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Clinical and metabolic associations of obesity and body mass index in antipsychotic-naïve first-episode schizophrenia patients and nonadherent chronic patients

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Abstract

Aim: We investigated the association between obesity and body mass index (BMI) with Positive and Negative Syndrome Scale (PANSS) psychopathology, age at disease onset, and parameters linked to the metabolic syndrome (fasting plasma lipid and glucose levels), among antipsychotic-naïve first-episode schizophrenia (AN-FES) patients and nonadherent chronic schizophrenia individuals.

Patients and methods: We recruited a total of 187 AN-FES patients or nonadherent chronic individuals who were treated at the Department of Psychiatry in the University Hospital Centre Sestre milosrdnice, Zagreb, Croatia, in 2015–2021. Clinical and anthropometric data together with plasma lipid and glucose parameters were collected immediately after patients' admission to the hospital. Patients were classified as obese with body mass index (BMI) ≥ 30, or as non-obese if overweight (BMI: 25 – 29.9) or of normal body weight (BMI: 18.5 – 24.9).

Results: After controlling for the possible confounders we found that only BMI significantly predicted clinical and metabolic variables. Among AN-FES patients, higher BMI values predicted lower levels of HDL cholesterol (HDL-c), and higher ratios for LDL cholesterol (LDL-c)/HDL-c and triglyceride/HDL-c, while among nonadherent individuals, higher BMI values predicted higher number of psychotic episodes, and lower PANSS general psychopathology scores. The contribution of BMI ranged from approximately 5.8% to 29.4%, with the lowest contribution observed for number of psychotic episodes, and the highest contribution for the LDL-c/HDL-c ratio.

Conclusion: Higher BMI contributes to an increased risk for dyslipidemia among AN-FES patients and to the higher number of psychotic episodes, and less severe clinical psychopathology among nonadherent chronic schizophrenia individuals.

body mass index; medication adherence; obesity; schizophrenia.

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INTRODUCTION

The prevalence of obesity in schizophrenia is two to three-fold greater compared with the general population [1,2]. Elevated obesity rates have

been reported among chronic patients receiving antipsychotic treatment as well as patients suffering a first schizophrenic episode [1,3]. It is important to elucidate the potential influence of obesity on metabolic parameters and the clinical presentation of schizophrenia among unmedicated patients, for several reasons. The use of antipsychotic medications (specifically, second-generation antipsychotics) is reportedly associated with weight gain, dyslipidemia, diabetes, and metabolic syndrome [4,5]. Metabolic abnormalities are a major contributor to cardiovascular diseases, which are consistently associated with excess morbidity and mortality among schizophrenia individuals [6]. Furthemore, antipsychotic-induced weight gain is associated with clinical improvement with antipsychotic treatment [7,8].

To date, several studies conducted predominantly in the Chinese population have investigated the potential associations between obesity, metabolic syndrome-related parameters, and clinical presentation of schizophrenia among chronic patients treated with antipsychotics [9-14]. Their findings indicate that obesity and higher BMI are associated with an elevated risk for dyslipidemia and diabetes but with less severe psychotic symptoms, as measured using Positive and Negative Syndrome Scale (PANSS) [9-14]. Furthemore, obesity and higher BMI decrease as well as increase cognitive functions [9,14] and are not correlated with age at schizophrenia onset [10-14]. On the other hand, data on the effect of obesity on the number of lifetime hospitalizations due to psychotic episodes are limited to a single study conducted in a United States population [10]. In that study, it was observed that patients with schizophrenia, schizoaffective, or bipolar disorder with BMI ≥ 25 had a greater number of hospitalizations compared with individuals with BMI < 25.

In one study conducted in the Spanish population the researchers investigated the possible association between overweight and obesity and several variables of clinical interest among patients with schizophrenia and bipolar disorder taking psychotropic medications [15]. They observed that obesity was associated with lower total PANSS scores and female sex among schizophrenia patients while overweight was associated with earlier disease symptoms, the use of mood-stabilizing medications and nonsmoking status among bipolar disorder individuals. However, they did not investigate the association between obesity and metabolic syndrome-related parameters.

