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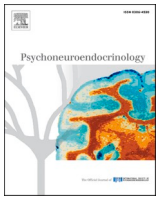

Fasting insulinemia as biomarker of illness relapse in patients with severe mental illness?

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ABSTRACT

Severe Mental Illness (SMI) is often associated with metabolic alteration and/or metabolic syndrome, which may determine an increased mortality due to a further increased cardiovascular risk. The relationship with metabolic syndrome is often bidirectional, resulting in a pathoplastic effect of these dysmetabolisms. Among the several hormones involved, insulin appears to play a key role, albeit not entirely clear. The aim of our real-world cross-sectional observational study is to investigate a set of metabolic biomarkers of illness relapse/recurrence/onset in a cohort of 310 adult SMI inpatients consecutively admitted to the Psychiatry Clinic of the Azienda Ospedaliero Universitaria of Marche, in Ancona (Italy), between February 2021 and February 2024. According to the stepwise multivariate regression model, a higher number of acute episodes per year was positively predicted by the age of illness onset, the lifetime number of suicidal attempts and fasting insulinemia and negatively by the participant's age. A second stepwise multivariate regression model using only the metabolic characteristics as independent variables, found that a higher number of acute episodes per year was predicted positively by the fasting insulinemia and red blood cells and negatively by the abdominal circumference. Overall, our findings could provide practical implications for the treatment and management of SMI patients, emphasizing the importance of monitoring and managing metabolic factors, particularly insulinemia, metabolic syndrome and insulin resistance. Finally, insulinemia could potentially act as metabolic biomarker of illness relapse, though more larger and longitudinal studies should be carried out to confirm these results.

1. Introduction

Severe mental illness (SMI) is defined as the presence of a highly disabling psychiatric disorder that encompasses multiple diagnostic categories, including schizophrenia and psychotic spectrum disorders, bipolar disorder, and major depression with psychotic symptoms (Zumstein and Riese, 2020). In 2021, it was estimated that around 14.1 million of adults were affected with SMIs, with a prevalence of approximately 5.5 % (NIMH, 2023). These conditions are associated with a life expectancy that is 10–20 years shorter than that of the general population (Plana-Ripoll et al., 2020). This mortality rate has been reported significantly high in both sexes and has been progressively increased over the years (Plana-Ripoll et al., 2020). Although the rate of deaths related to non-organic medical conditions, such as suicides and accidents, is overly high for this category of patients, only a minority of deaths among SMI sufferers are attributable to these causes (Ali et al., 2022). Indeed, the majority (approximately 70 %) of deaths seemed to be due to organic conditions, such as cardiovascular, respiratory, metabolic, infective, and neoplastic diseases (Nielsen et al., 2021). Cardiovascular diseases appear to be one of the main factors that may explain excess mortality in individuals with SMIs (Nielsen et al., 2021).

Evidence suggests that patients with SMIs have an increased risk of overweight, obesity and dysmetabolism, including metabolic syndrome (Afzal et al., 2021). The metabolic syndrome, i.e. the coexistence of abdominal obesity, hyperglycemia, hypertension, and dyslipidemia, implies an additional increased cardiovascular risk compared. In addition, it is associated with an increased overall and cardiovascular disease-related mortality, thus contributing to the reduced life expectancy of patients with severe mental disorders (Mottillo et al., 2010). Some authors suggested that such metabolic alterations do not only

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depend on a secondary effect of mental disorders (linked, for example, to psychopharmacotherapy and dysregulated lifestyles), but more likely there is a bidirectional relationship between SMI and metabolism, emphasizing on how the presence of a dysmetabolism may have a pathoplastic effect, influencing the course and severity of disease (Rajan and Menon, 2017). Insulin, in addition to its classic role in glycemic regulation, has multiple functions in the central nervous system. It acts as a growth factor and directly influences cognitive functions, such as memory (Kullmann et al., 2016). Thus, patients with type 2 diabetes (DM2) may display cognitive alterations, even in the absence of macrovascular complications (Cui et al., 2022). Furthermore, in SMI patients, the presence of DM2 is not only associated with worse physical health, but also with a worst psychiatric outcome, a poor response to psychopharmacotherapy and neurostructural and neurochemical alterations in the brain (Mazza et al., 2023). In bipolar patients, insulin resistance has been associated with a three times higher risk, compared to euglycemic controls, of developing a chronic and rapid-cycling disease, as well as a lower response to treatment with mood stabilizers (Steardo et al., 2019). In schizophrenic patients, the presence of insulin resistance has also been associated with greater severity of negative symptoms (Soontornniyomkij et al., 2019). Moreover, in depressed patients, an insulin resistance has been positively correlated with greater symptom severity (Watson et al., 2021).

In addition to insulin, cholesterol also plays a key role in the brain with pathoplastic effects on mental disorders. A close association has been found between low levels of total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol and increased suicide risk (Wu et al., 2016). In addition, low HDL cholesterol levels have been correlated with a higher prevalence of negative symptoms in schizophrenia, with the presence of cognitive impairments (particularly, in the memory and language domains) in bipolar disorder, and with longer duration of symptoms in major depression (Gjerde et al., 2018). Obesity has also been associated with a worsen outcome in patients with bipolar disorder and with accelerated brain aging in psychotic patients (McWhinney et al., 2021). Considering the above, it is not surprising that metabolic syndrome, which is highly prevalent in patients with SMI, contributes to cognitive decline and brain aging in schizophrenia and even interferes with the effectiveness of cognitive-behavioral therapy (Bora et al., 2017). Further evidence of the pathoplastic effect of dysmetabolism can be found in the evidence that some drugs used to treat metabolic disorders seemed to exert also positive effects at the cognitive and psychopathological levels. In particular, liraglutide, a hypoglycemic glucagon-like peptide-1 (GLP-1) receptor agonist drug, showed a beneficial effect on cognitive performance in a group of subjects with mood disorders not suffering from diabetes and a reduction in weight in patients with SMI (Barnard-Kelly et al., 2022).

Therefore, our preliminary research hypothesis is to verify whether there is a pathoplastic association between SMIs and a set of altered metabolic parameters which could act as possible biomarkers of illness relapse/recurrence and/or severity, to clinically characterize a dysmetabolism-determined subtype of SMI patients for developing more tailored clinical and therapeutic approaches.

2. Materials and methods

2.1. Study design and participants

All patients (>18 years) with SMI who were consecutively admitted to the Psychiatry Clinic of the Azienda Ospedaliero Universitaria of Marche, in Ancona (Italy), between February 2021 and February 2024, were prospectively recruited. Patients who had accepted to participate in the study, after providing informed consent, were interviewed, and assessed within the first 2–3 days of admission. Inclusion criteria included: (a) a diagnosis of SMI, according to the below definition suggested by the U.S. National Institute of Mental Health (NIMH); (b) having provided a written informed consent and the consent to participate in the study; (c) being able to conduct the clinician-administered interview (i.e., absence of cognitive impairment, mental retardation, language impairment and/or not understanding the Italian language).

For the definition of SMI, a modified version as provided by the NIMH was used, i.e. the patient should have reached (at least once in the last year) a score less than 60 at the Global Assessment of Functioning (GAF) (Kessler et al., 2003), and having received one of the following diagnoses in the past 12 months: schizophrenia, bipolar disorder, major depressive disorder with psychotic symptoms, schizophreniform disorder, schizoaffective disorder, chronic delusional disorder, not-otherwise specified psychotic disorder. During the hospitalization, whether the patient was not previously assessed in our inpatient unit, was administered the Structured Clinical Interview for Disorders of the DSM-5®-Version for the Clinician (SCID-5-CV; First et al., 2015) by an expert trained clinician, to confirm the above listed diagnosis. Each patient was also assessed with the Global Assessment of Functioning (GAF). The GAF is a scale in the DSM-IV, used by mental health specialists to subjectively assess an individual's social, occupational, and psychological functioning in response to various problems in life. Scores range from 100 (extremely high functioning) to 1 (severely impaired), divided into 10 levels (American Psychiatric Association, 2000).

