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Immuno-metabolic profile of patients with psychotic disorders and metabolic syndrome. Results from the FACE-SZ cohort

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ABSTRACT

Background: Metabolic syndrome (MetS) is a highly prevalent and harmful medical disorder often comorbid with psychosis where it can contribute to cardiovascular complications. As immune dysfunction is a key shared

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component of both MetS and schizophrenia (SZ), this study investigated the relationship between immune alterations and MetS in patients with SZ, whilst controlling the impact of confounding clinical characteristics including psychiatric symptoms and comorbidities, history of childhood maltreatment and psychotropic treatments.

Method: A total of 310 patients meeting DSM-IV criteria for SZ or schizoaffective disorders (SZA), with or without MetS, were systematically assessed and included in the FondaMental Advanced Centers of Expertise for Schizophrenia (FACE-SZ) cohort. Detailed clinical characteristics of patients, including psychotic symptomatology, psychiatric comorbidities and history of childhood maltreatment were recorded and the serum levels of 18 cytokines were measured. A penalized regression method was performed to analyze associations between inflammation and MetS, whilst controlling for confounding factors.

Results: Of the total sample, 25% of patients had MetS. Eight cytokines were above the lower limit of detection (LLOD) in more than 90% of the samples and retained in downstream analysis. Using a conservative Variable Inclusion Probability (VIP) of 75%, we found that elevated levels of interleukin (IL)-6, IL-7, IL-12/23 p40 and IL-16 and lower levels of tumor necrosis factor (TNF)-α were associated with MetS. As for clinical variables, age, sex, body mass index (BMI), diagnosis of SZ (not SZA), age at the first episode of psychosis (FEP), alcohol abuse, current tobacco smoking, and treatment with antidepressants and anxiolytics were all associated with MetS.

Conclusion: We have identified five cytokines associated with MetS in SZ suggesting that patients with psychotic disorders and MetS are characterized by a specific "immuno-metabolic" profile. This may help to design tailored treatments for this subgroup of patients with both psychotic disorders and MetS, taking one more step towards precision medicine in psychiatry.

1. Introduction

Psychotic disorders, including schizophrenia (SZ) and schizoaffective disorders (SZA), are among the most severe psychiatric illnesses. Compared to the general population, SZ and SZA have a reduced life expectancy of 10–20 years (Chang et al., 2011), mainly due to premature cardiovascular diseases (CVD), cancer or suicide (Laursen et al., 2012; Kowal et al., 2020). The increased risk of morbidity and mortality due to CVD (Vancampfort et al., 2015) is related not only to unhealthy lifestyle (smoking, excessive alcohol use, poor diet, bad sleep hygiene, low physical activity) (Henderson et al., 2015) and to side-effects of antipsychotics (Rojo et al., 2015) but also to delayed diagnosis and treatment of cardiovascular risk factors including metabolic syndrome (MetS) (Correll et al., 2017; Godin et al., 2018).

MetS is defined as a cluster of metabolic abnormalities including abdominal obesity, hypertension, atherogenic dyslipidemia and impaired fasting (NCEP, 2002). MetS is highly associated with SZ with an incidence of 24.2% in patients, versus 10% in the French general population (Godin et al., 2015). MetS is found in 42.7% of American SZ patients (McEvoy et al., 2005). It is also highly prevalent in people at high risk for SZ (Carney et al., 2016; Cordes et al., 2017) as well as in antipsychotic-naïve first episode psychosis (FEP) patients (Ryan et al., 2003; Thakore et al., 2002; Spelman et al., 2007; Chen et al., 2016; ; Pillinger et al., 2017a; b) indicating that long term exposure to psychotropic drugs (Pillinger et al., 2020) and/or to unhealthy lifestyle may not necessarily be intrinsic triggering factors but may be aggravating determinants of pre-existing metabolic dysfunctions in at least some psychotic patients. Consequently, similarly to other neuropsychiatric conditions, the biological underpinnings of SZ are widely thought to include metabolic dysregulation that may be exacerbated by medications and unhealthy lifestyle. As low grade inflammation is associated with both SZ (Khandaker et al., 2015) and MetS (McCracken et al., 2018), a bidirectional interaction between inflammation and metabolic dysfunction is thought to contribute to the overlapping pathophysiology of psychosis and comorbid CVD (Felger and Capuron, 2021).

