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Are plasma 25-hydroxyvitamin D and retinol levels and one-carbon metabolism related to metabolic syndrome in patients with a severe mental disorder?

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ABSTRACT

There is a scarcity of studies assessing the influence of biomarkers in metabolic syndrome in psychiatric patients. Our aim was to correlate serum or plasma levels of 25-hydroxyvitamin D (25-OH-VD), retinol, vitamin B12 (VB12), folate and homocysteine (Hcy), with the metabolic status, in a sample of 289 outpatients with Schizophrenia or Bipolar Disorder. Logistic regression and multiple linear regressions were performed to assess the ability of biomarkers to predict the presence of MetS, the number of risk factors for MetS, and insulin resistance indexes (HOMA and QUICKI). Regarding the association between biomarkers and the QUICKI index, the model explained 6.8% of the variance, with folate and 25-OH-VD levels contributing significantly to the model. The model predicting the number of MetS risk factors was significant and explained 21.7% of the variance, being 25-OH-VD and retinol the statistically significant factors. As for the impact of biomarkers on MetS, the model was statistically significant, being 25-OH-VD and retinol levels the significant factors. We report for the first time an association between MetS and both low 25-OH-VD and high retinol concentrations. Inflammation-related biomarkers may help identify patients with a high risk of MetS who might benefit from healthy lifestyle counselling and early intervention.

1. Introduction

Water-soluble vitamins, such as vitamin B12 (VB12) and folate or Vitamin B9, and fat-soluble vitamins, such as vitamin A (VA) and 25-hydroxyvitamin D (25-OH-VD) are dietary components necessary for life, and their deficiency may play a role in mental illness by increasing its risk, exacerbating symptoms, or delaying recovery (Dipasquale et al., 2013; Fasano, 2017). Vitamin deficiencies are more frequent in psychiatric patients than in the general population, but it is uncertain whether this deficiency is related to the psychiatric symptomatology and to the associated unhealthy lifestyle per se, or causally linked to the development of the illness itself (Mitra et al., 2017).

Vitamin deficiencies have also been linked to several medical conditions, such as metabolic syndrome and cardiovascular risk (Mozos and Marginean, 2015; Prasad and Kochhar, 2016; Skaaby, 2015), which are especially prevalent in patients with severe mental disorders such as schizophrenia and bipolar disorder (BD) (Bly et al., 2014; Crespo-Facorro et al., 2017).

The mechanisms through which vitamin deficiencies might be associated with psychiatric disorders are still unclear. Some of the proposed mechanisms of action involve their regulation of nerve growth factor release, an essential molecule for the neuronal survival of hippocampal and cortical neurons, their regulation of calcium homeostasis and β-amyloid deposition and their antioxidant and anti-inflammatory properties (Mitchel et al., 2014; Mitra et al., 2017).

Recent meta-analyses have described low 25-OH-VD levels in patients with first-episode psychosis (Firth et al., 2017), in chronic schizophrenia (Adamson et al., 2017; Lally et al., 2016), and in adult outpatients with BD and schizophrenia (Boerman et al., 2016). Consequences of 25-OH-VD deficiency point to increased susceptibility

Abbreviations: VA, Vitamin A; 25-OH-VD, 25-hydroxyvitamin D; VB12, Vitamin B12; Hcy, homocysteine; MetS, metabolic syndrome

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to mucosal damage leading to a chronic inflammatory condition (Kong et al., 2008) and to an increased risk of cardiovascular disease and related disorders such as stroke, hypertension, and heart failure (Liu et al., 2012) through its effect on body mass index (BMI) and type 2 diabetes mellitus (Vimaleswaran et al., 2013).

The one-carbon metabolism pathway consists of several biochemical reactions involved in DNA methylation, in which transfer of single-carbon groups occurs. The contribution of folate, as a methyl group donor in the synthesis of methionine from homocysteine (Hcy), requires VB12 as a cofactor (Liu et al., 2013). Several studies have evidenced the role of impaired single-carbon metabolism in clinical symptoms of schizophrenia (Misiak et al., 2014; Muntjewerff et al., 2006; Nishi et al., 2014) and bipolar disorder (Cao et al., 2016; Ghanizadeh et al., 2015; Kim and Moon, 2011; Mitchell et al., 2014; Salagre et al., 2017). Elevated Hcy levels have also been linked to higher cardiovascular risk (Blom and Smulders, 2011) and to metabolic syndrome in patients with bipolar and schizophrenic disorders (Vuksan-Ćusa et al., 2011, 2013). An association between folate status and changes in the expression of genes involved in lipid metabolism, obesity, and metabolic syndrome has also been established (da Silva et al., 2014), and both folate and VB12 have been related to elevated serum cholesterol in neuropsychiatric patients (Issac et al., 2015) and to the metabolic syndrome (MetS) (Ellingrod et al., 2012; Salagre et al., 2017). VA is a group of fat soluble unsaturated retinoids that includes retinols, retinals, retinoic acids, and several provitamin A carotenoids. VA is essential for preservation of the integrity of the epithelium, and its association with acquired immunity and the body's response to inflammation has been documented in multiple human and animal studies (Rubin et al., 2017). VA could also play a role in the aetiology of affective disorders (Bremner and McCaffery, 2008) and schizophrenia (Goodman, 1998; Lerner et al., 2016). Moreover, VA, its metabolites, and their binding proteins, such as retinol-binding protein 4 (RBP4), are under study for their association with the MetS (Chen et al., 2011; Christou et al., 2012), obesity (Frey and Vogel, 2011; Jeyakumar and Vajreswari, 2015), insulin resistance (Wolf, 2007), and lipid metabolism (Rocha et al., 2013). Plasma retinol concentrations reflect VA levels and their measurement is used to assess whole body VA status (Field et al., 2013).