All the study procedures were in accordance with the ethical standard of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The institutional Ethics Committee approved the study (Prot. 352/2022). This research study was conducted from data obtained for clinical purposes.

2.2. Evaluations

An *ad hoc* case report form was designed and administered by the clinician to assess socio-demographic (age, sex, education, marital status, and occupation) and clinical characteristics (psychiatric diagnosis, age of illness onset, number of relapses/hospitalizations, number of suicide attempts, medical comorbidities, and psychopharmacological history), familiarity for cardiovascular diseases, and lifestyle information (smoking habit and number of cigarettes consumed daily, alcohol consumption and amount of alcohol consumed per day, level of physical activity). All information, including the number of acute episodes/relapses per year, was obtained through a clinical interview conducted by

Table 1
AHA/NHLBI criteria for the definition of metabolic syndrome (Alberti et al., 2009).

	Presence of at least 3 of the following 5 criteria:	
	MALES	**FEMALES**
Abdominal Circumference	≥ 94 cm[a] ≥ 102 cm[b] ≥ 90 cm[c]	≥ 80 cm[a] ≥ 88 cm[b] ≥ 80 cm[c]
Triglyceridemia	≥ 150 mg/dl Or ongoing therapy for hypertriglyceridemia	≥ 150 mg/dl Or ongoing therapy for hypertriglyceridemia
Blood HDL cholesterol	< 40 mg/dl Or ongoing therapy for reduced HDL cholesterol	< 50 mg/dl Or ongoing therapy for reduced HDL cholesterol
Blood pressure	Diastolic ≥ 85 mmHg or Systolic ≥ 130 mmHg or Current antihypertensive therapy	Diastolic ≥ 85 mmHg or Systolic ≥ 130 mmHg or Current antihypertensive therapy
Fasting blood glucose	≥ 100 mg/dl Or ongoing therapy for hyperglycemia	≥ 100 mg/dl Or ongoing therapy for hyperglycemia

HDL: High-density lipoprotein.
[a] Europe
[b] Canada and United states
[c] Asia

Table 2
Sociodemographic, clinical and metabolic characteristics of the sample.

Sociodemographic, clinical and metabolic characteristics of the sample			
Age (Mean, SD)		43.5	14.9
Sex (n, %)	Man	165	53.2 %
	Woman	145	46.8 %
Ethnicity (n, %)	Caucasian	270	87.1 %
	African	18	5.8 %
	Asian	13	4.2 %
	South American	5	1.6 %
	Middle Eastern	4	1.3 %
Marital status (n, %)	Single	201	64.8 %
	In a relationship	68	21.9 %
	Separated/divorced	30	9.7 %
	Widower	11	3.5 %
Education level (Mean, SD)		11.5	4.4
Working status (n, %)	Blue collar	49	15.8 %
	White collar	35	11.3 %
	Student	23	7.4 %
	Unemployed	166	53.5 %
	Retired	37	11.9 %
Diagnosis (n, %)	Schizophrenia or other psychotic disorders	163	52.6 %
	Bipolar disorder	101	32.6 %
	Schizoaffective disorder	34	11 %
	Depression with psychotic symptoms	12	3.9 %
Age of onset of the disease (Mean, SD)		31.0	14.2
Duration of illness (Mean, SD)		12.6	12.1
Number of lifetime relapses (Mean, SD)		5.0	5.3
Number of relapses per year (Mean, SD)		0.7	0.7
Number of suicidal attempts (Mean, SD)		0.3	0.7
Organic disorders (n, %)	No	159	51.3 %
	Yes	151	48.7 %
Smoker (n, %)	No	140	45.2 %
	Yes	170	54.8 %
Smoked cigarettes per day (Mean, SD)		9.0	10.9
Daily alcohol use (n, %)	No	231	74.5 %
	Yes	79	25.5 %
Alcohol units per day (Mean, SD)		0.5	1.2
Physical activity (n, %)	No	126	40.6 %
	Light	116	37.4 %
	Moderate	55	17.7 %
	Intense	13	4.2 %
Family history of cardiovascular diseases (n, %)	No	179	57.7 %
	Yes	131	42.3 %
Weight (Mean, SD)		74.5	20.1
Body Mass Index (BMI) (Mean, SD)		25.6	6.4
Weight class (n, %)	Severe thinness	4	1.3 %
	Underweight	24	7.8 %
	Normal range	140	45.3 %
	Overweight	81	26.2 %
	Obese (Class I)	35	11.3 %
	Obese (Class II)	20	6.5 %
	Obese (Class III)	5	1.6 %
Abdominal circumference (cm) (Mean, SD)		91.9	16.5
Systolic blood pressure (mmHg) (Mean, SD)		119.4	10.9
Diastolic blood pressure (mmHg) (Mean, SD)		74.6	8.7
Total cholesterol (mg/dl) (Mean, SD)		168.6	38.9
High-density lipoprotein (HDL) (mg/dl) (Mean, SD)		52.8	15.9
Triglycerides (mg/dl) (Mean, SD)		111.1	72.5
Low-density lipoprotein (LDL) (mg/dl) (Mean, SD)		93.5	33.6
LDL/HDL ratio (Mean, SD)		1.9	1.0
Blood glucose (mg/dl) (Mean, SD)		88.3	28.3
Fasting insulinemia (μUI/ml) (Mean, SD)		12.1	12.5
HOMA index (Mean, SD)		2.8	3.4
Diabetes diagnosis (n, %)	No	289	93.2 %
	Yes	21	6.8 %
Insulin resistance (n, %)	No	212	69.7 %
	Yes	92	30.3 %
Drug-naive patients (n, %)	No	256	82.6 %
	Yes	54	17.4 %
White blood cells (*10^3/mm^3) (Mean, SD)		7.5	2.3
Red blood cells (*10^6/mm^3) (Mean, SD)		4.7	0.8
Platelets (*10^3/mm^3) (Mean, SD)		241.6	62.5
Neutrophils (*10^3/mm^3) (Mean, SD)		4.7	2.0
Lymphocytes (*10^3/mm^3) (Mean, SD)		2.0	0.7
Monocytes (*10^3/mm^3) (Mean, SD)		0.758	2.305
Eosinophils (*10^3/mm^3) (Mean, SD)		0.15	0.129
Basophils (*10^3/mm^3) (Mean, SD)		0.04	0.021
Neutrophil-to-Lymphocyte Ratio (NLR) (Mean, SD)		2.5	1.5
Basophil-to-Lymphocyte Ratio (BLR) (Mean, SD)		0.021	0.012
Metabolic Syndrome (n, %)	No	224	72.3 %
	Yes	86	27.7 %

health professionals, as part of a routine clinical practice, also involving the patient's family members, the patient's personal psychiatrist and the consultation of all hospital records. In our study, we considered relapse episodes as those accompanied by a significant functional impairment and requiring hospitalization in a psychiatric ward, as suggested in previous studies on SMI patients (Tohen et al., 2009; Olivares et al., 2013; Cristarella et al., 2022). All recruited patients underwent a general medical examination during which weight, height, and abdominal circumference (measured with a nonelastic tape at the beltline, approximately halfway between the lower edge of the ribs and the upper edge of the iliac crest, at full exhalation; WHO, 2011) were measured. The Body Mass Index (BMI), defined as the ratio of body weight in kilograms to the square of height in meters, was calculated. In addition, blood pressure was assessed by measuring it twice with a sphygmomanometer: the first measurement was conducted with the subject in clinostatism and the second one with the subject in orthostatism, approximately two minutes after the first. The average value between the two readings was used for the study. Finally, the following plasma parameters were measured: blood count with formula, glucose, triglycerides, total cholesterol, HDL cholesterol, and insulin.