Several factors contribute to the interactions between inflammation and metabolic dysfunction: (i) suboptimal mitochondrial function known to contribute to increased production of oxidants and their induction of pro-inflammatory cytokines, including via the Nod-like receptor pyrin containing 3 (NLRP3) inflammasome, making metabolic dysregulation, oxidants and pro-inflammatory cytokines intimately linked (Morris et al., 2016) and (ii) pro-inflammatory processes which stimulate lipid release into the bloodstream, thereby reducing high density lipoprotein (HDL) cholesterol, increasing triglyceride levels and altering glucose metabolism (Glass and Olefsky, 2012). It is also important to note that alterations in mitochondrial function, notably in cases of hyperglycemia, change the activation and deactivation of the metabolic processes underpinning immune cell activation and deactivation, indicating further the close association of metabolic processes with variations in immune-inflammatory statuses. Elevations in circulating pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-6 are frequently found in SZ (Miller et al., 2011), with relevance to treatment resistance (Mondelli et al., 2015; Howes et al., 2017) and negative symptoms, such as anhedonia, fatigue and cognitive decline (Goldsmith and Rapaport, 2020).

As such pro-inflammatory processes are important in the development of insulin resistance, type 2 diabetes and MetS (Hotamisligil, 2010), inflammation therefore constitute a shared biological underpinning to both metabolic dysfunction and SZ, similarly to other psychiatric conditions, including major depressive disorders (Lamers et al., 2020). It has also been shown that patients with psychotic disorders and MetS exhibit high total white blood cells (WBC) counts and elevated levels of high sensitivity C-reactive protein (hsCRP) (Miller et al., 2013). In the same study, it has been also showed that hsCRP is a significant predictor of MetS in SZ patients (Miller et al., 2013). Subsequent data in a large cohort confirmed the association of elevated CRP and WBC with MetS in a linear statistical model (Liemburg et al., 2018). Moreover, recent data showed also that elevated hsCRP in psychosis are associated with lower levels of high molecular weight adiponectin, a finding relevant to increased CVD risk in SZ (Lee et al., 2019). Finally several studies showed associations between MetS and inflammation in psychosis (Fan et al., 2010; Lasić et al., 2014; Kelly et al., 2019), while also highlighting discrepancies across samples, possibly due to the clinical and biological heterogeneity among the studied samples. Hence, identifying biologically homogeneous SZ subgroups in terms of MetS and inflammation may constitute a major advance towards the design of targeted therapeutic options.

We thus performed a cross-sectional analysis to clarify the associations between inflammatory markers and MetS in 310 patients with psychosis belonging to the FACE-SZ cohort (FondaMental Advanced Centers of Expertise for Schizophrenia) while controlling the impact of confounding clinical characteristics, including psychiatric symptoms and comorbidities, history of childhood maltreatment and treatments, which can influence the immune profile and/or MetS.

2. Methods

2.1. Participants

Patients belonging to the FondaMental Academic Centers of Expertise

for Schizophrenia (FACE-SZ) cohort were included in the present study. FACE-SZ is a French observational cohort of patients with SZ or SZA assessed and followed in ten University affiliated Expert Centers for Schizophrenia located in Bordeaux, Clermont-Ferrand, Créteil, Grenoble, Lyon, Marseille, Montpellier, Strasbourg, Versailles and coordinated by the non-profit foundation "Fondation FondaMental" (www.fondation-fondamental.org). Enrolment in the cohort is made after patient's consent and consists of yearly visits where standardized clinical assessment and biological screening are carried out, leading to personalized therapeutic recommendation (Schürhoff et al., 2015). A National network of schizophrenia expert centres: An innovative tool to bridge the research-practice gap. The overall criteria required for patient inclusion in the cohort are as follow: (i) diagnosis of schizophrenia, schizoaffective or schizophreniform disorders according to the DSM-IV-TR, (ii) first antipsychotic treatment maximum 10 years before the date of inclusion, (iii) first treatment more than 10 years with Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) $\leq$ 90 and Global Assessment of Functioning (GAF) (Startup et al., 2002) $\geq$ 40 altogether defining stable patients (iv) patients being able to write and read French, (v) patients having given written informed consent. The non-inclusion criteria are: (i) patient being pregnant or breastfeeding, (ii) non-membership to social security.

A subgroup of 310 from a total of 1491 patients belonging to the FACE-SZ cohort were selected based on the availability of information on both MetS and blood immune markers and included in the present study.