It was the aim of this study to correlate serum or plasma levels of 25-OH-VD, retinol, VB12, folate and Hcy with metabolic status (metabolic risk factors, absence or presence of the MetS and insulin sensitivity and resistance) in a sample of clinically stable outpatients with schizophrenia or bipolar disorder. Our hypotheses were 1) both disorders show lower vitamin and higher Hcy levels than the population reference values, 2) schizophrenia is associated with more severe alteration of biomarker levels than bipolar disorder and 3) altered vitamins and Hcy levels are associated with a higher number of metabolic risk factors and the presence of the MetS.

2. Methods

2.1. Study design and patients

A cross-sectional study was performed in 289 patients consecutively visited at an outpatient mental health clinic (Parc Sanitari Sant Joan de Deu, Barcelona, Spain) from October 2016 to February 2018.

Inclusion criteria were (a) age over 18; (b) a DSM-5 diagnosis of a schizophrenia spectrum disorder (including schizoaffective disorder) (n = 199) or bipolar disorder (n = 90) of more than 12 months' duration and at any phase of the illness; (c) no change in dosage or type of antipsychotic or mood stabilizer for the last 4 months, so as to avoid clinically unstable patients likely to experience changes in medication type and dosage; (d) able to understand the purpose of the study and having provided written informed consent to participate in the study; and (e) inclusion in the long-term prescription programme with the patient regularly attending appointments and thereby generating the corresponding medical records.

Exclusion criteria were designed to be minimal in order to obtain a heterogeneous and representative sample of all phases of the disorder. Patients were excluded from the study if they met clinical evidence criteria of active infection, active or chronic inflammatory or autoimmune diseases, or treatment with anti-inflammatory (non-steroid anti-inflammatory drug, corticosteroid, or other anti-inflammatory drug) or immunosuppressive medication.

Data were obtained in accordance with legal regulations on data confidentiality. Records were depersonalized, subsequently maintaining complete dissociation between patient identification and clinical data, as required by Spanish law governing the confidentiality of protected health information. The local Clinical Research Ethics Committee (Parc Sanitari Sant Joan de Deu, Barcelona) approved the study protocol (Ref. PIC-17-18).

2.2. Data extraction

Clinical data, including anthropometric measures, age, sex, and smoking status, were obtained from a database at Parc Sanitari Sant Joan de Deu, where all patient visits with mental health professionals are logged.

Pharmacological information, including antipsychotic, antidepressant, mood stabilizer, statin, glucose-lowering, and/or antihypertensive treatment was extracted from the regional prescription database, in which all of a subject's prescriptions are recorded.

2.3. Anthropometric variables and biochemical analysis

Subjects were examined fasting between 8:00 and 9:00 a.m. Anthropometric measures included body weight, body mass index (BMI = *weight* (kg)*/height* (meters squared)) and waist circumference (1 cm above navel) in cm. Smoking status (yes/no) was recorded.

Plasma (p) and serum (s) samples were taken from a cubital vein blood. Glucose (s), total cholesterol (s), high density lipoprotein (HDL) cholesterol (s), triglycerides (s), 25-OH-VD (s), and Hcy (p) were quantified with fully commercial kits from Abbott Diagnostics (Chicago, Illinois, USA), using the Architect ci8200 Analyzer. Insulin (s), vitamin B12 (s), and folate (s) were quantified using fully commercial kits from Siemens Healthineers (Erlangen, Germany), using the Immulite-Siemens XPi Analyzer. Retinol (p) was quantified by HPLC with UV detection (Perkin Elmer, Waltham, Massachusetts, USA), after sample protein precipitation with methanol and lyposoluble vitamin extraction with hexane. All biochemical analyses were performed at the Department of Clinical Chemistry, Hospital Sant Joan de Deu, (Esplugues de Llobregat, Barcelona, Spain).