We recently investigated the potential contribution of obesity to metabolic syndrome-related parameters (plasma lipid and glucose levels), PANSS scores and age at schizophrenia onset among chronic schizophrenia patients taking antipsychotic medications, from the Croatian population [16]. While we did not find evidence that obesity was associated with PANSS psychopathology or age at disease onset, we observed that obesity affected metabolic parameters in a gender-specific manner. Specifically, obese males exhibited higher plasma triglyceride levels compared with nonobese, while obese females had higher total cholesterol and LDL cholesterol (LDL-c) levels, compared with nonobese.

Only sparse data are available regarding the potential influence of obesity on clinical presentation of schizophrenia and metabolic parameters among unmedicated patients. In one study among antipsychotic-naïve first-episode schizophrenia (AN-FES) patients from the Chinese population the researchers found that obesity and higher BMI values were associated with higher plasma lipid levels. In contrast to the reports on chronic patients taking antipsychotic medications, they observed more severe PANSS psychopathology among patients with higher BMI, revealing that patients with higher BMI scored higher for positive symptom scores and total symptom scores, compared with those with lower BMI. Similar to other previous studies, they did not find any significant association between obesity and age of disease onset [17].

Patients who are nonadherent to antipsychotic medications may represent another model group of unmedicated schizophrenia patients in whom to study the effects of obesity on clinical psychopathology and metabolic parameters. A systematic review describes a high estimated prevalence (50%) of antipsychotic medication nonadherence among patients with chronic schizophrenia [18,19]. Additionally, higher BMI and distress from weight gain are reportedly associated with increased nonadherence to antipsychotics [1,20]. However, to our knowledge, no studies have examined the potential influence of obesi-

ty on clinical presentation and metabolic parameters among nonadherent schizophrenia patients.

In this study we aimed to investigate the association between obesity and BMI with PANSS psychopathology (as assessed using the PANSS scores and PANSS factors), age at disease onset, and parameters linked to the metabolic syndrome (fasting plasma lipid and glucose levels), among AN-FES patients and nonadherent chronic schizophrenia patients. Furthermore, we aimed to examine whether obesity and BMI might be associated with the number of psychotic episodes among nonadherent chronic patients.

Patients and methods

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Clinical Hospital Center Rijeka, Rijeka (protocol code: 003-05/20-1/82, number: 2170-29-02/1-20-2), Ethics Committee of Medical Faculty, University of Rijeka, Rijeka (protocol code: 003-08/20-01/15, number: 2170-24-09-8-20-2), and Ethics Committee of Clinical Hospital Center Sestre Milosrdnice, Zagreb (protocol code: 003-06/20-03/013, number: 251-29-11-20-01-5).

We recruited a total of 187 AN-FES patients or nonadherent chronic schizophrenia individuals who were treated at the Department of Psychiatry in the University Hospital Centre Sestre milosrdnice, Zagreb, Croatia, in 2015–2021. Table 1 presents patients' characteristics. The inclusion criteria were (1) Croatian citizenry; (2) age between 18 and 60 years; and (3) a confirmed diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria [21]. The exclusion criteria were (1) a history of neurological disorders that might affect cognitive functions (i.e., head injury, Parkinson's disease, Alzheimer disease); (2) current pregnancy or lactation, or history of pregnancy in the past 12 months; and (3) BMI within the underweight range (< 18.5).

AN-FES patients had never previously been treated with antipsychotic medications. Nonadherent chronic patients were—according to auto-anamnestic and hetero-anamnestic information—non-compliant with their antipsychotic medication usage, or had been off antipsychotic depot injections for at least 1 month. Mean age at first hospitalization at which the diagnosis of schizophrenia was used has been considered to approximately match the age of onset of the disease. PANSS data were recorded within 24 hours after admission to the hospital [22]. We divided the PANSS subscales into the following five symptom dimensions (factors): positive (P1, P3, P6, and G9), negative (N2, N3, N4, N6, and N7), excitement (P4, P7, and G1), depression (G2, G3, and G6), and cognitive (G10 and G12) [23-25].