2.2. Clinical data

A diagnosis of SZ or SZA was made on the basis of a semi-structured interview using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First, 1997). Current psychotic, depressive and manic symptomatology were respectively assessed with the PANSS (Kay et al., 1987), the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993) and the Young Mania Rating Scale (YMRS) (Young et al., 1978). History of childhood maltreatment was recorded with the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1994). All assessments were made using French versions of the above-mentioned scales. The other annotated clinical characteristics were age of SZ/SZA onset, history of Major Depressive Episode (MDE) and of suicide attempts, tobacco smoking (past and present), alcohol abuse, cannabis consumption and ongoing psychotropic treatment. Clinical assessments were made by a trained psychologist or psychiatrist.

2.3. Blood sample collection and processing

Venous blood was obtained from fasting subjects between 7:00 a.m. and 9:00 a.m. on weekdays. Five milliliters of peripheral blood were drawn by venipuncture and allowed to clot for 1 h before centrifugation (1500×*g*, 10 min). Serum samples were stored in 0.5 ml aliquots at −80 °C and thawed on ice at the time of analysis.

2.4. Cytokine levels

Serum samples were assessed for the levels of IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-12/IL-23p40, IL-13, IL-15, IL-16, IL-17A, TNF-α, TNF-β and IFN-γ using electrochemiluminescence (ECL)-based multiplex immunoassays (Meso Scale Discovery (MSD), Gaithersburg, MD, USA). Experiments were performed according to the manufacturer's instructions. Of the 18 tested cytokines, IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-10, IL-12p70, IL-13, TNF-β and IFN-γ were below the lower limit of detection (LLOD) in more than 10% of samples and were not included in the downstream analyses (Table 1).

2.5. Metabolic syndrome

In order to assess criteria defining MetS, anthropometric data and blood pressure were collected. Sitting blood pressure was recorded twice 30 s apart in the right arm after the participant had sat and rested for at least 5 min. Waist circumference was measured midway between the lowest rib and the iliac crest whilst the participants were standing. Fasting levels of serum/plasma triglyceride (TG), glucose, and high-density lipoprotein cholesterol (HDL-C) were determined by standardized routine methods. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters.

Presence of MetS was defined according to the criteria of ATEP III (NCEP, 2002), which requires that 3 or more of the following 5 criteria be met: hypertriglyceridemia ($\geq$1.7 mmol/L or use of lipid-lowering medication), high waist circumference (>94 cm for men and >80 cm for women), high fasting glucose concentration ($\geq$5.6 mmol/L or use of glucose-lowering medication), low HDL-C level (<1.03 mmol/L in men and <1.29 mmol/L in women) and high blood pressure ($\geq$130/85 mm Hg or use of antihypertensive medication). Patients with and without MetS are herein termed "MetS+" and "MetS-" respectively.

2.6. Statistical analysis and covariates

2.6.1. Multiple imputation (MI)

Clinical variables (*i.e.* current symptomatology, age of onset, history of maltreatment and attempted suicide and depression, addiction, and medication) and biological variables (cytokines) shown to impact MetS and/or immune phenotype were selected for this analysis. Missing data were imputed using the Multivariate Imputation by Chained Equations (mice) procedure in R (Buuren and Groothuis-Oudshoorn, 2010). We generated 10 independent MI datasets as per the recommended procedure regarding power considerations (Graham et al., 2007).

2.6.2. Resampling (R)

Traditional methods do not provide valid confidence intervals or p-values to test the significance of penalized regression coefficients. As an alternative, the non-parametric bootstrap has been used for inference in applications of penalized regression (Lamers et al., 2020). The bootstrap step involved 500 re-samplings for each of the 10 MI datasets (with replacement) to create 50 different samples of each MI dataset, with the full sample size. The regression model was subsequently fitted to each of the 10 × 500 samples of data.

2.6.3. Penalized regression

The caret (Kuhn, 2008) and glmnet (Friedman et al., 2010) R packages were used to implement Elastic Net penalized (or regularized) logistic regression models studying the association of MetS and cytokines, adjusting for potential confounders. The penalized regression framework uses linear models with penalties to avoid extreme parameters that may cause overfitting while simultaneously performing variable selection and addressing the issue of multicollinearity (correlation). In terms of goodness of the model, optimal λ and α hyperparameters for the penalized regression algorithm were chosen via 10-fold cross-validation, with the optimal tuning hyperparameters values chosen to minimize the log loss.

