

# Prevalence of metabolic syndrome according to the presence of negative symptoms in patients with schizophrenia

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**Background:** Metabolic syndrome (MetS) is one of the primary reasons for increased mortality in patients with schizophrenia. The mechanisms involved in its pathogenesis are not well understood.

**Objective:** To estimate the prevalence of MetS in adult outpatients with schizophrenia according to the presence or absence of negative symptoms.

**Materials and methods:** A retrospective cohort study using electronic medical records was conducted. The Positive and Negative Syndrome Scale negative-symptom factor (N1–N4, N6, G7, and G16) was used as a framework for characterizing negative symptoms. MetS was defined using the National Cholesterol Education Program Adult Treatment Panel III diagnostic criteria. An analysis of covariance model was used for correction, with significance at  $P < 0.05$ .

**Results:** One or more negative symptoms were present in 52.5% of a sample of 1,120 patients (mean age 46.8 years, men 58.4%). Dyslipidemia (48.7%), hypertension (38.2%), and diabetes mellitus (19.3%) were the most frequent comorbidities. The overall prevalence of MetS was 38.6% (95% confidence interval 35.7%–41.5%), and was significantly higher in those patients with negative symptoms (43.9% versus 34.9%,  $P = 0.002$ ). MetS was significantly associated with the presence of negative symptoms, age, and physical comorbidity (odds ratios 1.6, 1.2, and 1.2, respectively;  $P < 0.05$ ).

**Conclusion:** A sedentary lifestyle and lack of physical exercise due to negative symptomatology may contribute to MetS development. Further studies are necessary to confirm this association and the underlying pathophysiological mechanisms.

**Keywords:** cardiovascular risk, metabolic abnormalities, comorbidity, physical illness, schizophrenia, negative symptoms

## Introduction

Schizophrenia is one of the most severe mental disorders, and is among the twenty leading causes of disability worldwide.<sup>1</sup> The mortality rate in patients with schizophrenia is two to three times higher than that expected in the general population, with a reduction in life expectancy of 10–25 years.<sup>2</sup> Increased risk of suicide, an unhealthy lifestyle, poor physical health, and side effects of antipsychotic drugs are the four main reasons associated with excess early mortality in schizophrenia.<sup>3</sup> Natural causes of death include those deriving from cardiovascular events.<sup>4</sup> The high prevalence of cardiovascular risk factors in this population, such as obesity, dyslipidemia, alterations in carbohydrate metabolism, smoking, a sedentary lifestyle, and an unbalanced diet, as well as undesirable effects of antipsychotic drugs, explains the high cardiovascular morbidity and mortality rate in these patients.<sup>5</sup>

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Negative symptoms are a key element of schizophrenia, affecting patients' ability to cope with daily activities and having a negative impact on their quality of life.<sup>6,7</sup> Negative symptoms are relatively common, and account for much of the long-term morbidity and poor functional outcome of patients with schizophrenia.<sup>6,8,9</sup> Despite the introduction of atypical antipsychotics in the 1990s, their clinical management continues to be an unmet need.<sup>10</sup>

Compared with the general population, patients with schizophrenia are twice as likely to suffer from metabolic syndrome (MetS).<sup>11</sup> The prevalence of MetS in patients with schizophrenia varies, ranging between 11% and 69% depending on the methodology used and the study population, although some recent meta-analyses have estimated it to be around 32.5%.<sup>12–15</sup> Late onset, ethnicity, long duration of the illness, smoking, and exposure to antipsychotic drugs have generally been considered risk factors for developing MetS.<sup>11</sup> However, no studies have been conducted to date to assess its prevalence according to the presence of different types of symptomatic domains.

The aim of this study was to analyze the prevalence of MetS and its individual components in a population of outpatients with schizophrenia according to the presence or absence of negative symptoms.

## Materials and methods

### Data source and patients

This was a noninterventive, retrospective, cohort study using electronic medical records held by the health care provider Badalona Serveis Assistencials (BSA). Key inclusion criteria were: age  $\geq 18$  years; a diagnosis of schizophrenia according to *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV-TR criteria; outpatients who required care in 2011; being under antipsychotic treatment; inclusion in the long-term prescription program (with a record of daily dose, time interval, and duration of each treatment administered); and guaranteed regular patient follow-up (presenting two or more health care records in the computer system). Data for these analyses were obtained from an observational study focused on health care-resource utilization and associated costs in patients with schizophrenia from the city of Badalona.<sup>16</sup> The study protocol was approved by the investigational review board of the Hospital Universitari Germans Trias i Pujol (Badalona, Spain).