Height and weight were measured using standardized procedures. BMI was calculated as weight (in kg) divided by height squared (m^2). Patients were classified as obese with body mass index (BMI) values ≥ 30, or as non-obese if overweight (BMI: 25 – 29.9) or of normal body weight (BMI: 18.5 – 24.9) [26,27].

After an overnight fast, plasma total cholesterol, LDL cholesterol, HDL cholesterol (HDL-c), triglyceride, and glucose levels were determined, using an Abbott Architect c8000 analyzer. The following values were considered elevated: total cholesterol > 5.0 mmol/L, LDL-c > 3.0 mmol/L, triglycerides > 2.0 mmol/L, and glucose > 6.1 mmol/L; while HDL-c < 1.0 mmol/L was considered decreased [28].

Statistical analysis

Statistical analyses were performed using Statistica for Windows, version 13 (StatSoft, Inc., Tulsa, OK, USA). A P value of less than 0.05 ($P < 0.05$) was considered significant. To compare characteristics between different patient groups (AN-FES patients vs. nonadherent chronic schizophrenia individuals, and obese vs. nonobese), we used one-way analysis of variance (ANOVA) or chi-square (χ^2) tests. Correlations of BMI and patients' characteristics were examined using Pearson correlation coefficients. To further explore variables significantly associated with obesity and/or BMI we applied multiple regression analyses. Regression analyses were controlled for the possible effects of sex, smoking, obesity, and BMI for age at disease onset as well as age and illness duration for number of psychotic episodes, PANSS psychopathology and plasma lipid and glucose profiles (29-

36). We also controlled for the effects of antilipemic and antidiabetic medications and type of previously described antipsychotic medications (e.g., clozapine and olanzapine) when analyzing lipid and glucose profiles [4,5]. Significant effects ($P < 0.05$) were adjusted using Bonferroni correction.

RESULTS

The recruited patients included 67 AN-FES patients, of whom 6 (9.0%) were obese, and 120 nonadherent chronic schizophrenia individuals, of whom 15 (12.5%) were obese (Table 1 and Table 2). Data on intergroup comparisons (e.g., obese AN-FES patients vs. obese nonadherent chronic individuals and nonobese AN-FES patients vs. nonobese nonadherent chronic individuals) are available upon request. Compared with the AN-FES, the obese AN-FES patients scored significantly lower for depression factor (7.2 ± 1.9 vs. 10.0 ± 2.6, $P = 0.027$) and higher for excitement factor (9.8 ± 1.5 vs. 7.5 ± 2.5, $P = 0.030$); had significantly higher ratios for LDL-c/HDL-c (3.7 ± 2.1 vs. 2.2 ± 0.7, $P < 0.048$), and significantly higher glucose levels (5.7 ± 0.6 vs. 5.1 ± 0.7, $P = 0.034$). Compared with the nonobese nonadherent, obese nonadherent chronic individuals manifested significantly higher numbers of psychotic episodes (4.8 ± 1.7 vs. 3.8 ± 1.5, $P = 0.036$), scored significantly lower for total symptom score (92.3 ± 16.6 vs. 101.3 ± 17.0, $P = 0.049$) and positive factor (10.5 ± 3.2 vs. 13.0 ± 4.3, $P = 0.032$); experienced significantly lower HDL-c levels (1.0 ± 0.3 vs. 1.3 ± 0.3, $P = 0.003$), and significantly higher ratios for LDL-c/HDL-c (3.1 ± 1.1 vs. 2.6 ± 1.1, $P = 0.043$) and triglycerides/HDL-c (1.7 ± 1.1 vs. 1.3 ± 1.2, $P = 0.038$) (Table 2).