The penalized regression was used to select a subset of variables by calculating the Variable Inclusion Probability (VIP), i.e., the percentage of times each variable was kept in the model, with an associated coefficient different from zero, out of the 10 × 500 models. In the absence of asymptotically valid p-values which are (still) not available in high-dimensional regression, the VIP can be interpreted as the posterior probability of including a variable in the model and is used as a measure of the stability of the association (Bunea et al., 2011). After defining an appropriate threshold, the VIP is used to select predictors for follow-up analyses. Depending on the study, determining an appropriate threshold for the VIP can be challenging. In their landmark paper, (Bunea et al., 2011) recommended a "conservative threshold of 50%", which was chosen given their goal to "not to miss any possibly relevant predictors" (Bunea et al., 2011). However, this 50% threshold increases the risk of

Table 1
Cytokine levels in the study sample. Lower Limits of Detection (LLOD), Number of samples and percentage in which the signal was below the LLOD. Mean, median, minimum (Min.). maximum (Max.) concentrations are indicated. Crosses indicate the cytokines retained for further downstream analysis.

	LLOD (pg/ml)	Nb. < LLOD	% < LLOD	Mean	Median	Minimum	Maximum	Retained
IL-1alpha	0.09	240	77.4	2.177	1.16	0.17	12.53	
IL-1beta	0.05	197	63.5	1.305	0.24	0.02	61.61	
IL-2	0.09	222	71.6	899	0.3	0.05	20.78	
IL-4	0.02	214	69.0	84	0.05	0.01	0.77	
IL-5	0.14	234	75.5	877	0.56	0.21	8.79	
IL-6	0.06	13	4.2	2.106	0.64	0.12	122.14	yes
IL-7	0.12	0	0.0	12.306	11.465	2.1	34.96	yes
IL-8	0.07	0	0.0	45.097	10.11	2.97	1099.52	yes
IL-10	0.04	64	20.6	536	435	0.06	4.1	
IL-12p70	0.11	152	49.0	396	285	0.05	2.68	
IL-12/-23 p40	0.33	0	0.0	131.799	109.54	24.2	457.91	yes
IL-13	0.24	158	51.0	5.218	2.5	0.5	31.92	
IL-15	0.15	0	0.0	2.523	2.53	0.67	5.94	yes
IL-16	2.83	0	0.0	318.646	276.735	74.72	1230.03	yes
IL-17A	0.31	68	21.9	4.438	3.875	0.69	24.68	yes
TNF-alpha	0.04	0	0.0	4.931	2.495	0.6	141.5	yes
TNF-beta	0.08	58	18.7	545	415	0.11	2.34	
IFN-gamma	0.37	82	26.5	5.279	3.8	0.73	39.5	

false positives. In our study, we set a stringent VIP threshold at 75% to identify variables stably associated with MetS.

Confidence intervals for the estimated odds ratio of each variable were computed using the percentiles of these estimates over the 10×500 datasets, i.e. the percentile bootstrap method. The 95% CI, reported here, provides a range of values that are possible for the population. Such values that can be considered *per se* informative, departs from the binary decision of significance versus no significance. Moreover, given that classical p-values cannot be stem from the used penalized regression, we relied solely on the VIP for the selection of variables associated with metabolic syndrome. If a variable is selected in more than 75% of the bootstrap samples, we consider it important enough to put it forward, regardless of the fact that the correspondent 95% CI for the odds ratio might include the value 1.

3. Results

3.1. Sample characteristics

Our study sample consisted of 310 patients, comprised of 238 SZ and 72 SZA, as defined by DSM-IV TR criteria for SZ and SZA (Table 2). Patients had a mean age of 30 years and a mean age at onset of psychosis of 21 years. Three out of four patients were male and 32% had a secondary level of education. The prevalence of MetS in the studied sample was 25%. Among the 310 patients, 47% had suffered from moderate to severe childhood abuse, 20% had made at least one suicide attempt during their lifetime and 50% had previous record of major depressive episode (MDE). Half of the patients were tobacco smokers while 25% and 33% reported alcohol abuse and cannabis consumption respectively. The vast majority (83%) of patients in our study sample were treated with antipsychotics: 77% were treated with second generation antipsychotics, 7% with first generation antipsychotics and 16% with both. Twenty one percent of patients were currently treated with antidepressants, 18% with anxiolytics, 14% with anticholinergics and 6% with hypnotics. It is worthy to mention that no patient received mood-stabilizers (-regulators). Regarding current symptomatology, most patients had current psychotic symptoms as assessed by PANSS, but not depressive symptoms as indicated by the CDSS.