### Variables and measurement instruments

The seven items of the Positive and Negative Syndrome Scale (PANSS) Marder negative-symptom factor were

used as a framework for characterizing negative symptoms from the database text fields: blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive/apathetic social withdrawal (N4), lack of spontaneity and conversation flow (N6), motor retardation (G7), and active social avoidance (G16).<sup>17,18</sup> The number of chronic diseases (diagnoses), the Charlson Comorbidity Index, and the individual Case-Mix Index, obtained from the Adjusted Clinical Groups (a classification system based on the consumption of health care resources), were used to summarize general comorbidity variables for each patient.<sup>19,20</sup>

The clinical, biochemical and anthropometric parameters analyzed were systolic and diastolic blood pressure (mmHg), body mass index (BMI; kg/m<sup>2</sup>), basal blood glucose (mg/dL), serum triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol (mg/dL), and serum creatinine (mg/dL). The diagnosis of MetS was established when one same individual met three or more of the following components of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) diagnostic criteria: hypertriglyceridemia (fasting triglyceride concentration  $\geq 150$  mg/dL or treatment with triglyceride-lowering agents), dyslipidemia (fasting HDL cholesterol  $< 40$  mg/dL in males and  $< 50$  mg/dL in females), hypertension (systolic and diastolic blood pressure  $\geq 130/85$  mmHg or on antihypertensive medication), hyperglycemia (fasting plasma glucose concentration  $\geq 110$  mg/dL or on glucose-lowering drug treatment or a previous diagnosis of diabetes), and abdominal obesity (waist circumference  $> 102$  cm in males and  $> 88$  cm in females).<sup>21</sup> In our study, the waist-circumference measurement was replaced by the BMI. A BMI  $\geq 28.8$  kg/m<sup>2</sup> is considered to be equivalent to abdominal adiposity by different authors.<sup>22</sup>

### Statistical analysis

Patients were distributed into two groups according to the presence or absence of negative symptoms: group 1 for patients presenting one or more negative symptoms, and group 2 for patients without negative symptoms.

A descriptive univariate statistical analysis was performed with mean values, standard deviation (SD), and 95% confidence intervals (CIs), verifying normal distribution using the Kolmogorov–Smirnov test. The bivariate analysis included analysis of variance, the  $\chi^2$  test and Pearson's linear correlation. Logistic regression analysis was performed to obtain the variables associated with the patient profile (negative symptoms) and MetS, with the "Enter" method (Wald

statistic). SPSS version 19 was used, establishing statistical significance for  $P$ -values  $<0.05$ .

## Results

Of the initial selection of 88,798 subjects aged  $\geq 18$  years, 1,305 patients presented a diagnosis of schizophrenia and 1,120 were finally analyzed (Figure 1). Major sociodemographic and clinical characteristics of the patients are shown in Table 1. The mean age was 46.8 (SD 13.8) years, and 58.4% were male; 52.5% of the patients presented one or more negative symptoms ( $n=588$ , 95% CI 49.6%–55.4%). The prevalence of individual negative symptoms ranged from 26.1% (G16, active social avoidance) to 60.5% (N4, passive/apathetic social withdrawal). Only 27% of the patients simultaneously presented three or more negative symptoms.

Quetiapine (32.3%), risperidone (20.3%), and olanzapine (16.4%) were the most common antipsychotic drugs administered. Time on antipsychotic drugs since diagnosis was 15.5 (SD 15.3) years, slightly longer in patients with negative symptoms (16.5 versus 14.9,  $P=0.091$ ). Polypharmacy was common. The mean number of drugs per patient was 3.1 (SD 1.9), and was found to be significantly greater in group 1 (3.6 versus 2.6 for group 1 and group 2, respectively;  $P=0.002$ ).

Dyslipidemia (48.7%), hypertension (38.2%), and diabetes mellitus (19.3%) were the most frequent comorbid conditions. The total mean number of comorbid diagnoses was greater in group 1 than in group 2 (8.5 and 7.0, respectively;  $P<0.001$ ). Table 2 shows the prevalence of the main cardiovascular risk factors and MetS in the total sample. The overall prevalence of MetS was 38.6% (95% CI 35.7%–41.5%), and was significantly higher in patients with negative symptoms (43.9% versus 34.9%,  $P=0.002$ ). Three or more components of MetS were found in 44% of the sample. MetS was associated with the presence of negative symptoms (odds ratio [OR] 1.6, 95% CI 1.3–2.0), age (OR 1.2, 95% CI 1.1–1.4), and physical comorbidity (resource-utilization bands; OR 1.2, 95% CI 1.1–1.3;  $P<0.05$ ).