Table 1. Patients' characteristics

	Antipsychotic-naïve first-episode patients (N = 67)	Nonadherent chronic patients (N = 120)	*P*
Age, years	29.0 ± 10.0	43.3 ± 14.0	**< 0.001**
Males/females	42/25	56/64	**0.035**
Nonobese/obese	61/6	105/15	0.461
Age of onset, years	28.5 ± 10.0	28.9 ± 11.4	0.799
Number of psychotic episodes	-	3.9 1.6	**-**
Illness duration	0.5 ± 0.9	14.4 ± 12.0	**< 0.001**
Smokers (yes/no)	37/30	62/58	0.640
Other psychoactive substance users (yes/no)	10/57	14/106	0.522
Somatic comorbidities (yes/no)			
Cardiovascular	2/65	8/112	0.283
Diabetes	0/67	7/113	0.052
Other	5/62	9/111	0.993
PANSS positive symptom score	22.8 ± 5.7	22.8 ± 6.7	0.952
PANSS negative symptom score	26.6 ± 7.8	27.1 ± 7.7	0.660
PANSS general psychopathology score	51.5 ± 10.1	50.8 ± 8.2	0.587
PANSS total symptom score	100.9 ± 20.0	100.7 ± 17.4	0.930
PANSS positive factor	13.6 ± 3.5	12.8 ± 4.3	0.231
PANSS negative factor	13.9 ± 6.1	13.8 ± 5.8	0.883
PANSS depression factor	9.8 ± 2.7	9.5 ± 3.1	0.570
PANSS excitement factor	7.7 ± 2.4	8.8 ± 2.8	**0.023**
PANSS cognitive factor	5.8 ± 2.3	5.9 ± 2.0	0.969

Total cholesterol (mmol/L)	4.4 ± 0.8	5.0 ± 1.1	**< 0.001**
LDL cholesterol (mmol/L)	2.6 ± 0.7	3.1 ± 0.9	**< 0.001**
HDL cholesterol (mmol/L)	1.2 ± 0.3	1.2 ± 0.3	0.463
Triglycerides (mmol/L)	1.3 ± 0.7	1.4 ± 1.0	0.364
LDL/HDL	2.3 ± 0.9	2.7 ± 1.1	**0.026**
Triglycerides/HDL	1.3 ± 1.1	1.3 ± 1.2	0.860
Glucose (mmol/L)	5.1 ± 0.7	5.7 ± 1.5	**0.003**
Body mass index (kg/m^2)	23.4 ± 3.9	25.3 ± 4.6	**0.005**

Differences were compared using one-way ANOVA, with the exceptions of sex and smoking status, for which the $\chi 2$ test was used.