2.4. HOMA, QUICKI, and metabolic syndrome assessment

The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index was calculated as follows: *glucose* (mmol/L) × *insulin* (mIU/mL)*/22.5*, with higher values indicating increased insulin resistance (Gutch et al., 2015). The quantitative insulin sensitivity check index (QUICKI) was calculated as follows: *1/(log insulin* (mIU/L) + *log glucose* (mg/dL)), with higher values reflecting increased insulin sensitivity (Gutch et al., 2015).

Subjects were classified as positive or negative for the MetS according to the US National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III, modified criteria (NCEP Expert Panel, 2002). MetS was rated as positive when subjects presented at least three of the following five components (factors): (a) serum triglycerides ≥ 1.7 mmol/L or being on fibrate or nicotinic acid therapy; (b) serum HDL cholesterol < 1.0 mmol/L in males or < 1.3 mmol/L in females; (c) systolic/diastolic blood pressure ≥ 130/85 mmHg or being on antihypertensive treatment; (d) fasting serum glucose ≥ 6.1 mmol/L or being on glucose-lowering treatment or previous diagnosis of

diabetes mellitus; and/or (e) abdominal obesity (waist circumference >102 cm in males and >88 cm in females) or BMI > 30 kg/m^2. In the present study, we alternatively used one of the usual MetS components, waist circumference, along with determination of BMI – this constituting one of the modified NCEP ATP III criteria for diagnosis of the MetS. In this context, the corresponding individual diagnostic component for the MetS was BMI > 30 kg/m^2. This value was considered to be equivalent to obesity or abdominal adiposity and is included in the first World Health Organization (WHO) definition of the MetS (Alberti and Zimmet, 1998; Huang, 2009).

2.5. Sample size and statistical analysis

Sample size was calculated based on the following criteria: power level 80%; alpha level 0.05; expected between-group differences 10%; expected standard deviation 40. The number of subjects per group was estimated to be 90.

Between-group differences in clinical and demographic variables were assessed using chi-square analysis for categorical variables and Student's *t*-test for continuous variables. Mean biomarker concentrations in the whole sample were tested against a hypothesized test value (laboratory reference values obtained in a supposedly healthy population) using a one-sample *t*-test. Partial correlation coefficients using age, diagnoses, and sex as covariates were calculated to test for associations between biomarkers and both MetS risk factors and HOMA and QUICKI indexes. Logistic regression was used to assess the ability of biomarkers (25-OH-VD, retinol, VB12, folate, and Hcy) to predict the presence of the MetS, while multiple linear regressions were performed to test whether the biomarkers significantly predict the number of risk factors for the MetS, the level of insulin resistance (HOMA index), and the level of insulin sensitivity (QUICKI index). Dummy variables were used for categorical variables such as DSM-5 diagnosis (schizophrenia spectrum disorders = 00; bipolar disorder = 01), and sex (male = 00; female = 01). Standardized beta estimates were used to determine which variable had the strongest effect on biomarkers.

The level of statistical significance was set at two-tailed $\alpha = 0.05$. Statistical analyses and sample size estimations were performed using the SPSS software package for Windows version 23.0 (SPSS, Chicago, IL).

3. Results

3.1. Demographic and clinical variables

As shown in Table 1, no differences in sex, age, and BMI were noted between patients with schizophrenia and those with BD. However, patients with schizophrenia showed significantly higher mean waist circumference (102.7 vs 96.6 cm, $p = 0.003$), mean plasma insulin concentrations (14.1 vs 10.3 mU/L, $p = 0.04$), lower QUICKI values (0.347 vs 0.368, $p = 0.01$), higher number of risk factors for the MetS (1.7 vs 1.3, $p = 0.004$), and higher percentage presenting the MetS (23.7 vs 12.2%, $p = 0.04$) than patients with BD. Non-significant trends towards higher serum glucose concentrations (5.3 vs 4.9 mmol/L, $p = 0.08$) and increased HOMA values (3.7 vs 2.3, $p = 0.06$) were noted in patients with schizophrenia. As expected, the use of antipsychotic medication was more frequent in schizophrenic patients (98.5 vs 65.6%, $p < 0.001$), while mood stabilizers were more often prescribed in BD (96.7 vs 24.2%, $p < 0.001$).

3.2. Biomarker levels

When comparing the mean biomarker levels to the general population reference concentrations, mean 25-OH-VD concentrations in the whole sample were significantly below the laboratory reference value of 20 ng/mL ($t = -5.03$, $p < 0.001$) (Table 2). Serum levels of folate and VB12 were within reference values and well above the laboratory minimum cut-off (>7 nmol/L for folate and >142 pmol/L for VB12) (folate: $t = 11.49$, $p < 0.001$; VB12: $t = 20.934$, $p < 0.001$). Mean Hcy levels were significantly above the maximum laboratory reference cut-off value of 12.8 μmol/L ($t = 2.79$, $p = 0.006$), while plasma retinol concentrations were within the upper limit of the reference interval of 2.11 μmol/L, not reaching statistical significance ($t = -1.48$, $p = 0.14$).