3.2. Association between circulating cytokine levels, clinical variables and MetS

As expected, advanced age (mean OR = 1.28, 95% CI [1.03, 1.74]), being a male (mean OR = 1.61, 95% CI [1.03, 2.34]), and BMI (mean OR = 2.19, 95% CI [1.76, 2.68]) were associated with MetS **(Table 3)**. We also found that elevated serum levels of IL-6, IL-7, IL-12/IL-23p40 and IL-16 and lower serum levels of TNF-α levels were associated with increased odds of MetS after adjustment for covariates and confounders (Table 3). Among these five cytokines, IL-7 contributed the most to the regression model as indicated by its OR and its VIP (90%). Concerning the strength of associations, the median OR of IL-6, IL-7, IL-12/IL-23p40, IL-16 and TNF-α were 1.17 (95% CI [0.95, 1.5]), 1.28 (95% CI [1.02, 1.64]), 1.19 (95% CI [0.98, 1.57]), 1.12 (95% CI [0.87, 1.5]) and 0.84 (95% CI [0.64, 1.00]), respectively.

In terms of clinical variables, a diagnosis of SZ, age of SZ onset, alcohol abuse, current tobacco smoking and prescription of antidepressants and anxiolytics were associated with increased odds of MetS after adjustment for cytokines. Conversely prescription of hypnotics was associated with lower odds of MetS. We did not observe any significant association between MetS and education levels, childhood maltreatment and current depressive and psychotic symptomatology assessed by the CDSS and PANSS respectively. For the observed associations, the mean OR [95% CI] of SZ diagnosis, age of FEP onset, alcohol abuse and current tobacco smoking, use of antidepressant, anxiolytics and hypnotics were as follows: 1.20 [0.94, 1.88], 1.13 [0.91, 1.46], 1.23 [0.92, 1.74], 1.34 [1.02, 2.09], 1.30 [1, 1.84], 1.4 [1.02, 2.01] and 0.73 [0.42, 1.11] respectively.

4. Discussion

In a sample of 310 patients with psychosis systematically assessed for MetS, clinical symptomatology and peripheral cytokine levels, we confirm previous data showing the high prevalence of MetS in SZ patients as compared to the observed frequencies in the French general population i.e. 13.7% and 6.6% respectively in males and females (Vernay et al., 2013). We observed a MetS incidence of 25%, a finding comparable to what has already been reported in several cohorts of patients with SZ (Mitchell et al., 2013; Vancampfort et al., 2015; Godin et al., 2015). Using penalized logistic regression, we found that MetS is associated with a specific immune signature defined by elevated serum levels of IL-6, IL-7, IL-12/23p40 and IL-16 along reduced serum levels of TNF-α, after adjustment for covariates. Several clinical and socio-demographical variables were also associated with increased odds of MetS in our sample: age, sex, BMI, diagnosis of SZ (not SZA), older age of FEP onset, history of alcohol abuse, current tobacco smoking and prescription of antidepressants and anxiolytics. In contrast, hypnotics use was associated with a lower likelihood of MetS.

Our observations suggest that patients with psychosis and MetS are characterized by a specific "immuno-metabolic" profile, paralleling recent work on MetS in Major Depressive Disorder (MDD) (Lamers et al.,

Table 2
Characteristics of patients. For each categorical variable, the number (Nb.) and percentage (%) of patients with and without MetS are indicated. For each continuous variable, mean and standard deviation (SD) are indicated. Statistical tests (* Chi-square; ° Mann & Whitney) for comparing MetS+ and MetS- patients and corresponding p-values after adjustment for multiple testing are indicated. Differences between groups were considered to be statistically significant when adjusted p-values were <0.05. Non-significant (n.s.) statistical differences are indicated.