PANSS, Positive and Negative Syndrome Scale; bold type, $P < 0.05$

Table 2. Patients' characteristics according to obesity

	Antipsychotic-naïve first-episode patients			Nonadherent chronic patients		
	Nonobese (N = 61)	Obese (N = 6)	*P*	Nonobese (N = 105)	Obese (N = 15)	*P*
Age, years	28.0 ± 8.4	38.8 ± 19.7	**0.011**	43.7 ± 14.0	41.0 ± 14.0	0.481
Sex (males/females)	39/22	4/2	0.894	49/56	9/6	0.333
Age of onset, years	27.6 ± 8.4	38.2 ± 19.8	**0.013**	29.5 ± 11.8	24.8 ± 7.0	0.139
Number of psychotic episodes	-	-	-	3.8 ± 1.5	4.8 ± 1.7	**0.026**
PANSS positive symptom score	22.9 ± 5.6	22.5 ± 6.1	0.868	23.1 ± 6.7	20.1 ± 6.0	0.091
PANSS negative symptom score	27.3 ± 7.6	21.5 ± 7.0	0.077	27.1 ± 7.4	25.1 ± 9.0	0.335
PANSS general psychopathology score	51.9 ± 10.2	47.2 ± 5.6	0.266	51.0 ± 8.1	46.9 ± 6.8	0.062
PANSS total symptom score	102.1 ± 20.0	91.2 ± 10.7	0.192	101.3 ± 17.0	92.3 ± 16.6	0.056
PANSS positive factor	13.5 ± 3.5	14.4 ± 3.0	0.599	13.0 ± 4.3	10.5 ± 3.2	**0.032**
PANSS negative factor	14.2 ± 6.1	11.2 ± 5.7	0.305	13.6 ± 5.5	13.2 ± 5.7	0.816
PANSS depression factor	10.0 2.6	7.2 ± 1.9	**0.029**	9.5 ± 3.1	9.2 ± 2.2	0.746
PANSS excitement factor	7.5 ± 2.5	9.8 ± 1.5	0.050	9.0 ± 2.7	7.9 ± 3.2	0.174
PANSS cognitive factor	5.9 ± 2.4	5.8 ± 0.4	0.937	6.0 ± 2.0	4.9 ± 1.8	0.053
Total cholesterol (mmol/L)	4.3 0.8	4.7 ± 1.2	0.264	5.0 ± 1.2	4.7 ± 0.6	0.277
LDL cholesterol (mmol/L)	2.5 ± 0.6	3.0 ± 0.9	0.123	3.1 ± 1.0	3.0 ± 0.6	0.584
HDL cholesterol (mmol/L)	1.2 ± 0.3	1.0 ± 0.5	0.112	1.3 ± 0.3	1.0 ± 0.3	**0.016**
Triglycerides (mmol/L)	1.3 ± 0.7	1.8 ± 0.8	0.151	1.4 ± 1.0	1.5 ± 0.6	0.744
LDL/HDL	2.2 ± 0.7	3.7 ± 2.1	**< 0.001**	2.6 ± 1.1	3.1 ± 1.1	0.085
Triglycerides/HDL	1.2 ± 0.9	2.6 ± 2.3	**0.004**	1.3 ± 1.2	1.7 ± 1.1	0.216
Glucose (mmol/L)	5.1 ± 0.7	5.7 ± 0.6	**0.041**	5.7 ± 1.5	5.9 ± 2.1	0.632
Body mass index (kg/m^2)	22.5 ± 3.0	31.8 ± 1.4	**< 0.001**	24.0 ± 3.1	34.2 ± 3.4	**< 0.001**

Differences were compared using one-way ANOVA, with the exception of sex

PANSS, Positive and Negative Syndrome Scale; bold type, $P < 0.05$

Among both AN-FES patients and nonadherent chronic individuals, Pearson correlation coefficients indicated significant negative correlations between BMI values and sex (r = –0.32,

$P = 0.008$ and r = –0.24, $P = 0.008$) as well as significant negative correlations between BMI and HDL-c levels (r = –0.49, $P < 0.001$ and r = –0.26, $P = 0.004$). Negative correlation coefficients for sex indicate lower BMI among female patients. Among AN-FES patients, BMI positively correlated with triglyceride levels (r = 0.40, $P = 0.001$), ratios for LDL-c/HDL-c (r = 0.54, $P < 0.001$) and triglyceride/HDL-c (r = 0.50, $P < 0.001$), and glucose levels (r = 0.28, $P = 0.020$). Furthermore, among nonadherent individuals, BMI positively correlated with number of psychotic episodes (r = 0.20, $P = 0.028$) and negatively with PANSS general psychopathology scores (r = –0.27, $P = 0.003$), PANSS total symptom scores (r = –0.21, $P = 0.019$), and PANSS cognitive factor (r = –0.19, $P = 0.035$) (Table 3).

Table 3. Pearson correlation coefficients and P values for patients' characteristics according to body mass index