The presence of metabolic syndrome was assessed according to the unified diagnostic criteria of the American Heart Association (AHA) and the National Heart, Lung and Blood Institute (NHLBI) (Table 1; Alberti et al., 2009). The presence of insulin resistance was also evaluated according to the Homeostasis Model Assessment-Insulin Resistance (HOMA-IR). The HOMA-IR is a simple mathematical homeostasis model that requires measurement of fasting blood glucose and insulin concentrations and is obtained as the product of basal insulinemia (μU/ml) times basal blood glucose (mmol/ml) divided by 22.5 (Matthews et al., 1985). The cut-off for defining insulin resistance varies widely in the literature (from 1.7 to 3.875; Tang et al., 2015). In our study, a cut-off value of HOMA-IR equal to or greater than 2.5 was chosen by convention; this cut-off for insulin resistance appears to be the most widely accepted cut-off in the international literature (Yamada et al., 2011). Neutrophil-to-Lymphocyte Ratio (NLR) and Basophil-to-Lymphocyte Ratio (BLR) were also calculated, as they are considered as possible biomarkers of inflammation (Ekinci and Ekinci, 2017).

2.3. Statistical analysis

Data analysis was performed using the Statistical Package for Social Science for MacOS (SPSS) Software, version 27.0.1.0. (IBM Corp., November 2021, Armonk NY). All the analyses were two-sided with α of 0.05. Descriptive statistics were performed to describe the sociodemographic and clinical characteristics of the sample. Clinical, sociodemographic, and metabolic categorical variables were summarized using frequency (N) and percentage (%). After analyzing the continuous variables for skewness, kurtosis, normality distribution through the Shapiro-Wilk test, and the equality of variances by Levene test, parametric or non-parametric statistical tests were used, when appropriate. a new variable, episodes per year, was created through the ratio of the number of disease relapses to the duration of illness. For patients at their first episode of disease requiring a hospitalization, it was conventionally chosen to assign 1. Normally distributed continuous variables were represented using the average mean and standard deviation (SD), whether normally distributed, or the median and 95 % Confidence Interval (95 % CI) when not normally distributed. To compare all

Table 3
Sociodemographic and clinical characteristics of the sample stratified based on sex, psychopharmacology, presence of insulin resistance or metabolic syndrome.

				Drug-naive patients			Insulin resistance			Metabolic Syndrome		
				No	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**
Males (n; %)				134 (52.3 %)	31 (57.4 %)	χ^2=0.459 p=0.498	115 (54.2 %)	46 (50.0 %)	χ^2=0.464 p=0.496	122 (54.5 %)	43 (50.0 %)	χ^2=0.497 p=0.481
Females (n; %)				122 (47.7 %)	23 (42.6 %)		97 (45.8 %)	46 (50.0 %)		102 (45.5 %)	43 (50.0 %)	
	Males	**Females**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**
Age (M; SD)	40.5 (14.2)	46.9 (14.9)	**<0.001**[a]	43.2 (14.3)	44.7 (17.4)	0.572[a]	42.9 (14.9)	44.9 (14.9)	0.282[a]	43.3 (14.6)	43.8 (15.7)	0.794[a]
Ethnicity (n, %)	**Males**	**Females**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**
Caucasian	137 (83.0 %)	133 (91.7 %)	χ^2=6.253 p=0.181	224 (87.5 %)	46 (85.2 %)	χ^2=3.825 p=0.430	184 (86.8 %)	82 (89.1 %)	χ^2=4.036 p=0.401	198 (88.4 %)	72 (83.7 %)	χ^2=0.043 p=0.836
African	11 (6.7 %)	7 (4.8 %)		14 (5.5 %)	4 (7.4 %)		10 (4.7 %)	7 (7.6 %)		9 (4.0 %)	9 (10.5 %)	
Asian	10 (6.1 %)	3 (2.1 %)		9 (3.5 %)	4 (7.4 %)		10 (4.7 %)	2 (2.2 %)		10 (4.5 %)	3 (3.5 %)	
South American	4 (2.4 %)	1 (0.7 %)		5 (2.0 %)	0 (0.0 %)		4 (1.9 %)	1 (1.1 %)		3 (1.3 %)	2 (2.3 %)	
Middle Eastern	3 (1.8 %)	1 (0.7 %)		4 (1.6 %)	0 (0.0 %)		4 (1.9 %)	0 (0.0 %)		4 (1.8 %)	0 (0.0 %)	
Educational level (M; SD)	11.4 (4.6)	11.6 (4.2)	0.54[b]	11.4 (4.4)	12 (4.4)	0.288[b]	11.7 (4.7)	11 (3.5)	0.274[b]	11.6 (4.5)	11.2 (4.2)	0.441[a]
Age of illness onset (M; SD)	29.6 (14.4)	32.7 (13.8)	**0.008**[b]	29.0 (12.2)	40.9 (18.5)	**<0.001**[a]	30.2 (13.9)	33.3 (14.8)	0.065[b]	31.0 (14.3)	31.2 (14.0)	0.914[a]
Duration of illness (years) (M; SD)	11.0 (10.6)	14.4 (13.3)	**0.038**[b]	14.3 (11.6)	4.5 (10.7)	**<0.001**[b]	12.9 (12.6)	11.6 (10.7)	0.584[b]	12.5 (12.1)	13.0 (12.0)	0.705[a]
Relapse number (M; SD)	4.8 (4.8)	5.1 (5.8)	0.535[b]	5.7 (5.5)	1.4 (0.8)	**<0.001**[a]	4.4 (4.0)	6.1 (7.1)	0.169[b]	4.9 (4.5)	5.1 (6.9)	0.363[b]
Marital status (n, %)	**Males**	**Females**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**
Single	127 (77.0 %)	74 (51.0 %)	χ^2=24.138 **p<0.001**	166 (64.8 %)	35 (64.8 %)	χ^2=2.027 p=0.567	136 (64.2 %)	61 66.3 %	χ^2=0.808 p=0.848	145 (64.7 %)	56 (65.1 %)	χ^2=0.429 p=0.513
In a relationship	25 (15.2 %)	43 (29.7 %)		55 (21.5 %)	13 (24.1 %)		46 21.7 %	20 21.7 %		47 (21.0 %)	21 (24.4 %)	
Separated/ divorced	11 (6.7 %)	19 (13.1 %)		27 (10.5 %)	3 (5.6 %)		21 9.9 %	9 9.8 %		23 (10.3 %)	7 (8.1 %)	
Widower	2 (1.2 %)	9 (6.2 %)		8 (3.1 %)	3 (5.6 %)		9 (4.2 %)	2 (2.2 %)		9 (4.0 %)	2 (2.3 %)	
Working status (n, %)	**Males**	**Females**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**
Blue collar	33 (20.0 %)	16 (11.0 %)	χ^2=7.728 p=0.102	40 (15.6 %)	9 (16.7 %)	χ^2=2.989 p=0.560	38 (17.9 %)	11 (12.0 %)	χ^2=18.838 **p<0.001**	35 (15.6 %)	14 (16.3 %)	χ^2=0.007 p=0.931
White collar	20 (12.1 %)	15 (10.3 %)		27 (10.5 %)	8 (14.8 %)		32 (15.1 %)	2 (2.2 %)		26 (11.6 %)	9 (10.5 %)	
Student	8 (4.8 %)	15 (10.3 %)		19 (7.4 %)	4 (7.4 %)		18 (8.5 %)	5 (5.4 %)		15 (6.7 %)	8 (9.3 %)	
Unemployed	86 (52.1 %)	80 (55.2 %)		142 (55.5 %)	24 (44.4 %)		97 (45.8 %)	64 (69.6 %)		119 (53.1 %)	47 (54.7 %)	
Pensioner	18 (10.9 %)	19 (13.1 %)		28 (10.9 %)	9 (16.7 %)		27 (12.7 %)	10 (10.9 %)		29 (12.9 %)	8 (9.3 %)	
Diagnosis (n, %)	**Males**	**Females**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**
Schizophrenia or other psychotic disorders	100 (60.6 %)	63 (43.4 %)	χ^2=11.823 **p=0.008**	124 (48.4 %)	39 (72.2 %)	χ^2=10.518 **p=0.015**	112 (52.8 %)	49 (53.3 %)	χ^2=1.138 p=0.768	113 (50.4 %)	50 (58.1 %)	χ^2=1.814 p=0.612
Bipolar disorder	42 (25.5 %)	59 (40.7 %)		91 (35.5 %)	10 (18.5 %)		71 (33.5 %)	28 (30.4 %)		75 (33.5 %)	26 (30.2 %)	
Schizoaffective disorder	19 (11.5 %)	15 (10.3 %)		31 (12.1 %)	3 (5.6 %)		20 (9.4 %)	12 (13.0 %)		27 (12.1 %)	7 (8.1 %)	
Depression with psychotic symptoms	4 (2.4 %)	8 (5.5 %)		10 (3.9 %)	2 (3.7 %)		9 (4.2 %)	3 (3.3 %)		9 (4.0 %)	3 (3.5 %)	
Number of suicidal attempts (M; SD)	0.2 (0.6)	0.3 (0.7)	0.275[b]	0.3 (0.7)	0.1 (0.3)	0.165[b]	0.3 (0.7)	0.3 (0.6)	0.763[b]	0.3 (0.7)	0.3 (0.6)	0.693[b]
Organic disorders	**Males**	**Females**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**
No (n; %)	96 (58.2 %)	63 (43.4 %)	χ^2=6.253 6.706	133 (52.0 %)	26 (48.1 %)	χ^2=0.258 p=0.611	114 (53.8 %)	42 (45.7 %)	χ^2=1.694 p=0.193	115 (51.3 %)	44 (51.2 %)	χ^2=0.001 p=0.978
Yes (n; %)	69 (41.8 %)	82 (56.6 %)	**p=0.010**	123 (48.0 %)	28 (51.9 %)		98 (46.2 %)	50 (54.3 %)		109 (48.7 %)	42 (48.8 %)	