## Discussion

MetS is one of the primary reasons for increased mortality in patients with schizophrenia. In recent years, numerous studies have been published on the prevalence of MetS in different clinical settings and using several methodological approaches, presenting figures ranging from 11% to 69%.<sup>11</sup> In five studies previously conducted in Spain, the prevalence of MetS in patients with schizophrenia was 19%–36.8% using the NCEP-ATP III diagnostic criteria.<sup>13,14,23–25</sup> Gutiérrez-Rojas et al recently published a new study in which the



**Figure 1** Study diagram.

**Notes:** \*Patients were excluded for the following reasons: missing or inconsistent data ( $n=33$ ; 17.8%), lost to follow-up ( $n=45$ ; 24.3%), moved to other areas ( $n=37$ ; 20.0%), and other reasons ( $n=70$ ; 37.9%).

**Table 1** Baseline characteristics of the study series

	Group 1 n=588	Group 2 n=532	Total n=1,120	P-value
<b>Sociodemographic characteristics</b>				
Mean age, years	47.3 (12.2)	46.5 (14.8)	46.8 (13.8)	0.351
<b>Range</b>				
18–44 years	40.0%	47.9%	44.6%	
45–64 years	57.0%	43.2%	48.8%	
65–74 years	2.8%	8.6%	6.3%	
≥75 years	0.2%	0.3%	0.3%	<0.001
Sex, male	67.7%	52.0%	58.4%	<0.001
<b>Overall comorbidity</b>				
Mean number of comorbidities	8.5 (4.7)	7.0 (4.1)	7.6 (4.4)	<0.001
Mean Charlson Index	0.5 (0.8)	0.4 (0.7)	0.5 (0.8)	0.130
Mean RUBs	3.1 (0.6)	3.0 (0.7)	3.0 (0.7)	0.098
<b>Comorbid diagnoses</b>				
Hypertension	44.1%	34.1%	38.2%	0.001
Diabetes mellitus	22.5%	17.1%	19.3%	0.024
Dyslipidemia	54.1%	44.9%	48.7%	0.002
Obesity	28.4%	18.7%	22.7%	0.001
Active smoking	28.4%	30.5%	29.6%	0.443
Alcoholism	7.2%	5.4%	6.2%	0.227
Vascular events	19.0%	16.3%	17.4%	0.245
Bronchial asthma	8.7%	5.6%	6.9%	0.041
COPD	5.9%	3.6%	4.6%	0.073
Neuropathies	3.9%	3.0%	3.4%	0.409
Disease duration, mean, years	19.9	18.2	18.9	0.093
Time under antipsychotic treatment, mean, years	16.5	14.9	15.5	0.091
Number of CNS-active drugs, mean	3.6	2.6	3.1	0.002
<b>Antipsychotic drugs</b>				
Quetiapine	34.5%	30.8%	32.3%	0.194
Risperidone	18.1%	21.8%	20.3%	0.131
Olanzapine	13.8%	18.3%	16.4%	0.046

**Notes:** Group 1, presence of one or more negative symptoms; group 2, absence of negative symptoms.

**Abbreviations:** RUBs, resource-utilization bands; COPD, chronic obstructive pulmonary disease; CNS, central nervous system.

prevalence was found to be 59.5% in a sample of overweight patients defined by a BMI >25 kg/m<sup>2</sup>.<sup>26</sup>

Our study once again confirms the high prevalence of MetS in a population of adult outpatients with schizophrenia (38.6%). However, it also found that the prevalence of MetS was associated with the presence of negative symptoms (OR 1.6, 95% CI 1.3–2.0).

Negative symptoms, such as blunt affect, lack of motivation, asociality, and impoverished speech are better predictors of functioning than positive symptoms, and are often associated with a poor response to available pharmacological treatments.<sup>6</sup> In our study, 52% of the patients presented one or more negative symptoms, the most common being passive/apathetic social withdrawal and emotional withdrawal.

It has been suggested that advanced-age patients with long-standing disease, patients with certain comorbidities, and those taking atypical antipsychotic drugs like clozapine and olanzapine have a greater risk of suffering from MetS.<sup>15,27,28</sup> However, no

studies have yet been conducted to assess its prevalence according to the presence of different types of symptom domains.