	Antipsychotic-naïve first-episode patients (N = 67)	Nonadherent chronic patients (N = 120)
Age	r = 0.21; $P = 0.077$	r = –0.13; $P = 0.179$
Gender (Males/females)	r = –0.32; **$P = 0.008$**	r = –0.24; **$P = 0.008$**
Age of onset	r = 0.20, $P = 0.091$	r = –0.17; $P = 0.075$
Number of psychotic episodes	-	r = 0.20; **$P = 0.028$**
PANSS positive symptom score	r = –0.09; $P = 0.468$	r= –0.11; $P = 0.228$
PANSS negative symptom score	r = –0.17; $P = 0.172$	r = –0.10; $P = 0.234$
PANSS general psychopathology score	r = –0.13; $P = 0.309$	r = –0.27; **$P = 0.003$**
PANSS total symptom score	r = –0.16; $P = 0.209$	r = –0.21; **$P = 0.019$**
PANSS positive factor	r = –0.03, $P = 0.821$	r = –0.17; $P = 0.059$
PANSS negative factor	r = –0.07; $P = 0.657$	r = –0.00; $P = 0.970$
PANSS depression factor	r = –0.19; $P = 0.186$	r = –0.03; $P = 0.667$
PANSS excitement factor	r = 0.20; $P = 0.169$	r = –0.11; $P = 0.255$
PANSS cognitive factor	r = –0.07, $P = 0.620$	r = –0.19; **$P = 0.035$**
Total cholesterol (mmol/L)	r = 0.11; $P = 0.368$	r = –0.09; $P = 0.293$
LDL cholesterol (mmol/L)	r = 0.19; $P = 0.125$	r = –0.07; $P = 0.462$
HDL cholesterol (mmol/L)	r = –0.49; **$P < 0.001$**	r = –0.26; **$P = 0.004$**
Triglycerides (mmol/L)	r = 0.40; **$P = 0.001$**	r = 0.11; $P = 0.226$
LDL/HDL	r = 0.54; **$P < 0.001$**	r = 0.13; $P = 0.140$
Triglycerides/HDL	r = 0.50; **$P < 0.001$**	r = 0.16; $P = 0.072$
Glucose (mmol/L)	r = 0.28; **$P = 0.020$**	r = 0.01; $P = 0.895$

PANSS, Positive and Negative Syndrome Scale; bold type, $P < 0.05$

Multiple regression analyses revealed that only BMI significantly predicted investigated variables. Among AN-FES patients, the BMI values predicted levels of HDL-c ($\beta = –0.50$, $P = 0.001$), and ratios for LDL-c/HDL-c ($\beta = 0.54$, $P < 0.001$) and triglyceride/HDL-c ($\beta = 0.63$, $P = 0.010$). Furthermore, among nonadherent chronic individuals, the BMI values predicted the number of psychotic episodes ($\beta = 0.24$, $P = 0.008$), and PANSS general psychopathology scores ($\beta = –0.29$, $P = 0.002$). The contribution of BMI ranged from approximately 5.8% to 29.4%, with the lowest contribution observed for number of psychotic episodes (R^2 change = 0.058), and the highest contribution for the LDL-c/HDL-c ratio (R^2 change = 0.294) (Table 4).

Table 4. Clinical and metabolic parameters predicted by body mass index [a,b]

Antipsychotic-naïve first-episode patients (N = 67)				
	β	R^2 change	F[c]	*P*
HDL cholesterol	–0.41	0.246	21.32	**< 0.001**
LDL cholesterol/HDL cholesterol	0.48	0.294	27.10	**< 0.001**
Triglycerides/HDL cholesterol	0.34	0.252	21.94	**< 0.001**
Nonadherent chronic patients (N = 120)				
	β	R^2 change	F[c]	*P*
Number of psychotic episodes	0.24	0.058	7.24	**0.008**
PANSS general psychopathology score	–0.29	0.085	10.12	**0.002**

PANSS, Positive and Negative Syndrome Scale; bold type, $P < 0.05$

[a,b] Candidate predictor variables for age at disease onset included sex, smoking, obesity and BMI; candidate predictor variables for lipid and glucose profiles, number of psychotic episodes, and PANSS psychopathology included age, illness duration, sex, smoking, obesity, and body mass index; lipid and glucose profiles were also controlled for the effects of antilipemic and antidiabetic medications and type of previously described antipsychotic medications (e.g., clozapine and olanzapine)

[c] Criteria used for predictor variable's entry or removal: F to enter = 3, F to remove = 1

