mooney et al., 2006). Additionally, the patients with mood disorders tend to have engaged in cannabis misuse that in turn contributes to the development of psychotic symptoms (van Rossum et al., 2009).

The first finding emerging from our study is that albumin plasma levels were significantly higher in substance-induced psychotic patients with respect to the other diagnostic groups. Among non-enzymatic antioxidants, albumin, uric acid, and bilirubin are efficient defenses; in particular, albumin inhibits lipid peroxidation by binding copper ions and serves as a scavenger of ROS (Reddy et al., 2003). Subjects with SIPD might present stronger defenses against oxidative stress relative to patients affected by schizophrenia, bipolar disorder, and major depressive disorder. However, the specific properties of the various substances may affect the biological systems in different ways. In fact, while cannabinoids seem to reduce oxidative stress (Atalay et al., 2020), amphetamines and cocaine may increase the generation of free radicals into the brain (Jitcă et al., 2021). These different effects, as well as the potential dehydration of substance abusers, could represent a confounding factor in interpreting our results. Alternatively, and consistent with our findings, previous studies showed that albumin plasma levels are lower in subjects affected by schizophrenia (Solberg et al., 2019) and major depressive disorder (Liu et al., 2015) or during acute mania and depression phases (Huang, 2002) (relative to healthy subjects).

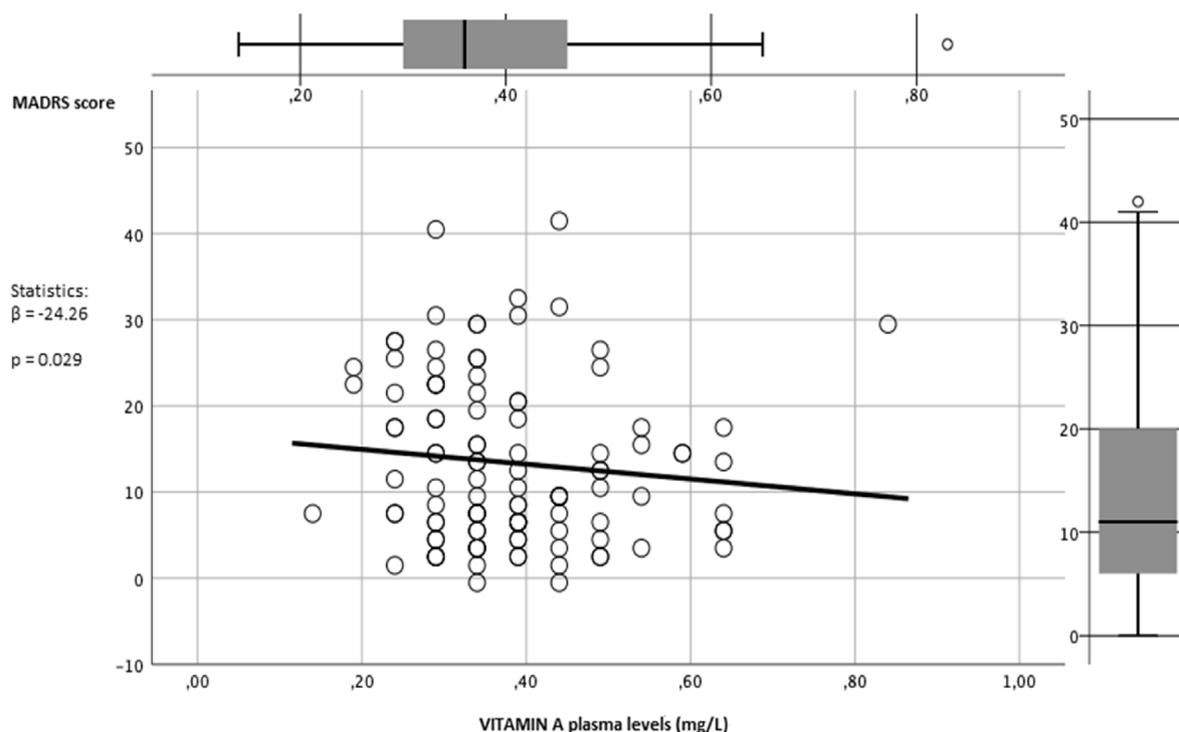


Fig. 3. The association between MADRS scores and vitamin A plasma levels.