(*continued on next page*)

Table 3 (*continued*)

				Drug-naive patients			Insulin resistance			Metabolic Syndrome		
				No	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**
Smoker	**Males**	**Females**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**
No (n; %)	59 (35.8 %)	81 (55.9 %)	χ^2=12.596 **p<0.001**	106 (41.4 %)	34 (63.0 %)	χ^2=8.367 **p=0.004**	106 (50.0 %)	32 (34.8 %)	χ^2=5.994 **p=0.014**	106 (47.3 %)	34 (39.5 %)	χ^2=1.521 p=0.217
Yes (n; %)	106 (64.2 %)	64 (44.1 %)		150 (58.6 %)	20 (37.0 %)		106 (50.0 %)	60 (65.2 %)		118 (52.7 %)	52 (60.5 %)	
Smoked cigarettes per day (M; SD)	10.9 (11)	6.9 (10.5)	**<0.001**[b]	9.8 (11.1)	5.5 (9.2)	**0.004**[b]	7.6 (9.8)	12.2 (12.8)	**0.003**[b]	8.3 (10.3)	11.1 (12.2)	0.065[b]
Daily alcohol use	**Males**	**Females**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**
No (n; %)	115 (69.7 %)	116 (80.0 %)	χ^2=4.314 **p=0.038**	195 (76.2 %)	36 (66.7 %)	χ^2=2.122 p=0.145	168 (79.2 %)	58 (63.0 %)	χ^2=8.829 **p=0.003**	174 (77.7 %)	57 (66.3 %)	χ^2=4.252 **p=0.039**
Yes (n; %)	50 (30.3 %)	29 (20.0 %)		61 (23.8 %)	18 (33.3 %)		44 (20.8 %)	34 (37.0 %)		50 (22.3 %)	29 (33.7 %)	
Alcohol units per day (M; SD)	0.5 (1.2)	0.4 (1.2)	**0.04**[b]	0.5 (1.3)	0.5 (0.8)	0.192[b]	0.3 (0.9)	0.7 (1.5)	**0.002**[b]	0.4 (0.9)	0.8 (1.7)	**0.021**[b]
Physical activity (n, %)	**Males**	**Females**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**
None	66 (40.0 %)	60 (41.4 %)	χ^2=12.794 **p=0.005**	107 (41.8 %)	19 (35.2 %)	χ^2=1.279 p=0.734	79 (37.3 %)	44 (47.8 %)	χ^2=3.992 p=0.407	90 (40.2 %)	36 (41.9 %)	χ^2=4.250 p=0.373
Light	51 (30.9 %)	65 (44.8 %)		93 (36.3 %)	23 (42.6 %)		85 (40.1 %)	31 (33.7 %)		87 (38.8 %)	29 (33.7 %)	
Moderate	40 (24.2 %)	15 (10.3 %)		46 (18.0 %)	9 (16.7 %)		37 (17.5 %)	15 (16.3 %)		40 (17.9 %)	15 (17.4 %)	
Intense	8 (4.8 %)	5 (3.4 %)		10 (3.9 %)	3 (5.6 %)		11 (5.2 %)	2 (2.2 %)		7 (3.1 %)	6 (7.0 %)	
Family history of CV diseases (n, %)	**Males**	**Females**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**
No	103 (62.4 %)	76 (52.4 %)	χ^2=3.170 p=0.075	149 (58.2 %)	30 (55.6 %)	χ^2=0.128 p=0.720	119 (56.1 %)	58 (63.0 %)	χ^2=1.260 p=0.262	127 (56.7 %)	52 (60.5 %)	χ^2=0.362 p=0.548
Yes	62 (37.6 %)	69 (47.6 %)		107 (41.8 %)	24 (44.4 %)		93 (43.9 %)	34 (37.0 %)		97 (43.3 %)	34 (39.5 %)	

[a] t-test; [b]Mann–Whitney U test. n: sample size; SD: standard deviation; M: mean; CV: cardiovascular; **In bold significant p-values.**

demographic and categorical variables in each group, the $\chi 2$ Test was used. Parametric (independent samples Student's t-test and two-way tailored analysis of variance [ANOVA]) or nonparametric statistical tests (U-Mann–Whitney and Kruskal–Wallis tests) were performed, when appropriate, to compare all the sociodemographic, clinical, and metabolic characteristics across sex (males/females), diagnosis (psychotic disorders/mood disorders), being drug naive or not, having insulin resistance and having metabolic syndrome. Before specifically assessing the predictors of relapses related to metabolic characteristics, two preliminary stepwise multivariate linear regression analyses were run. The first was run to investigate whether some socio-demographic, clinical and metabolic predictors are potentially associated with a higher number of relapses (as assessed by using episodes per year as dependent variable). The second stepwise multivariate regression analysis, adjusted for the sex and age as covariates, was run to investigate only which metabolic predictors are associated with a higher number of relapses (as assessed by using episodes per year as dependent variable). At the end, a simple linear regression between fasting insulinemia and episodes per year (as dependent variable) was performed to assess whether fasting insulinemia could be alone a predictor of relapses. The latter analysis was carried out both in the total dataset and within a sub-group obtained after excluding those patients at their first hospitalization and without a previous psychiatry history. To fulfill the theoretical assumptions of the regression analyses, the normality of the residuals was checked, and outliers (n=1) were removed to normalize the dependent variable.