A 25-OH-VD deficiency appeared in 72.9% of patients (schizophrenia: 73.7%, BD: 71.1%; $X^2 = 0.02$, $p = 0.89$). As 25-OH-VD levels are influenced by sun exposure, with lower levels in winter and early spring, patients were classified into two groups according to the blood sampling date: extended winter (November to March) and extended summer (April to October) (Cashman et al., 2016). No significant differences were found in mean 25-OH-VD concentrations between extended summer and extended winter: 16.8 ng/mL in winter (schizophrenia: 16.6 ng/mL, BD: 17.3 ng/mL) and 16.5 ng/mL in summer (schizophrenia: 16.0 ng/mL, BD: 17.4 ng/mL) (t = 0.25, $p = 0.80$). However, 71.3% of the sample presented a 25-OH-VD deficiency (<20 ng/mL) in winter (schizophrenia: 72.7%, BD: 68%) as compared with a 25-OH-VD deficiency of 75% in summer (75% in both diagnostic groups), this difference being non-significant ($X^2 = 0.10$, $p = 0.75$).

As for folate and VB12, 18.8% of the sample presented a folate deficiency (schizophrenia: 20.6%, BD: 14.9%; $X^2 = 0.76$; $p = 0.39$), and only 1.8% of patients showed low VB12 (schizophrenia: 1.3%, BD: 3.0%; $X^2 = 0.12$, $p = 0.73$). Hyperhomocysteinaemia was found in 45.4% of the sample (schizophrenia: 42.5%, BD: 51.8%; $X^2 = 1.67$, $p = 0.20$). Retinol deficiency was found in only 0.9% of patients (schizophrenia: 1.3%, BD: 0.0%; $X^2 = 0.00$, $p = 1$), while elevated retinol levels were present in 37.3% of the overall sample (schizophrenia: 37.9%, BD: 36.0%; $X^2 = 0.002$; $p = 0.96$). As indicated by the *p* values, no statistically significant differences between diagnoses were found in any of the biomarker levels.

3.3. Prediction models of metabolic syndrome

3.3.1. HOMA and QUICKI index

After controlling for age, sex, and diagnostic categories, partial correlations were calculated between QUICKI and HOMA index and plasma biomarker concentrations. The QUICKI index was significantly correlated with 25-OH-VD ($r = 0.20$, $p = 0.01$) and folate levels ($r = 0.15$, $p = 0.02$), while the HOMA index did not show any significant association with any of the studied biomarkers.

A linear multiple regression was performed to evaluate the association between the studied biomarkers and HOMA and QUICKI indexes, while controlling for age, sex, and diagnosis. Regarding the QUICKI index, the model obtained explained 6.8% of the variance (F = 2.57, $p = 0.01$). Folate and 25-OH-VD levels, along with psychiatric diagnosis, made a significant contribution to the model (Table 3). This model was not statistically significant for the HOMA index.

3.3.2. MetS risk factors

After controlling for age, sex, and diagnostic categories, partial correlations were calculated between MetS risk factors and plasma biomarker concentrations. A larger waist circumference was significantly correlated with lower 25-OH-VD levels ($r = -0.18$, $p = 0.02$). Higher glucose concentrations were associated with lower 25-OH-VD levels ($r = -0.18$, $p = 0.01$), and a trend towards significance was observed between glucose concentrations and higher retinol levels ($r = 0.16$, $p = 0.05$). Serum triglyceride concentrations significantly correlated with lower 25-OH-VD levels ($r = -0.22$, $p = 0.002$) and higher Hcy levels ($r = 0.13$, $p = 0.03$).

Linear multiple regression was used to assess the ability of biomarkers to predict the total number of MetS risk factors, after controlling for age, sex, and psychiatric diagnosis. The model obtained explained 21.7% of the variance (F = 4.47, $p < 0.001$). As seen in

Table 1
Sociodemographic and clinical characteristics of the sample.