The underlying pathophysiological mechanisms involved in the pathogenesis of MetS in schizophrenia are not well understood.<sup>15</sup> A sedentary lifestyle and lack of physical exercise due to decreased spontaneity and drive, as well as other negative symptoms, may contribute to a higher prevalence of MetS. The presence of negative symptoms may also reduce help-seeking and physical health controls, and has recently been negatively correlated with BMI and positively correlated with HDL cholesterol in a sample of 372 chronic inpatients under antipsychotic treatment for more than 2 years. The authors suggested that patients with negative syndrome may have a different lipid pathophysiology in comparison with those who are less severe in this domain.<sup>29</sup> Most evidence has emphasized the importance of extrinsic factors (calorie intake, lifestyle, antipsychotic medication) in its development, but the involvement of genetic factors is also supported.<sup>11</sup>

**Table 2** Prevalence of the main cardiovascular risk factors and metabolic syndrome

	Group 1 n=588	Group 2 n=532	Total n=1,120	P-value
<b>CVRFs, mean (SD)</b>				
Systolic blood pressure, mmHg	125.1 (16.5)	125.0 (17.6)	125.0 (17.2)	0.935
Diastolic blood pressure, mmHg	74.7 (10.8)	74.1 (11.0)	74.3 (10.9)	0.362
Body mass index, kg/m <sup>2</sup>	29.3 (5.6)	28.6 (5.7)	28.9 (5.7)	0.049
Glucose, mg/dL	102.1 (32.8)	99.7 (31.8)	100.7 (32.2)	0.229
Triglycerides, mg/dL	134.7 (100.9)	130.1 (74.0)	132.0 (86.3)	0.394
Total cholesterol, mg/dL	202.3 (44.1)	194.5 (40.8)	197.8 (42.3)	0.003
HDLc, mg/dL	54.8 (15.4)	52.4 (16.1)	53.4 (15.8)	0.015
LDLc, mg/dL	121.5 (39.0)	116.8 (34.3)	118.8 (36.4)	0.039
Serum creatinine, mg/dL	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)	0.851
<b>Metabolic syndrome</b>				
Prevalence*	43.9%	34.9%	38.6%	0.002
<b>Components</b>				
BMI >28.8 kg/m <sup>2</sup>	50.2%	42.4%	45.6%	0.010
BP >130/85 mmHg (or treatment)	49.1%	42.0%	44.9%	0.018
Triglycerides >150 mg/dL (or treatment)	27.1%	24.3%	25.4%	0.298
Fasting blood glucose >110 mg/dL	22.7%	19.2%	20.6%	0.152
HDLc <40 (men) or <50 (women) mg/dL	19.4%	20.7%	20.2%	0.605
<b>Number of components</b>				
1	20.7%	23.9%	22.6%	
2	22.5%	21.8%	22.1%	
3	21.6%	19.0%	20.1%	
4	15.9%	12.4%	13.8%	
5	6.3%	3.5%	4.6%	0.006

**Notes:** \*Defined according to the modified National Cholesterol Education Program Adult Treatment Panel III criteria. Group 1, presence of one or more negative symptoms; group 2, absence of negative symptoms.

**Abbreviations:** CVRFs, cardiovascular risk factors; BMI, body mass index; BP, blood pressure; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; SD, standard deviation.

Our study has several limitations inherent to research based on population databases. The PANSS is not routinely completed in mental health services. Collecting negative symptoms from open text in the medical records may be associated with an underestimation of the true prevalence of these symptoms, due to the underregistration of them by the clinicians. In addition, the most severe cases were possibly not included in the study because they are usually not seen as outpatients. Furthermore, patients with subclinical or severe forms were not identified, as they were not all seen as outpatients and/or treatment adherence or other variables, such as socioeconomic levels, were not evaluated.

Future research regarding schizophrenic patients with MetS should focus on the clinical impact, longitudinal follow-up to understand the factors that contribute to developing MetS, the pathophysiology of schizophrenia, and its impact on quality of life.<sup>15</sup> Despite increased cardio-metabolic risk in patients with mental disorders receiving antipsychotic drugs, metabolic monitoring is low in routine clinical practice.<sup>30</sup> It is important to identify high-risk patients and educate them about preventive measures.<sup>31</sup> A sensible

approach when prescribing antipsychotic drugs is also advisable, as well as reviewing the medication regularly in order to maintain a balance between adequate symptomatic control and the development of metabolic abnormalities. Moreover, one of the most important objectives of pharmacological research should be to develop new antipsychotic agents with reduced associated risk, fast action, greater effect on negative, affective, and cognitive symptoms, and improved rate of recurrence, along with reduction or disappearance of cumulative comorbidity.

In conclusion, the prevalence of MetS in patients with schizophrenia is high. MetS was associated with age, comorbidity, and the presence of negative symptoms. Due to the proven impact that negative symptoms have on the subjective well-being, functioning, and quality of life of patients, and probably also on their predisposition to develop metabolic disorders, it is essential for clinicians to detect them early and to decide on the best-possible therapeutic approach. Further studies need to be undertaken in order to replicate the findings of this association, and to gain a better understanding of the underlying mechanisms.



## Disclosure

This study was funded by Roche Farma, Spain. ASM is an employee of BSA, the health care provider that owns the database that was the subject of this study. JM and ERB are employees of Roche Farma. RNA has no conflicts of interests to declare.

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