3. Results

3.1. Socio-demographic and clinical characteristics of the sample

According to the abovementioned inclusion criteria, participation in the study was proposed to 343 (28.3 %) eligible patients among all 1211 inpatients consecutively admitted to the Unit of Clinical Psychiatry, Department of Neurosciences, Azienda Ospedaliero Universitaria of Marche, Ancona (Italy) during the timeframe from February 2021 to February 2024. Among these, 5 (1.4 %) refused the participation in the study and 28 (8.3 %) following a further diagnostic assessment which excluded a confirmed SMI. Finally, 310 (90.4 %) inpatients were recruited and participated in the study. The sample consisted of 165 males (53.4 %) and 145 females (46.6 %), with a mean age of 43.4 years (SD = 14.8). Males displayed a significant lower mean age than females ($p < 0.001$), as well as patients with a psychotic disorder who had a significant lower mean age than patients with mood disorders ($p = 0.003$). Most of the patients had Caucasian origin (87.1 %; n = 271). The mean education level was 11.5 (SD = 4.4) years. Regarding marital status, 64.8 % (n = 201) were unmarried. Most of the sample were unemployed (53.5 %; n = 166) (Table 2).

Most of the sample (52.6 %; n = 163) had a diagnosis belonging to the schizophrenia spectrum disorders. The mean age of the illness onset was 31.0 (SD = 14.2) years, and the mean duration of illness was 12.7 (SD = 12.1) years. The mean number of acute episodes, identified as hospitalizations, was 5.0 (SD = 5.3), with an average of 0.70 (SD = 0.73) acute episodes per year (median = 0.5; 95 % Confidence Interval [95 % IC] = 0.61–0.77; range = 0–9.5). Around 19.4 % (n = 60) of the sample declared at least one suicidal attempt during their lifetime. Patients with a mood disorder had a significant higher mean number of suicidal attempts than patients with a psychotic disorder ($p = 0.014$).

Table 4
Metabolic characteristics of the sample stratified on sex, psychopharmacology, presence of insulin resistance or metabolic syndrome.

		Sex			Drug-naive patients			Insulin resistance			Metabolic Syndrome		
		Males	**Females**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**
Weight (M; SD)		78.8 (18.7)	69.6 (20.6)	**<0.001**[a]	75.2 (20.5)	71.3 (17.6)	0.205[a]	70.5 (1.6)	82.7 (25.1)	**<0.001**[a]	74 (21.1)	75.8 (17.1)	0.456[a]
Body Mass Index (BMI) (M; SD)		25.3 (5.6)	25.9 (7.2)	0.412[a]	25.9 (6.6)	24.1 (5.3)	0.065[a]	24.2 (5.2)	28.4 (7.6)	**<0.001**[a]	25.4 (6.7)	26.1 (5.5)	0.396[a]
Weight class (n, %)	Severe thinness	2 (1.2 %)	2 (1.4 %)	χ^2=20.877	4 (1.6 %)	0 (0.0 %)	χ^2=8.271	3 (1.4 %)	1 (1.1 %)	χ^2=27.256	4 (1.8 %)	0 (0 %)	χ^2=8.397
	Underweight	6 (3.6 %)	18 (12.5 %)	**p=0.002**	16 (6.3 %)	8 (15.1 %)	p=0.219	21 (10.0 %)	3 (3.3 %)	**p<0.001**	17 (7.6 %)	7 (8.1 %)	p=0.210
	Normal range	88 (53.3 %)	52 (36.1 %)		116 (45.3 %)	24 (45.3 %)		111 (52.6 %)	27 (29.3 %)		104 (46.6 %)	36 (41.9 %)	
	Overweight	46 (27.9 %)	35 (24.3 %)		66 (25.8 %)	15 (28.3 %)		47 (22.3 %)	32 (34.8 %)		60 (26.9 %)	21 (24.4 %)	
	Obese (Class I)	16 (9.7 %)	19 (13.2 %)		31 (12.1 %)	4 (7.5 %)		19 (9.0 %)	16 (17.4 %)		22 (9.9 %)	13 (15.1 %)	
	Obese (Class II)	5 (3.0 %)	15 (10.4 %)		19 (7.4 %)	1 (1.9 %)		9 (4.3 %)	10 (10.9 %)		11 (4.9 %)	9 (10.5 %)	
	Obese (Class III)	2 (1.2 %)	3 (2.1 %)		4 (1.6 %)	1 (1.9 %)		1 (0.5 %)	3 (3.3 %)		5 (2.2 %)	0 (0 %)	
Abdominal circumference (cm) (M; SD)		92.8 (14.1)	90.8 (19)	0.298[a]	92.7 (16.6)	88 (15.8)	0.057[a]	88.3 (14.6)	99.7 (18)	**<0.001**[a]	90.8 (16.3)	94.8 (17.1 %)	0.056[a]
Systolic blood pressure (mmHg) (M; SD)		120.4 (10.6)	118.2 (11.2)	0.077[a]	119.6 (11.1)	118.2 (9.6)	0.381[a]	118.5 (11)	120.9 (10.3)	0.077[a]	119.5 (10.9)	119.1 (10.8 %)	0.74[a]
Diastolic blood pressure (mmHg) (M; SD)		75.1 (9.6)	74 (7.5)	0.089[b]	74.6 (9)	74.5 (7.2)	0.88[b]	74.9 (7.8)	73.5 (10.4)	0.47[b]	75.1 (7.6)	73.2 (11)	0.083[a]
Total cholesterol (mg/dl) (M; SD)		162.9 (35.4)	175 (41.8)	**0.007**[a]	167.5 (38.6)	173.6 (40.5)	0.293[a]	166.2 (36.8)	173.9 (42.9)	0.111[a]	168 (39.6)	170 (37.3)	0.68[a]
High-density lipoprotein (HDL) (mg/dl) (M; SD)		48.6 (14.6)	57.6 (16.2)	**<0.001**[a]	52.3 (15.8)	55.3 (16.7)	0.214[a]	53.5 (15.9)	50.8 (16)	0.179[a]	53.5 (16.4)	51 (14.8)	0.21[a]
Triglycerides (mg/dl) (M; SD)		113.3 (82.7)	108.5 (58.9)	0.675[b]	112.5 (76.1)	104.2 (52)	0.556[b]	98.4 (47.7)	140.6 (105.7)	**<0.001**[b]	111.5 (78.4)	110 (54.6)	0.586[b]
Low-density lipoprotein (LDL) (mg/dl) (M; SD)		91.6 (33.4)	95.6 (33.8)	0.295[a]	92.7 (33.6)	97.5 (33.4)	0.337[a]	93 (31.6)	95 (37.7)	0.639[a]	92.1 (33.6)	97 (33.4)	0.336[a]
LDL/HDL ratio (M; SD)		2.1 (1.1)	1.8 (0.8)	**0.009**[b]	1.9 (1)	2 (1)	0.899[b]	1.9 (1.0)	2 (1)	0.187[b]	1.9 (0.9)	2.1 (1.1)	0.124[b]
Blood glucose (mg/dl) (M; SD)		86.8 (20.2)	89.9 (35.4)	0.336[a]	88 (29.2)	89.5 (23.8)	0.225[b]	82.3 (16.0)	102 (43)	**<0.001**[b]	87.5 (25.6)	90.3 (34.7)	0.447[a]
Fasting insulin (μUI/ml) (M; SD)		11.8 (11.4)	12.4 (13.7)	0.598[b]	12.2 (12.6)	11.5 (12.1)	0.541[b]	6.6 (2.9)	24.8 (16.3)	**<0.001**[b]	12.3 (13.9)	11.6 (8)	0.13[b]
HOMA index (M; SD)		2.8 (3.4)	2.8 (3.3)	0.451[b]	2.8 (3.4)	2.8 (3.3)	0.808[b]	1.3 (0.6)	6.2 (4.5)	**<0.001**[b]	2.8 (3.7)	2.7 (2.2)	0.713[a]
White blood cells (*10^3/mm^3) (M; SD)		8.1 (2.4)	6.9 (2.0)	**<0.001**[a]	7.6 (2.4)	7.1 (1.8)	0.144[a]	7.4 (2.4)	7.7 (2.1)	0.284[a]	7.5 (2.2)	7.7 (2.5)	0.516[a]
Red blood cells (*10^6/mm^3) (M; SD)		4.9 (0.7)	4.5 (0.7)	**<0.001**[a]	4.7 (0.8)	4.7 (0.6)	0.653[a]	4.7 (0.8)	4.8 (0.7)	0.352[a]	4.6 (0.7)	4.8 (0.9)	0.101[a]
Platelets (*10^3/mm^3) (M; SD)		240.7 (64.8)	242.7 (60.0)	0.772[a]	241 (62.5)	244.6	0.7[a]	237.8 (60.3)	249.1 (66.9)	0.15[a]	243.7 (66.1)	236.3 (52)	0.355[a]
Neutrophils (*10^3/mm^3) (M; SD)		5 (2.1)	4.2 (1.6)	**<0.001**[a]	4.7 (2)	4.4 (1.8)	0.377[a]	4.6 (2)	4.8 (1.7)	0.589[a]	4.6 (1.9)	4.8 (2.2)	0.394[a]
Lymphocytes (*10^3/mm^3) (M; SD)		2.1 (0.7)	2 (0.7)	0.072[a]	2 (0.7)	2 (0.7)	0.835[a]	2 (0.7)	2.1 (0.7)	0.084[a]	2 (0.7)	2 (0.7)	0.982[a]
Monocytes (*10^3/mm^3) (M; SD)		0.9 (3.1)	0.5 (0.2)	0.128[a]	0.6 (0.2)	1. 3 (5.5)	0.046[a]	0.8 (2.8)	0.6 (0.2)	0.532[a]	0.8 (2.7)	0.6 (0.3)	0.552[a]
Eosinophils (*10^3/mm^3) (M; SD)		0.167 (0.149)	0.132 (0.099)	0.1[b]	0.157 (0.131)	0.12 (0.113)	**0.044**[b]	0.152 (0.137)	0.151 (0.113)	0.894[b]	0.152 (0.127)	0.146 (0.135)	0.433[b]
Basophils (*10^3/mm^3) (M; SD)		0.043 (0.023)	0.037 (0.018)	**0.007**[a]	0.041 (0.022)	0.037 (0.018)	0.324[a]	0.039 (0.02)	0.044 (0.023)	0.033[a]	0.041 (0.022)	0.039 (0.019)	0.63[b]