Variable	Missing value [%]	Total	MetS+	MetS-	p-value
N		310	77 [24.84%]	233 [75.16%]	
Age	0	30.37 ± 8.43	33 ± 9	28 ± 8	0.0024
Sex: F [%] *	0	26.13	14	30	0.0058
Education: Bac%*	17	32.26	35.06	31.33	0.0518
Maltreatment: Yes%*	0	47.1	49.35	46.35	0.7771
BMI mean ± SD°	8	27.09 ± 5.77	30.78 ± 5.27	25.83 ± 5.39	<0.0001
Diagnosis of SZA % *	0	23.25	18	25	0.5872
Age of onset mean ± SD°	4.5	21.17 ± 5.86	22 ± 6	21 ± 6	0.0518
Suicide attempt lifetime: Yes %*	4	20	20	21	0.8036
Violent suicide attempt lifetime %*	4	4.2	5.2	3.9	0.3761
History of MDE %*	10	50	51	42	0.6293
Calgary: mean ± SD°	3	3.71 ± 4.07	4 ± 4.34	3.6 ± 4	0.7094
PPANSS mean ± SD°	6	14.14 ± 5.97	15 ± 7	14 ± 6	0.6461
NPANSS mean ± SD°	5	17.95 ± 7.15	19 ± 6	18 ± 7	0.0671
GPANSS mean ± SD°	5	33.6 ± 10.46	35 ± 11	33 ± 10	0.2767
PANSS mean ± SD°	16	65.63 [± 20.37]	65.03 [± 23.06]	61.35 [± 25.74]	0.1464
Alcohol%*	18	25.48	42	27	0.03
Cannabis%*	9	33.23	37	36	0.881
Tobacco%*	2	50.32	58	49	0.1477
Antipsychotics Yes%*	8	82.9	93	90	0.3691
Antidepressants Yes%*	8	20.97	30	20	0.0872
Anxiolytics Yes%*	8	18.06	32	16	0.0033
Anticholinergics %*	8	14	13	12	0.5096
Hypnotics %*	8	6	6.5	5.4	>0.9999
IL6: mean ± SD°	0	2.02 ± 8.66	1.79 ± 4.36	2.094 ± 9.67	0.02
IL7: mean ± SD°	0	12.31 ± 5.99	13.83 ± 6.43	11.8 ± 5.76	0.01
IL8: mean ± SD°	0	76.63 ± 277.86	46.88 ± 143.1	44.51 ± 124.2	0.4303
IL1223p40: mean ± SD°	0	131.8 ± 80.88	137.6 ± 79.55	129.9 ± 81.39	0.2614
IL15: mean ± SD°	0	2.52 ± 0.68	2.513 ± 0.58	2.527 ± 0.71	0.9772
IL16: mean ± SD°	0	318.65 ± 176.67	346.8 ± 175.7	309.3 ± 176.4	0.04
IL17a: mean ± SD°	0	3.53 ± 3.13	3.695 ± 3.8	3.403 ± 2.96	0.8532
TNF-α: mean ± SD°	0	4.93 ± 11.51	3.644 ± 3.661	5.4 ± 13.1	0.053

2020). In patients with MDD, these authors identified two groups of depressed patients. The first is referred to as an "immuno-metabolic" subtype defined by the associations between MetS and increased appetite, weight gain, hypersomnia, fatigue, leaden paralysis along with peripheral inflammation. The second group, referred as "melancholic subgroup" was positively associated with childhood maltreatment and negatively with MetS (Lamers et al., 2020). Although patients with psychosis and comorbid MetS have been previously found to have more depressive symptoms (Suttajit and Pilakanta, 2013) and MDD (Lamers et al., 2018), we did not find any association between MetS and current symptomatology or history of MDD.

As expected, we found that age, gender and BMI are associated with MetS, a widely replicated association both in psychiatric (Medeiros-Ferreira et al., 2013) and non-psychiatric settings (Slagter et al., 2017). In terms of treatment, we found that MetS is associated with the use of antidepressants and anxiolytics but not of hypnotics totally in line with previously reported findings in psychiatric patients (Hiles et al., 2016; Penninx and Lange, 2018). We also found that alcohol abuse is linked to MetS, a well-known association in the general population as shown in a recent meta-analysis (Sun et al., 2014). Thus, risk factors for MetS observed in the general population are also relevant in patients with psychosis.

In addition, we found that the risk of having MetS increase along the age of FEP. Hypothetically, this could reflect the involvement of a particular immuno-genetic background in SZ etiology. We recently reported an association between late onset SZ and the Human Leukocyte Antigen (HLA)-8.1 ancestral haplotype, known to increase both autoimmunity and inflammation (Tamouza et al., 2020). Such association, if is also observed in the late onset immuno-metabolic subtype, may provide clues to understand the pathophysiological processes underpinning the associations of MetS and late onset SZ. This hypothesis is under consideration in an ongoing prospective study.

In terms of immune phenotype, increased levels of five cytokines, namely IL-6, IL-7, IL-12/IL-23p40 and IL-16 were found to be associated with MetS. Elevated levels of IL-6 have repeatedly been associated with SZ as compared healthy controls. Moreover, the frequently reported association of IL-6 with MetS may arises from its status of adipokine, its increased production by adipocytes and its role in lipid metabolism, insulin sensitivity and blood pressure control (Aroor et al., 2013). Furthermore, IL-6 was found to interacts with severity of MetS (Srikanthan et al., 2016) and is associated with obesity and visceral fat accumulation (Trayhurn and Wood, 2004). Thus, increased IL-6 in patients with SZ and MetS appears to be coherent as such observation replicate previous findings both in MetS and SZ.