	Schizophrenia $N = 199$	BD $N = 90$	Total sample $N = 289$	Test	p value
Sex (% men)	51.8%	47.8%	50.5%	$X^2 = 0.25$	$p = 0.62$
Age (years)	47 ± 12	49 ± 14	47 ± 13	$t = -1.30$	$p = 0.19$
BMI (kg/m^2)	29.6 ± 5.5	29.3 ± 8.6	29.5 ± 6.6	$t = 0.25$	$p = 0.80$
Waist circumference (cm)	102.7 ± 16.9*	96.6 ± 12.5	100.7 ± 15.8	$t = 2.96$	$p = 0.003$
men	105.0 ± 16.7	99.0 ± 12.1	103.3 ± 15.6		
women	100.1 ± 16.8	94.4 ± 12.7	98.1 ± 15.7		
Glucose (mmol/L)[a]	5.3 ± 1.6	4.9 ± 1.5	5.2 ± 1.6	$t = 1.76$	$p = 0.08$
Insulin (mU/L)[a]	14.1 ± 15.0*	10.3 ± 10.3	12.8 ± 13.7	$t = 2.07$	$p = 0.04$
HDL (mmol/L)[a]	1.2 ± 0.3	1.3 ± 0.3	1.2 ± 0.3	$t = -1.58$	$p = 0.12$
men	1.1 ± 0.3	1.2 ± 0.3	1.1 ± 0.3		
women	1.3 ± 0.4	1.4 ± 0.3	1.3 ± 0.4		
Triglycerides (mmol/L) [a]	1.8 ± 1.1	1.6 ± 0.9	1.7 ± 1.1	$t = 1.88$	$p = 0.06$
No. of risk factors for the MetS[b]	1.7 ± 1.2*	1.3 ± 1.1	1.5 ± 1.2	$t = 2.86$	$p = 0.004$
MetS (% yes)	23.7%*	12.2%	20.1%	$X^2 = 4.41$	$p = 0.04$
HOMA index	3.7 ± 5.3	2.3 ± 2.6	3.2 ± 4.4	$t = 1.87$	$p = 0.06$
QUICKI index	0.34 ± 0.06*	0.36 ± 0.06	0.354 ± 0.06	$t = -2.51$	$p = 0.01$
Smoking (% yes)	59.3%	58.2%	58.7%	$X^2 = 0.00$	$p = 1$
Antipsychotic (% yes)	98.5%*	65.6%	88.2%	$X^2 = 71.72$	$p < 0.001$
Mood stabilizers (% yes)	24.2%*	96.7%	46.9%	$X^2 = 127.44$	$p < 0.001$
Antidepressants (% yes)	27.9%	31.1%	28.9%	$X^2 = 0.17$	$p = 0.68$
Statin treatment (% yes)	20.2%	11.1%	17.4%	$X^2 = 2.96$	$p = 0.08$
Hypoglycaemic treatment (% yes)	9.1%	7.8%	8.7%	$X^2 = 0.02$	$p = 0.89$
Antihypertensive (% yes)	17.3%	16.7%	17.1%	$X^2 = 0.00$	$p = 1$

Quantitative variables are expressed as mean ± SD.
[a] Laboratory reference values: glucose: 3.9–6.1 mmol/L, Insulin < 19.5 mU/L, HDL > 1.04 mmol/L, Triglycerides: 0.46–2.3 mmol/L.
[b] Metabolic risk factors: (1) serum triglycerides ≥ 1.7 mmol/L or being on fibrate or nicotinic acid therapy; (2) serum HDL cholesterol <1.0 mmol/L in males or <1.3 mmol/L in females; (3) systolic/diastolic blood pressure ≥ 130/85 mmHg or being on antihypertensive treatment; (4) fasting serum glucose ≥ 6.1 mmol/L or being on glucose-lowering treatment or previous diagnosis of diabetes mellitus; and/or (5) abdominal obesity (waist circumference >102 cm in males and >88 cm in females) or BMI > 30 kg/m^2.

Table 3, a higher number of MetS risk factors were found, in decreasing order of influence, in patients with lower 25-OH-VD levels, older age, a diagnosis of schizophrenia, female gender, and higher levels of retinol.

3.4. Presence of the MetS

Direct logistic regression was performed to assess the impact of plasma biomarker levels on the likelihood of the MetS. The full model containing all predictors was statistically significant ($\chi 2$ (8, $N = 131$) = 29.58, $p < 0.001$). The model as a whole explained between 20.2% (Cox and Snell R square) and 29.4% (Nagelkerke R square) of the variance and correctly classified 77.1% of cases. Only age, serum 25-OH-VD and plasma retinol made a statistically significant contribution to the model. The strongest predictor of the MetS was plasma retinol, with an odds ratio (OR) of 2.27. Serum 25-OH-VD showed an OR of 0.883, and the OR for age was 0.59. Therefore, in our sample, higher levels of VA, lower levels of 25-OH-VD, and older age were associated with a greater likelihood of presenting the MetS.

Table 3
Multivariate predictors of insulin resistance and MetS risk factors.

	Standardized coefficient β	p value
Multivariate predictors of insulin resistance (QUICKI index)		
Low serum folate	$\beta = 0.16$	$p = 0.009$
Low serum 25-OH-VD	$\beta = 0.15$	$p = 0.01$
Schizophrenia	$\beta = 0.13$	$p = 0.03$
Multivariate predictors of MetS risk factors		
Low serum 25-OH-VD	$\beta = -0.24$	$p = 0.003$
Older age	$\beta = 0.24$	$p = 0.004$
Schizophrenia	$\beta = -0.18$	$p = 0.02$
Women	$\beta = 0.17$	$p = 0.05$
High plasma retinol	$\beta = 0.16$	$p = 0.04$

Order of predictors reflects their higher contribution to the overall model.