DISCUSSION

After controlling for the possible confounders we found that only BMI significantly predicted clinical and metabolic variables. Specifically, among AN-FES patients, higher BMI values predicted lower levels of HDL-c, and higher ratios for LDL-c/HDL-c and triglyceride/HDL-c, while among nonadherent chronic schizophrenia individuals, higher BMI values predicted higher number of psychotic episodes, and lower PANSS general psychopathology scores (Table 4). Therefore, our results indicate that AN-FES patients and nonadherent chronic patients differed in the effects of BMI. Although nonadherent chronic individuals were off antipsychotic treatment at the time of assessment, it cannot be excluded that prior antipsychotic treatment was cumulatively protective regarding PANSS psychopathology during the variable illness duration. At the same time, the lack of prior exposure to antipsychotics among AN-FES patients might have more easily permitted the detection of the deteriorating effects of elevated BMI on plasma lipid and glucose levels.

Our results indicating that higher BMI predicts higher plasma lipid levels coincide with data reported in studies conducted among chronically medicated schizophrenia patients from Chinese and United States populations [9-14]. Our data indicating that higher BMI predicts less severe PANSS psychopathology coincide with data reported in studies conducted among chronically medicated schizophrenia patients from Chinese, United States and Spanish populations [9-15]. The deteriorating effects of obesity on lipid and glucose metabolism are concordant with prior reports on the effects of obesity on lipid and glucose profiles in the general population [37-39]. Higher BMI were also related to higher plasma lipid levels among AN-FES patients from Chinese population [17]. However, in a Chinese study higher BMI was associated with more severe PANSS psychopathology [17], while in the current study we found no significant association between BMI and any of the PANSS data in this patent group. These discrepancies in the results found between our study and Chinese study could potentially be attributed to ethnic differences. Distributions of polymorphisms in genes that may be risk variants for obesity and/or schizophrenia susceptibility, including dopaminergic and serotoninergic neurotransmission genes, reportedly vary across different ethnicities [40-42]. Our previous findings among chronic schizophrenia patients under antipsychotic treatment indicate that obese patients exhibited higher plasma lipid levels compared to

nonobese. In our previous work we also found no association between obesity and PANSS psychopathology in male or female patients [16]. Importantly, in our previous study we only determined obesity status, while BMI values were also considered in the current study. In addition, when assessing PANSS psychopathology, we previously only determined PANSS scores, while PANSS scores and PANSS factors were also considered in the current study. Our finding indicating that higher BMI predicts higher numbers of psychotic episodes among nonadherent patients adds to the results of one study conducted in a United States population among medicated patients with various chronic psychotic disorders [10]. We speculate that increased nonadherence to antipsychotic medications, reportedly observed among patients with higher BMI, is likely to increase the number of psychotic episodes among these patients [1,19]. Our results indicating no association between obesity and age of disease onset among nonadherent patients are concordant with prior reports among chronically medicated patients as well as antipsychotic-naïve patients [10-17]. However, our data herein indicate that obese AN-FES patients present with approximately 10.5 years age at disease onset compared to nonobese AN-FES individuals (Table 2).

Higher levels of the hormone leptin are reportedly linked to obesity and may contribute to the apparently protective effects of obesity and BMI on the clinical presentation of schizophrenia [43-45]. Produced by fat cells (adipocytes) proportionally to fat stores, leptin reaches the brain via the bloodstream and vagus nerve, and enters it by transcytosis across the blood-brain barrier [43,46]. Leptin has been hypothesized to modulate signalling by dopamine and serotonin, key neurotransmitters in psychosis [47,48]. In animal models, leptin also facilitates learning, spatial memory, and long-term potentiation and modulates synaptic plasticity in the hippocampus [43,49,50]. An inverse relationship between serum leptin and positive symptoms among medicated chronic schizophrenia patients has been observed recently [45], while one study on healthy elderly individuals indicated that higher serum leptin protects against cognitive decline [43]. Considering that AN-FES patients are likely to be obese for some time before illness onset, and in line with findings indicating protective effects of leptin on positive symptoms and cognition [43,45], we speculate that obesity, by promoting leptin production and consequently attenuating prodromal symptoms, might be associated with later onset of schizophrenia. Importantly, one study retrospectively investigated prodromal symptoms in first-episode psychosis and reported that positive and cognitive symptoms specifically were the strongest predictors of recent-onset first-episode psychosis [51].