Among the tested cytokines, the OR of IL-7 was the strongest contributor to the regression model. IL-7 is involved in T cell survival and recruitment from the thymus (Tan et al., 2001). Association between IL-7 and MetS may appear at a first sight somewhat controversial as some studies showed no association in the general population (Saidijam et al., 2014; Pilatz et al., 2017), while other demonstrated that IL-7 signaling is related with inflamed adipose tissue, insulin resistance phenotype and therefore with MetS and type 2 diabetes (Saxena and Sachin, 2018). Interestingly, in preclinical models, IL-7 receptor KO mice exhibit reduced visceral adiposity and body weight gain, as well as enhanced insulin sensitivity and glucose homeostasis (M. Lee et al., 2015). Only a few studies have reported an association between IL-7 and SZ (Frydecka et al., 2018). Of interest, a recent study found increased levels of IL7 in patients with SZ, MetS and treated with atypical antipsychotics and specifically with risperidone (Boiko et al., 2021) but without adjustment by covariates. Further studies are thus needed to clarify the role of IL7 in the physiopathology of MetS, notably when interacting with medication.

Surprisingly, we found that patients with MetS have lower odds of TNFa compared to patients without. This result is unexpected as raised TNF-α is, among others, produced by dysregulated adipocytes (Aroor et al., 2013) and classically strongly linked to glucose tolerance, insulin sensitivity and cholesterol metabolism, all processes altered in MetS (Maruotti et al., 2015). Raised levels of TNFa has been also associated with psychosis as compared to controls independently from MetS.

Table 3
Associations between cytokines and MetS. Median Odds Ratios [OR], 95% Confidence Interval [CI] and Variable Inclusion Probability [VIP] are shown. Variables stably associated with MetS were determined based on VIP >0.75 are bolded and labeled with a dot.

	Median OR	95%CI	VIP		Median OR	95%CI	VIP
CLINICAL/SOCIODEMOGRAPHICAL VARIABLES				BIOLOGICAL VARIABLES			
Age	1.28	[1.028,1.736]	**0.94**	**IL-6 [pg/ml]**	1.17	[0.948,1.504]	**0.76**
Sex [Female]	0.61	[0.399,0.879]	**1**	**IL-7 [pg/ml]**	1.28	[1.023,1.645]	**0.95**
Sex [Male]	1.61	[1.033,2.397]	**0.98**	**IL-8 [pg/ml]**	1.01	[0.765,1.384]	0.61
Level of Education	1.13	[0.897,1.474]	0.71	**IL-12/IL-23 p40 [pg/ml]**	1.19	[0.98,1.569]	**0.77**
Child Abuse [No]	0.94	[0.72,1.207]	0.66	**IL-15 [pg/ml]**	0.93	[0.745,1.134]	0.62
Child Abuse [Yes]	1.07	[0.832,1.38]	0.66	**IL-16 [pg/ml]**	1.12	[0.868,1.483]	**0.75**
BMI	2.19	[1.763,2.683]	**1**	**IL-17A [pg/ml]**	0.99	[0.733,1.241]	0.64
Diagnosis of SZ	1.2	[0.943,1.882]	**0.79**	**TNF-alpha [pg/ml]**	0.84	[0.639,0.996]	**0.78**
Diagnosis of SZA	0.84	[0.55,1.061]	**0.79**				
Age of FEP	1.13	[0.908,1.464]	**0.75**				
Suicide attempts [no]	1.09	[0.699,1.65]	0.53				
Suicide attempts	0.83	[0.504,1.457]	0.6				
Violent Suicide attempts	1.23	[0.425,3.444]	0.62				
History of MDE [No]	0.997	[0.747,1.345]	0.65				
History of MDE [Yes]	1.001	[0.745,1.334]	0.65				
CDSS	1.02	[0.788,1.277]	0.66				
PPANSS	1.11	[0.862,1.501]	0.68				
NPANSS	1.11	[0.921,1.412]	0.71				
GPANSS	0.92	[0.715,1.154]	0.55				
Alcohol consumption [No]	0.81	[0.568,1.083]	**0.83**				
Alcohol consumption [Yes]	1.23	[0.923,1.736]	**0.82**				
Use of cannabis [No]	1.05	[0.747,1.583]	0.62				
Use of cannabis [Yes]	0.95	[0.636,1.326]	0.62				
Tobacco smoking [No]	0.68	[0.444,0.965]	**0.91**				
Tobacco smoking [Current]	1.34	[1.018,2.091]	**0.8**				
Tobacco smoking [Past]	1.15	[0.539,2.369]	0.59				
Antidepressants [No]	0.77	[0.533,0.997]	**0.88**				
Antidepressants [Yes]	1.3	[1,1.835]	**0.87**				
Anxiolytics [No]	0.71	[0.483,0.963]	**0.94**				
Anxiolytics t[Yes]	1.4	[1.023,2.009]	**0.92**				
Anticholinergics [No]	0.97	[0.642,1.492]	0.66				
Anticholinergics [Yes]	1.03	[0.673,1.543]	0.66				
Hypnotics [No]	1.38	[0.9,2.589]	**0.78**				
Hypnotics [Yes]	0.73	[0.415,1.111]	**0.78**				
Anti_psychotics [No]	0.67	[0.276,1.319]	**0.75**				
Anti_psychotics [Yes]	1.49	[0.76,3.531]	0.74				