(*continued on next page*)

Table 4 (*continued*)

		Sex			Drug-naive patients			Insulin resistance			Metabolic Syndrome		
		Males	Females	p-value	No	Yes	p-value	No	Yes	p-value	No	Yes	p-value
Neutrophil-to-Lymphocyte Ratio (NLR) (M; SD)		2.72 (1.72)	2.37 (1.19)	0.058[b]	2.55 (1.47)	2.54 (1.66)	0.633[b]	2.62 (1.65)	2.41 (1.1)	0.488[a]	2.5 (1.3)	2.68 (1.86)	0.36[a]
Basophil-to-Lymphocyte Ratio (BLR) (M; SD)		0.022 (0.014)	0.02 (0.009)	0.271[b]	0.021 (0.013)	0.02 (0.01)	0.718[b]	0.021 (0.012)	0.022 (0.012)	0.639[a]	0.021 (0.013)	0.02 (0.01)	0.426[a]
Insulin resistance (n, %)	No	115 (71.4 %)	97 (67.8 %)	χ^2=0.464 p=0.496	174 (69.3 %)	38 (71.7 %)	χ^2=0.117 p=0.732				162 (73.6 %)	50 (59.5 %)	χ^2=5.737 **p=0.017**
	Yes	46 (28.6 %)	46 (32.3 %)		77 (30.7 %)	15 (28.3 %)					58 (26.4 %)	34 (40.5 %)	
Drug-naive patients (n, %)	No	134 (81.2 %)	122 (84.1 %)	χ^2=0.456 p=0.498				174 (82.1 %)	77 (83.7 %)	χ^2=0.117 p=0.732	187 (83.5 %)	69 (80.2 %)	χ^2=0.456 p=0.499
	Yes	31 (18.8 %)	23 (15.9 %)					38 (17.9 %)	15 (16.3 %)		37 (16.5 %)	17 (19.8 %)	
Diabetes diagnosis (n, %)	No	156 (94.5 %)	133 (91.7 %)	χ^2=0.973 p=0.324	237 (92.6 %)	52 (96.3 %)	χ^2=0.976 p=0.323	202 (95.3 %)	81 (88.0 %)	χ^2=5.229 **p=0.022**	211 (94.2 %)	78 (90.7 %)	χ^2=1.205 p=0.272
	Yes	9 (5.5 %)	12 (8.3 %)		19 (7.4 %)	2 (3.7 %)		10 (4.7 %)	11 (12.0 %)		13 (5.8 %)	8 (9.3 %)	

[a] t-test; [b]Mann–Whitney U test. In bold significant p-values. M: mean; SD: standard deviation; n: sample size; %: percentage.

Regarding lifestyle, 54.8 % (n = 170) of the patients were smokers, with a mean number of cigarettes smoked per day of 16.5 (SD = 9.7). While 25.5 % (n = 79) of patients declared a regular alcohol intake, with an average of 1.8 (SD = 1.7) alcoholic units daily consumed. Patients who were drug naïve (at the time of hospitalization) smoked significantly less cigarettes than other patients (p = 0.004). Around 40.5 % (n = 126) of the sample do not regularly practice physical activityAll sociodemographic and characteristics are described in Table 2 **and** Table 3.

3.2. Metabolic profile of the sample

Regarding metabolic and anthropometric characteristics, the mean weight of the sample was 74.5 (SD = 20.1) kg, while the mean BMI was 25.6 (SD = 6.4 kg/m^2). The sample was also stratified according to BMI and only the 45 % (n = 140) of the sample had a normal weight. Around 19.7 % (n = 61) of the sample could be defined obese according to their BMI at the time of hospitalization. The mean systolic blood pressure was 119.5 (SD = 10.8) mmHg while diastolic pressure was 74.7 (SD =8.6) mmHg. Patients with a psychotic disorder had a significant lower systolic blood pressure than patients with mood disorder (p = 0.031). The mean total cholesterol was 168.6 (SD = 38.9) mg/dl, HDL cholesterol was 52.8 (SD =15.9) mg/dl, LDL cholesterol was 93.5 (SD =33.5) mg/dl and the mean triglyceride value was 111 (SD =72.5) mg/dl. The mean LDL/HDL ratio was 1.9 (SD =1.0). Around 27.7 % (n=86) of the sample displayed a comorbid metabolic syndrome. The mean fasting blood glucose value was 88.3 (SD = 28.3) mg/dl, fasting insulinemia was 12.1 (SD = 12.5) μUI/ml and the resulting mean HOMA index was 2.8 (SD = 3.3). Around 29.7 % (n = 82) of the sample had insulin resistance according to the HOMA index. Furthermore, being unemployed is associated with insulin resistance (p < 0.001). The mean abdominal circumference was 91.9 (SD = 16.5) cm. Regarding the blood count, the mean red blood cells were 4.7 (SD = 0.7 * $10^6/mm^3$), the mean blood cells were 7.5 (SD = 2.2 * $10^3/mm^3$), the mean platelets were 241 (SD = 62.5 * $10^3/mm^3$), the mean neutrophils were 4.7 (SD = 1.9 * $10^3/mm^3$), the mean lymphocytes were 2 (SD = 0.7 * $10^3/mm^3$), the mean monocytes were 0.7 (SD = 2.3 * $10^3/mm^3$), the mean eosinophils were 0.1 (SD = 0.1 * $10^3/mm^3$), the mean basophils were 0.04 (SD = 0.02 * $10^3/mm^3$) the mean NLR was 2.5 (SD = 1.5) and the mean BLR 0.02 (SD = 0.01).Patients with a psychotic disorder had a significantly higher mean number of platelets than patients with a mood disorder (p = 0.019). Otherwise, patients who were drug naïve had a significantly lower mean number of eosinophils compared to other patients (p = 0.044). Patients with insulin resistance had significantly higher numbers of basophils (p = 0.033), compared to those without comorbid insulin resistance. All metabolic characteristics are summarized in Table 3 **and** Table 4**.**

3.3. Predictive factors for illness relapse

According to the stepwise multivariate regression model, a higher number of acute episodes per year is positively predicted by the age of illness onset (Beta coefficient, β=0.696; p < 0.001), the lifetime number of suicidal attempts (β = 0.253; p < 0.001) and fasting insulinemia (β = 0.126; p = 0.006) and negatively by the participant's age (β = −0.776; p < 0.001). These variables significantly predicted illness relapse [F (4290) = 46.0; p < 0.001; R^2 = 0.380] (Table 5).