4. Discussion

One of the main findings of the present study concerns the ability of biomarkers to predict the number of MetS risk factors and the likelihood of presenting the MetS. To our knowledge, this is the first study to simultaneously include serum Hcy, 25-OH-VD, and retinol levels as variables in prediction models of the MetS.

4.1. Biomarker levels

4.1.1. Vitamin D

25-OH-VD deficiency has been reported in 2–30% of European

Table 2
Mean plasma levels of biomarkers.

	Laboratory reference values*	Whole sample $N = 289$	Test value used	One-sample t	p value
25-OH-VD (ng/mL)	20–100	17.2 ± 7.6	20	$t = -5.03$	$p < 0.001$
Folate (nmol/L)	>7.0	14.5 ± 10.7	7.0	$t = 11.49$	$p < 0.001$
Vitamin B 12 (pmol/L)	>142	328 ± 140	142	$t = 20.93$	$p < 0.001$
Homocysteine (μmol/L)	<12.8	14.3 ± 8.7	12.8	$t = 2.79$	$p = 0.006$
Retinol (μmol/L)	0.88–2.11	2.0 ± 0.6	2.11	$t = -1.48$	$p = 0.14$

* Laboratory reference values for the general population. All values are expressed as mean ± SD.

general population, with higher levels of 25-OH-VD in northern countries compared with Mediterranean areas (Hilger et al., 2014). This north-south difference is thought to be related to dietary factors and 25-OH-VD supplementation, as well as to differences in skin pigmentation between populations (Valipour et al., 2014). People with a psychiatric disorder are more likely to present a 25-OH-VD deficiency than the general population (Chiang et al., 2016). Mean rates of 25-OH-VD deficiency ranging between 63.2% and 75% have been reported in patients with schizophrenia (Adamson et al., 2017; Rylander and Verhulst, 2013; Valipour et al., 2014) and BD (Boerman et al., 2016), which are in line with the 73.7% and of 71.1% rates of 25-OH-VD deficiency noted in our patients with schizophrenia and BD, respectively. Our reported mean serum 25-OH-VD level of 17.2 ng/mL in the whole sample is also in agreement with values of 12.4 ng/mL (Lally et al., 2016) and of 17.5 ng/mL (Salavert et al., 2017) shown in outpatients with a psychotic disorder and with values of 18.4 ng/mL in bipolar patients in remission (Altunsoy et al., 2018) and of 19.3 ng/mL in bipolar depression (Marsh et al., 2017).

Lower rates of 25-OH-VD deficiency have been reported in other studies, with values of 30.3% in patients with bipolar disorder (Boerman et al., 2016) and of 38.7% (Doğan Bulut et al., 2016) and 49% (Lally et al., 2016) in patients with schizophrenia. One possible explanation for these lower rates is the different definition of 25-OH-VD deficiency used across studies. In a recently published consensus, serum total 25-OH-VD concentration is considered the best marker to describe vitamin D status, and should not include the concentration of other vitamin D metabolites (Sempos et al., 2018). This same consensus considers that 25-OH-VD concentrations between 20 ng /mL and 50 ng/mL appear to be sufficient and safe in the general population, as values below 30 ng/mL could be associated with an increased risk of osteomalacia. In previous publications, while the most frequent cut-off point used is 20 ng/mL, which is the value proposed by the Endocrine Society (Mangin et al., 2014), some studies have used cut-off values of 10 or 30 ng/mL, thus respectively increasing or decreasing the prevalence of 25-OH-VD deficiency. Other possible factors are, as previously mentioned, sample seasonality, sun exposure, diet, and ethnicity (Valipour et al., 2014), but also the use of different laboratory assays and unstandardized 25-OH-VD values (Burdette et al., 2017; Rabenberg et al., 2018; Sempos et al., 2018).

A correlation between season of sampling and 25-OH-VD levels, with higher 25-OH-VD levels in summer than in winter, has been reported in a systematic review including patients with a psychotic disorder (Adamson et al., 2017). In our sample, no significant differences between extended summer and extended winter were noted in mean serum 25-OH-VD concentrations. The ethnicity and country of the study could be possible explanations for this discrepancy, as none of the studies reporting seasonal differences were conducted in the Mediterranean area.