Nevertheless, chronic SZ has previously associated with decreased TNFa versus healthy controls but MetS presence or even BMI were not assessed (Lv et al., 2015). The herein observed association should be taken with caution and need further replication.

We also found that IL-12/IL-23p40 was positively associated with MetS in patients with SZ. IL-12/IL-23p40 is a chain common to the heterodimeric cytokines IL-12 and IL-23. IL-12/23 p40 is necessary for both IL-12 and IL-23 expression and its increase may reflect raised activity of either or both cytokines. As the IL-23/IL-17 immune axis is important to SZ pathophysiology (Borovcanin et al., 2015; Debnath and Berk, 2017; Tahmasebinia and Pourgholaminejad, 2017), the observed IL-12/23 p40 increase in our patients may likely reflect that of the IL-23 pro-inflammatory cytokine. Previous data showed increased IL-12/23 p40 levels in SZ patients, versus healthy controls (Bedrossian et al., 2016). Increased serum p40 levels was observed in women with obesity, positively correlated with fat mass, and negatively with HDL-C as well as associated with higher levels of triglycerides and total cholesterol, all components of the MetS (Nikolajuk et al., 2015). As our data shows no significant role for IL-17, it may be hypothesized that the raised levels of IL-12/23 p40 acts to suppress Th17 cells, the main producers of IL-17, as previously shown (Kim et al., 2012). It of interest to mention that low levels of cathelicidin (LL-37) have been reported in SZ (Kozlowska et al., 2018). As LL-37 modulate the upregulation of IL-17 production (Minns et al., 2021), future research will be required to dissect the potential interplay between LL-37, IL-17 production and their interactions with IL-12/23 p40.

To date, only one study has reported heightened IL-16 levels to be associated with MetS and type 2 diabetes in the general population, but without adjustment for other variables (Zak et al., 2007). Although considered a pro-inflammatory cytokine, the relative paucity of studies on IL-16 only allows to hypothesize that its increase may be part of a general pro-inflammatory response in the course of MetS and SZ, with parallels to previous data on other less frequently reported cytokines, such as IL-7 (Frydecka et al., 2018). However, recent data shows IL-16 to be positively correlated specifically with subcutaneous adipose tissue levels in the upper body (Strand et al., 2021), suggesting that it may be associated with more particular aspects of MetS.

The data presented here provide novel insights into the pathophysiological processes underlying MetS in a subgroup of patients with SZ. Much of this data is supported by previous studies, including the role of immuno-inflammatory processes and clinical characteristics. MetS is classically associated with ageing/telomer shortening and immunosenescence (Révész et al., 2018), as well as oxidative stress and low-grade chronic inflammation, both at risk factors also observed in SZ settings (Cardinali and Hardeland, 2017). Such processes may be seen as a combination of inflammaging interactions with "meta-inflammation", with overfeeding contributing to insulin resistance, obesity, MetS and organs impairment (Gregor and Hotamisligil, 2011; Franceschi et al., 2018).

We must acknowledge some limitations in our study. We did not consider differences in treatment duration or type of antipsychotics, although most patients received second-generation antipsychotics. Our sample of patients may not be fully representative of the entire spectrum of SZ given the observed mean age of 30 years. Penalized regression shrinks estimates: therefore, ORs should be interpreted with caution as a measure of the strength of association between MetS and cytokines or clinical variables. Also, the lack of longitudinal follow-up of biological markers and clinical features highlights the need for a prospective study

recording other markers of oxidative stress, microbiota, telomere length/genomic data, and information on diet, exercise and circadian rhythms.

In summary, the present study confirms the high incidence of Mets in patients with SZ and shows a cytokine signature associated with metabolic syndrome. These results may allow to take a step towards precision medicine in psychiatry.

Declaration of competing interest

All authors declare that they have no competing interests.

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