Considering another stepwise multivariate regression model using only the metabolic characteristics as independent variables, a higher number of acute episodes per year is predicted positively by the fasting insulinemia (β = 0.170; p = 0.004) and red blood cells (β = 0.129; p = 0.023) and negatively by the abdominal circumference (β = −0.150; p = 0.011). These variables significantly predicted illness relapse [F (3297) = 46.0; p < 0.001; R^2 = 0.53] (Table 6).

A simple linear regression was observed between the number of illness relapses per year and fasting insulinemia [β = 0.125; F (1300) = 4.756; R^2 = 0.016; p = 0.030] (Fig. 1). This finding was also confirmed by conducting the simple linear regression between the number of acute

Table 5
Stepwise multivariate linear regression with sociodemographic, clinical and metabolic characteristics (episodes per year as dependent variable).

	B	SE	β	t	p-value
Age	−0.028	0.002	−0.776	−12.236	**<0.001**
Age of onset of the disease	0.026	0.002	0.696	10.951	**<0.001**
Suicidal attempts	0.209	0.038	0.253	5.447	**<0.001**
Fasting insulinemia (μUI/ml)	0.006	0.002	0.126	2.753	**0.006**

In bold significant p-values. SE: standard error.

Table 6
Stepwise multivariate linear regression with only metabolic characteristics (episodes per year as dependent variable).

	B	SE	β	t	p-value
BMI	−0.013	0.005	−0.153	−2.585	**0.010**
Fasting insulinemia (μUI/ml)	0.007	0.003	0.170	2.872	**0.004**
RBC (*10^6/mm^3)	0.091	0.040	0129	2.279	**0.023**

BMI: Body Mass Index; RBC: red blood cells. In bold significant p-values.

episodes per year and fasting insulinemia within the sub-group of the dataset obtained after excluding patients at their first hospitalization [$\beta = 0.225$; $F(1263) = 14.001$; $R^2 = 0.051$; $p < 0.001$].

4. Discussion

To the best of our knowledge, no pathognomonic metabolic biomarkers of illness relapse/onset/recurrence have been clearly and specifically identified among patients with SMIs, despite it has been widely documented a higher co-occurrence with metabolic alterations and the metabolic syndrome (Rajan and Menon, 2017; Afzal et al., 2021; Watson et al., 2021). Therefore, our study aimed at investigating within a cohort of inpatients affected with SMIs, recruited by a real-world setting, a set of metabolic alterations potentially associated with illness relapse. Our findings could help in defining a subtypization of SMI patients considering the metabolic profile, as well as investigating whether specific metabolic biomarker(s) could serve as potential candidate(s) in determining a clinical and therapeutic phenotypization of SMI patients, particularly verifying whether insulinemia could act as possible disease progression and illness relapse biomarker.

The prevalence of metabolic syndrome in our cohort of SMI patients is around 27.7 %. This prevalence is considerably higher compared to that reported in the general Italian population, ranging from 16 % to 18 % (Miccoli et al., 2005; Cicero et al., 2006). However, considering prevalence studies of metabolic syndrome in patients with SMIs, our finding is indeed slightly lower, as documented in a larger meta-analysis which reported a prevalence rate of metabolic syndromes in SMI patients of around 32.6 % (Vancampfort et al., 2017). While studies carried out specifically on the Italian sample, documented prevalence rates ranging from 26 % to 30 %, by confirming our data (Carrà et al., 2014). On the other hand, our finding underlines the need to carefully investigate metabolic alterations and metabolic syndrome in all SMI patients, to early manage and treat comorbid condition, to improve treatment management and clinical outcomes of SMI as well, as comorbid metabolic syndrome has been associated with a more chronic, severe, and progressive SMI clinical course and worst outcomes and prognosis (Penninx and Lange, 2018). Moreover, in our sample, metabolic syndrome did not appear to be associated with specific socio-demographic and/or clinical variables, except with concurrent alcohol consumption. While previous epidemiological studies found that the prevalence of metabolic syndrome usually increased with age, both in the general population and in SMI patients (Hirode and Wong, 2020). In addition, in our sample, it was not found any difference between the prevalence of metabolic syndrome and/or other metabolic parameters depending on the SMI diagnosis. The high prevalence of metabolic syndrome can be explained as a collaterality of psychopharmacotherapy or due to a dysregulated lifestyle, as partly confirmed in our study where metabolic syndrome was associated with alcohol use (Henderson et al., 2015). However, recent findings also suggested that metabolic syndrome could be more likely explained considering a multifactorial nature in which immune-endocrinological (e.g., the hypothalamic-pituitary-adrenal axis, in particular glucocorticoid hormones that have a specific effect on pancreatic β-cells responsible of producing insulin), metabolic (e.g., inflammatory cytokines and the mechanisms of lipogenesis and lipolysis, in particular leptin, interleukin-6, tumor necrosis factor-α and C-reactive protein), genetic (e.g., shared genes involved in cardiovascular, metabolic and psychiatric problems), and the microbiota hypotheses could mutually interact and act in determining the onset and/or maintenance of a metabolic syndrome (Rogers et al., 2016).

Furthermore, in our sample, the prevalence of insulin resistance, by setting 2.5 as the cutoff for the HOMA index, was around 29.7 %. However, the prevalence of insulin resistance in previously published studies is very heterogeneous, due to the choice of the type of HOMA

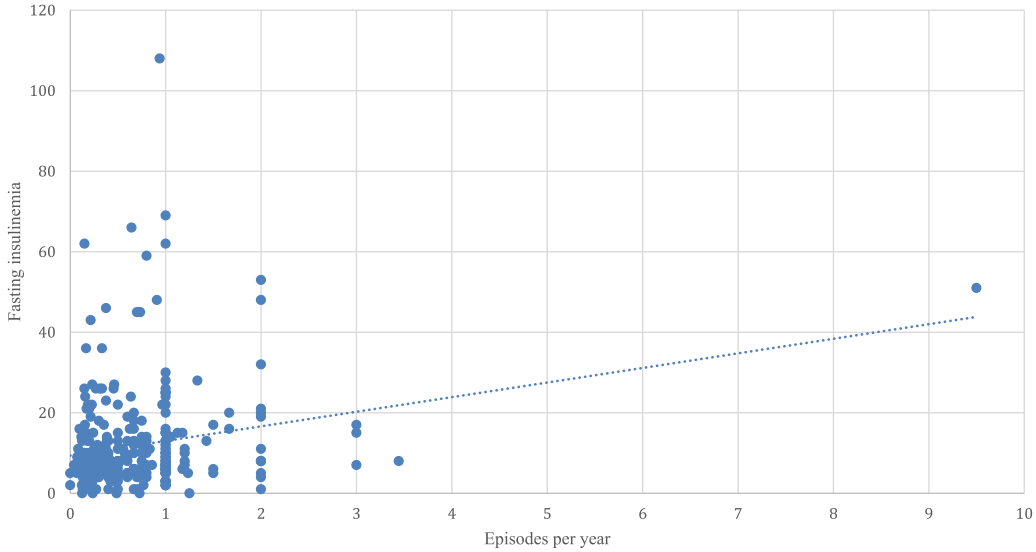

Fig. 1. Scatter plot of fasting insulin levels and episodes per year.