Interestingly, in our sample, lower vitamin E plasma levels and a reduced number of T lymphocytes were associated with the presence of lifetime psychotic symptoms, independent from psychiatric diagnosis. Vitamin E is an important endogenous non-enzymatic antioxidant and its reduction in psychotic patients appears consistent with the demonstrated weakening of antioxidant defenses in individuals affected by schizophrenia (Davison et al., 2018). In addition, a decreased number of T cells, combined with a dysfunction of lymphocytes, has been already reported for patients affected by psychotic disorders (Bergink et al., 2014). This finding supports the theory of a more prominent activation of humoral immunity versus cell-mediated immunity in the case of schizophrenia (Altamura et al., 2014).

Third, a negative association emerged between vitamin A plasma levels and MADRS scores. Vitamin A is involved in several different biological functions (Rubin et al., 2017) including the regulation of circadian rhythms which are deeply altered in case of mood disorders (Buoli et al., 2018, 2019). Previous literature has demonstrated that vitamin A plasma levels decrease in the case of global over-inflammation (Rubin et al., 2017), but the neurobiological mechanisms underlying the relationship between vitamin A and depression still require clarification (Hu et al., 2020). Similar to vitamin E, albumin, and other molecules, vitamin A is part of the endogenous non-enzymatic antioxidant system and was negatively associated with the severity of depressive symptoms in our sample. In corroboration with our results, a recent study reported reduced plasma levels of vitamin A in depressed women than healthy controls (Xue et al., 2020).

This study includes some limitations including the relatively small sample size and the specific selection of some peripheral markers. Moreover, the total sample was partially imbalanced in favor of those having psychotic mood disorders and some factors such as gender, nutrition, potential dehydration. In addition, and taking supplements might have influenced the values of biomarkers; in this regard, an occasional alcohol use in the last 4 weeks before recruiting can not be excluded. In addition, it is widely accepted that heavy cannabis use may represent a risk factor for the development of schizophrenia in predisposed subjects (Michaels and Novakovic, 2015), and this aspect should be factored into the interpretation of our results regarding substance-induced psychotic patients. However, a recent editorial by Tandon and Shariff (2019) pointed out that substance abuse *per se* does not cause schizophrenia, also among subjects who developed psychotic symptoms after such abuse, supporting the hypothesis that substance-induced psychotic patients may never develop schizophrenia, even though they were heavy/early cannabis users. Finally, for the present study, we measured inexpensive and reproducible biomarkers, excluding to dose cytokines plasma levels for this reason. Similar to other recent studies, it may be advantageous to measure cytokine plasma levels in future analyses.

5. Conclusions

The main results regarding the weakness of the non-enzymatic antioxidant system (albumin, vitamin A and E) in patients affected by psychotic disorders not induced by substance misuse, supports the hypothesis that major psychiatric disorders may be related with an increased vulnerability to oxidative stress, differently from SIPD. Moreover, the psychotic dimension, independent from diagnosis, seems to be associated with an activation of humoral immunity, corroborating the hypothesis that a dysregulation of immune system, with an imbalance between inflammation and the antioxidant system, may be involved in the etiopathogenesis of psychotic disorders. Nevertheless, caution is necessary in interpreting our findings, considering some of the methodological limitations.

This exploration of the relationship between inflammatory markers/non-enzymatic antioxidants plasma levels and psychotic symptoms yielded valuable pilot data and interesting results. The results encourage further studies with larger and more balanced samples, and with a wider

range of peripheral markers aimed at the identification of potential biological markers in mental disorders.

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Declaration of competing interest

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

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