To date, relatively little attention has been paid to the association between obesity and cognitive symptoms. The observation that obesity and BMI do not predict cognitive factor score disagrees with the results of a recent Chinese study of chronically medicated schizophrenia patients indicating that obesity might negatively influence cognitive factor scores [14]. It also disagrees with the findings of another Chinese study of chronically medicated schizophrenia patients indicating that patients who are obese or have higher BMI experience decreased cognitive functions as assessed by a more specific cognitive test, such as a neuropsychological battery [9]. Therefore, our findings indicate that the relationship between obesity and cognitive symptoms may be different among unmedicated schizophrenia patients compared with patients taking antipsychotic medications.

Intriguingly, the obesity rates among both patient groups were not elevated compared with the rates reported for the general Croatian population. Indeed, data on the obesity rates for the general Croatian population indicated a higher prevalence of obesity, estimated at approximately 20% (26). Moreover, BMI values among AN-FES patients were within the reference range and among nonadherent chronic patients indicated that they were only slightly overweight [27,52] (Table 1 and Table 2). The observed obesity-associated variations of plasma lipid levels also did not exceed normal plasma lipid levels reported for the general Croatian population (28) (Table 2). In addition to the fact that our study sample consisted of unmedicated patients, these findings may be related to the low mean age of our patients, particularly the AN-FES patients, which makes it likely that they had been obese for only a short period (Table 1).

Studies investigating the correlates of obesity among medicated chronic schizophrenia patients have reported that obesity rates range from 16.4% to 20.9% for the Chinese population [9,11-14], while the obesity rate among patients in the studies conducted in the United States population and Spanish populations was estimated at 32% and 24%, respectively [10,15]. Our previous data for medicated schizophrenia patients indicated obesity rates of 26.6% among males and 30.8% among females [16]. Finally, obesity rates among AN-FES patients for the Chinese population was estimated at 10.8% [17].

Importantly, weight gain, mainly caused by enhanced appetite and food intake, may indirectly increase plasma lipid and glucose levels, but it has also been shown that dyslipidemia and diabetes can occur independently of weight gain in patients treated with antipsychotics [53-56]. Unhealthy diet is another possible modulator of plasma lipid and glucose profiles, particularly among patients with longer illness duration [57]. Many studies indicate that schizophrenia patients have a dietary pattern characterized by low consumption of fibre, folate, and polyunsaturated and monounsaturated fatty acids, and high intake of saturated fat and calories [58-60].

The limitations of our study are related to the small sample, thus leaving open the possibility that some minor effects were not detected; to the unbalanced number of obese and nonobese patients, which might have led to bias in the statistical analyses; and to the assessment of non-adherence by anamnestic information. Our sample also lacked data regarding the patients' dietary habits, which might have influenced metabolic parameters [61,62]. A strength of our study is that it is the first study to investigate the effects of obesity among unmedicated individuals with schizophrenia. Moreover, this study was conducted in an ethnically and geographically homogeneous patient cohort.

In conclusion, our present results indicate that higher BMI contributes to an increased risk for dyslipidemia among AN-FES schizophrenia patients, and to the higher number of psychotic episodes, and less severe clinical psychopathology among nonadherent chronic schizophrenia individuals. Based on the latter, it could be speculated that association between higher BMI and less severe clinical psychopathology may occur regardless of antipsychotics-induced weight gain. Importantly, obesity and/or BMI are associated with increased medication non-adherence [1,6] and a higher number of hospitalizations [10]. Thus, apparent protective effects of BMI on PANSS psychopathology, observed in the current study, should not lead clinicians to prescribe lower doses of antipsychotic medications. Furthermore, our observations of lower HDL-c levels, higher LDL-c/HDL-c and triglyceride/HDL-c ratios among unmedicated individuals with higher BMI support the possibility that those patients might be at additional risk for dyslipidemia before initiating antipsychotic therapy. This possible risk should also be considered when prescribing antipsychotics.

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