index cut-off. Some studies have shown a prevalence of insulin resistance of around 15.5 % in the general population (Friedrich et al., 2012), 32 % among bipolar disorder patients, and 37.8 % in a sample of patients affected with schizophrenia spectrum disorder (Lin et al., 2020). Therefore, our findings are partially comparable with previously published literature, which reported approximately a double incidence of insulin resistance among SMI patients compared to the general population. Our study clearly found an association between the presence of insulin resistance and the number of acute episodes per year in our cohort of SMI patients. Hence, one could argue that insulinemia could be further investigated as a potential longitudinal biomarker of SMI severity and illness relapse/recurrence. Indeed, our finding appeared to confirm the association between insulin resistance and a more severe SMI course, as already documented for patients affected by bipolar disorder. In our study, it was not found any statistically significant differences in insulin resistance rates between drug-naïve SMI patients and patients with ongoing psychopharmacological treatment. At the same time, drug-naive patients do not seem to differ in other metabolic variables from patients with a longer history of SMI. This data supports the hypothesis that insulin resistance and other dysmetabolism, rather than a side effect of psychotropic medication(s), could represent a metabolic biomarker more likely associated with the natural psychopathological cycle of SMI course (Tomasik et al., 2019; Calkin, 2019). Our data also found that insulin resistance is predictably associated with higher body weight, higher BMI, increased abdominal circumference, higher triglycerides, alcohol consumption and smoking. At the same time, it has been found that insulin resistance is significantly higher in unemployed compared to employed patients, by suggesting that a work impairment (expression of a functional deficit, more likely due to the illness impact of daily life and patient's functioning) could be a possible accelerometer of sedentarily which could determine a higher risk for developing insulin resistance and, hence, worsen SMI severity and illness relapse.

Furthermore, in our study, it has been found higher average platelet levels within the sub-sample of SMI patients affected with schizophrenia spectrum disorders, compared to those with mood disorders. Although the interpretation of this finding could be not easy, platelets have been proposed in other studies as possible markers of illness and relapse, as they are influenced by oxidative stress (Yu et al., 2020). Finally, platelets are involved in dopamine metabolism as they are characterized by dopaminergic receptors on the membrane, so they could play a role in the mechanisms of onset of schizophrenia spectrum disorders (Yu et al., 2020). At the same time, our findings found that drug-naive patients displayed lower eosinophil levels compared to SMI patients with ongoing psychopharmacological treatment, by suggesting a possible role of platelet levels as biomarker for illness severity, particularly for schizophrenia spectrum disorder and for patients under psychopharmacological treatment, as already suggested (Tsamakis et al., 2021). However, the present findings should be furtherly confirmed in larger and longitudinal studies.

Finally, according to the results obtained in regression analyses, insulin appeared to play a role in illness relapses/recurrence among SMI patients. Exacerbations were predicted by higher insulin levels, higher age of onset, a higher number of suicidal attempts and a lower age. While entering in the model only the metabolic variables, SMI relapse was significantly predicted by higher insulin and red blood cell levels. This role of insulin in predicting relapse is in line with data in the literature. For example, it has been shown that depressed patients display higher insulin levels during acute episodes compared to euthymic phases (Fernandes and Berk, 2017). In bipolar patients, the presence of insulin resistance has been found to determine a greater disease severity (Cairns et al., 2018; Miola et al., 2023). At the same time, a relationship was found between insulin and response to antipsychotics and risk of relapse among patients affected with schizophrenia spectrum disorder (Schwarz et al., 2012).

Overall, despite these preliminary and promising findings, our study has several limitations which should be adequately addressed and discussed before generalizing our results. Firstly, as our study aimed to preliminarily evaluate whether there is some interesting research direction to be deepened in the field of biomarker of illness relapse among patients affected by SMI, we performed only a cross-sectional investigation and with a relatively modest sample size. Further longitudinal, larger, and more homogeneously distributed samples in terms of SMI diagnosis to confirm our findings, also controlling for potential confounders (i.e., drug-naive versus type of psychopharmacological medication, and so forth), but also assessing the possible association (if any) between insulin levels and the length of hospitalization, as well as including a longitudinal trajectory of insulin levels at the discharge time as well as during a follow-up period. Secondly, the real-world exploratory design of the study, does not guarantee controlling all other potential confounding biases, in spite of our restrictive exclusion criteria and our adjustments for each of the above-described potential confounders. Thirdly, the use of clinical interviews and questionnaires to collect data on lifestyles and behaviors (e.g. alcohol use, cigarettes smoked etc.) could be subject to recall and self-report bias, affecting the accuracy of collected data. Fourthly, the absence of a control group may also have led to an error in the interpretation of the results and in generalization. Fifthly, measurements of metabolic parameters may vary due to various factors (e.g. acute stress, food intake before blood sampling, and so on), which should be carefully controlled in further confirmatory studies. Sixthly, the presence of other non-psychiatric comorbidities (like thyroid diseases, hypertension etc.) might influence blood tests and not be completely separated from the effects of the SMIs themselves. Seventhly, the use of the GAF scale to assess patients' global function is subjective and may not accurately reflect clinical variations in patients with SMIs. Furthermore, the choice of HOMA index cutoff may not be the most appropriate for all populations and, hence, it may influence the results. Finally, another significant limitation requiring a discussion is the lack of a proxy measure of adrenergic activity during the collection of blood sample of insulinemia, e.g. resting heart rate, considering that all blood samples and measures were collected during the first days of hospitalizations, a period which usually could be more likely associated with higher perceived stress levels for the patient. Therefore, further real-world observational studies should also consider the inclusion of other confounding variables, such as resting heart rate assessment or other proxy markers of adrenergic activity which could influence the insulin levels.

On the other hand, despite the above-mentioned limitations, all laboratory measurements from blood samples were performed at the same time and at the same department with a high sensitivity immunoturbidimetry assay blinded to depression scores, minimizing the risk for differential test results due to different assays or other confounding factors. Furthermore, the study integrated the most up-to-date psychiatric and medical competence possible, ensuring a comprehensive assessment of both the mental and physical health of the patients. The statistical analysis additionally considered confounding variables such as age, gender, and other demographic factors, improving the reliability of the conclusions.

5. Conclusions

In conclusion, our study could provide practical implications for the treatment and management of patients with SMI, emphasizing the importance of monitoring and managing metabolic factors, particularly insulinemia, metabolic syndrome and insulin resistance. Further studies using a longitudinal approach could confirm whether these biomarkers could be useful in longitudinal monitoring and in identifying early illness relapse risk over the time. Indeed, our findings also suggest the need to follow a more integrated approach in the treatment of SMIs, combining both psychiatric and medical interventions, to improve the overall health and functioning of SMI patients. Finally, as this is a relatively unexplored topic, further research directions should be incentivized to identify hypothetical new blood biomarkers of SMI

relapse. These would be crucial for preventing illness relapse, monitoring the effectiveness of therapeutic interventions, and improving clinical outcomes and illness prognosis. Similarly, the current results demonstrate the importance of managing concomitant metabolic factors in patients with SMIs.

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CRediT authorship contribution statement

Michele Fiorani: Writing – original draft, Resources, Project administration, Investigation, Data curation. **Giulio Longo:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis. **Laura Orsolini:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Umberto Volpe:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Conceptualization. **Silvia Bellagamba:** Investigation, Data curation. **Diana Corona:** Data curation. **Brodinela Marpepa:** Data curation. **Eleonora Manfredi:** Investigation, Data curation. **Luciano Cavallo:** Investigation, Data curation.

Declaration of Competing Interest

The authors declare no conflict of interest.

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