4.1.2. One-carbon metabolism: folate, vitamin B12, homocysteine

High Hcy and low folate levels suggesting impaired one-carbon metabolism and increased methylation processes have been repeatedly reported in affective (Baek et al., 2013; Salagre et al., 2017) and psychotic disorders (Ding et al., 2017; Moustafa et al., 2014; Wang et al., 2016). This evidence is in line with our finding of 45.4% of the overall sample showing increased levels of Hcy, together with mean Hcy concentrations significantly higher than the reference values. Furthermore, geographical differences in folate levels seem to exist, with lower levels in patients versus controls in Asian but not in European countries (Cao et al., 2016). Our reported mean folate concentrations of 14.5 nmol/L are very similar to the value of 17.58 nmol/L obtained in a sample of 139 first-episode psychosis patients from the same geographical area as our sample (Ayesa-Arriola et al., 2012). As for VB12, our finding of unimpaired serum concentrations in the studied patients is in agreement with results reported in a recent meta-analysis (Cao et al., 2016).

4.1.3. Vitamin A

To our knowledge, this is the first study to determine plasma retinol levels in a large sample of patients with severe mental disorders. The retinoid signalling system is thought to be involved in the pathogenesis of schizophrenia, with downregulation of cerebrospinal fluid retinoid transporters causing decreased transport of retinol to the brain (Lerner et al., 2016). Isotretinoin (13-*cis*-retinoic acid), an isomer of VA used in dermatology, is known to have psychiatric adverse effects, including depression, psychosis, and suicide (Bremner et al., 2012). Case reports of retinol toxicity leading to psychotic and affective symptoms have been described, with all symptoms disappearing once vitamin intake was discontinued (Bremner et al., 2012). There is only one published study assessing retinol in a psychiatric sample (McCreadie et al., 2000). In this study, performed in a small sample of thirty patients with a first episode of psychosis, mean retinol concentrations were elevated and similar to our reported mean value of 2.08 μmol/L.

4.2. HOMA and QUICKI indexes

Increased insulin resistance is considered to be an inflammatory state leading to a greater risk of the MetS and contributing significantly to cardiovascular disease (Calkin and Alda, 2015). HOMA and QUICKI are the most widely used indices for assessing insulin resistance. Both are based on fasting glucose and insulin measures, and mainly differ by the log transformation of these variables in the QUICKI index. In general, methods using logarithmic transformation should be preferred because the relationships between insulin and glucose levels are hyperbolic rather than linear. Increased HOMA index, reflecting higher insulin resistance, has been widely reported in patients with bipolar disorder (Calin and Alda, 2015; Guha et al., 2014) and schizophrenia (Arranz et al., 2004; Pillinger et al., 2017; Steiner et al., 2018; Tsai et al., 2010). HOMA index in our patients with schizophrenia but not BD was above the cut-off value of 2.38, confirming the state of insulin resistance reported in these patients.

The QUICKI index is thought to have a better correlation with insulin sensitivity than the HOMA index, especially in obese and diabetic subjects (Gutch et al., 20155). A cut-off value ≤ 0.357 has been proposed (Kawada, 2013) to reflect higher risk for the MetS and low insulin sensitivity. Few studies have assessed insulin sensitivity in psychiatric samples using the QUICKI index (Koponen et al., 2015; Timonen et al., 2006) and none in patients with schizophrenia. Our study reports for the first time the status of insulin sensitivity using the QUICKI index in severe psychiatric disorders and shows a QUICKI index lower than the cut-off value of 0.357 in patients with schizophrenia but not BD, suggesting low insulin sensitivity (higher insulin resistance) in these patients.

Furthermore, while no association was found between biomarkers and HOMA index, a lower QUICKI index, i.e. impaired insulin sensitivity, was found in subjects with decreased folate and 25-OH-VD concentrations. These findings suggest that the QUICKI index may be more sensitive to metabolic disturbances than the HOMA index in patients with a severe mental disorder.

4.3. Metabolic syndrome

High rates of MetS and cardiovascular disease have been consistently reported in BD (31–33% rates), and schizophrenia (37–47% rates) (Bly et al., 2014; Crespo-Facorro et al., 2017; Lee et al., 2013; Mitchell et al., 2013). In our study, 23.7% of patients with schizophrenia and 12.2% with BD met criteria for the MetS, which is in agreement with the MetS prevalence of 24.6% in schizophrenia (Arango et al., al.,2008) and of 22.4% in BD (Garcia-Portilla et al., 2009) found in Mediterranean areas. In line with these findings, a higher number of metabolic risk factors was found in our patients with schizophrenia as compared with BD.

Dietary factors, including vitamin deficiency and lifestyle, may contribute to the higher presence of the MetS in psychiatric patients (Lee et al., 2013; Nunes et al., 2014). Low grade chronic inflammation also appears to be involved in the pathophysiology of MetS (McIntyre et al., 2010). In recent years, there has been increasing interest in the relationship between 25-OH-VD, insulin secretion, peripheral insulin resistance, low grade inflammation, and the MetS. An anti-inflammatory role of 25-OH-VD has been reported through several mechanisms, mainly a decrease in pro-inflammatory cytokines and a reduction in oxidative stress (Mitra et al., 2017). The main circulating form of VD, 1,25-dihidroxyvitamin D, influences insulin sensitivity and the regulation of metabolic functioning in the general population (Chiang et al., 2016). Furthermore, 25-OH-VD deficiency has been linked to several MetS risk factors, including hypertension (Pilz and Tomaschitz, 2010), increased waist circumference, increased serum triglycerides, total cholesterol and fasting glucose concentrations (Lally et al., 2016), and to an increased metabolic risk (Bruins et al., 2018). Studies using logistic regression models concur with our finding that low 25-OH-VD levels predict the presence of the MetS (Lally et al., 2016; Yoo et al., 2018). Hyperhomocysteinaemia is also a risk factor for cardiovascular disease and the MetS in patients with BD and schizophrenia (Vuksan-Ćusa et al., 2011), as Hcy levels are positively correlated with blood pressure, waist circumference, triglycerides, and glycaemia (Vuksan-Ćusa et al., 2011, 2013). In agreement with these studies, Hcy levels in our sample correlated with several MetS risk factors, such as waist circumference and serum glucose and triglyceride levels, although Hcy levels did not significantly predict the MetS.

Regarding retinol, studies on retinoid treatment inducing dyslipidaemia (Lerner et al., 2016) and the relationship of isotretinoin treatment to high levels of Hcy (Schulpis et al., 2001) suggest its involvement in inflammatory and metabolic processes. As retinol is mainly stored in the liver, high blood levels of retinol and retinyl esters are considered potential markers of impaired liver function, leading to increased liver fat content and subsequent insulin resistance and the MetS (Beydoun et al., 2013; Yoo et al., 2018). Although no studies have assessed the relationship between retinol levels and the MetS in psychiatric samples, studies in the general population have shown that higher levels of retinol and retinyl esters positively correlated with MetS risk factors, such as elevated triglyceride levels, HOMA-IR, uric acid, and hypertension, and inversely correlated with HDL cholesterol (Beydoun et al., 2011, 2013). Our study shows for the first time the association between high retinol levels and metabolic risk factors and prediction of the MetS.

Several studies have described an increase in morbimortality related to higher intakes of retinol (Field et al., 2013). In line with these results, a prospective cohort study has shown that, while high 25-OH-VD is associated with a lower all-cause mortality, a high intake of retinol attenuates the inverse association between 25-OH-VD and overall mortality (Schmutz et al., 2016). A possible explanation for this negative association could be related to the fact that retinol and vitamin D receptors (VDR) are closely coupled, as they belong to the same subfamily of receptors (Garcia-Villalba et al., 1996). VDR forms a heterodimer with the retinoid receptor alpha (RXR-alpha), which mediates the effect of vitamin D (Field et al., 2013). It has been hypothesized that high retinol levels may moderate the effect of vitamin D by metabolites competitively binding RXR-alpha, and rendering it unavailable to form a heterodimer with 25-OH-VDR (Field et al., 2013).

The main strength of the present study relates to the large number of patients included and the broad inclusion criteria, allowing a representative sample of outpatients with a severe mental disorder. The biomarkers used are easily measurable, inexpensive, and available to most psychiatrists for routine patient assessment. Moreover, the gathered data made it possible to control for confounders such as age, diagnostic categories and sex. Still, there are significant limitations. First, the lack of a control group prevented assessing associations between MetS and biomarker levels in subjects without a psychiatric disorder. However, this limitation was partially overcome by the existence of population reference intervals for all biological biomarkers. Another limitation is the different size of the diagnostic subgroups, with a smaller group of bipolar patients. Finally, the years of illness were not included in the controlling variables, and could influence the risk of MetS. However, we did not find differences in mean age between diagnostic groups to justify its inclusion.

In conclusion, our results support the previously published data establishing a high prevalence of MetS, 25-OH-VD and folate deficiency, and hyperhomocysteinaemia in patients with a severe mental disease. We report for the first time an association between MetS and both low 25-OH-VD and high retinol concentrations. Our results also suggest the utility of the QUICKI index to assess insulin sensitivity in psychiatric patients.

The reported results concur with preclinical and clinical data linking psychosis with chronic inflammation and MetS. We propose that monitoring of inflammation-related biomarkers, including one-carbon metabolism and vitamins, during the course of severe mental disorders may better identify those patients with a higher risk of presenting MetS, who might benefit from healthy lifestyle counselling and early intervention.

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Declaration of interest

B.Arranz has served as consultant, advisor or CME speaker for the following entities: Adamed, Janssen, Lundbeck, Otsuka, Pfizer and Servier.

J. L. Bogas reports no conflicts of interest.

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