Correlations Between Clinical and Metabolic Variables and Smoking among Antipsychotic-Naïve First-Episode and Nonadherent Chronic Patients with Psychosis

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Abstract - An interaction between smoking and antipsychotic medications could potentially affect treatment efficacy and promote metabolic side effects. We investigated the contribution of smoking status towards Positive and Negative Syndrome Scale (PANSS) scores and metabolic syndrome- related parameters (plasma lipid and glucose concentrations, and body mass index) among two groups of unmedicated patients with psychosis from the Croatian population: antipsychotic-naïve first-episode patients and nonadherent chronic patients. Previous data are inconsistent regarding the effects of smoking on clinical psychopathology among antipsychotic-naïve or minimally medicated patients with first-episode psychosis, and no studies have examined the potential influence of smoking on clinical psychopathology and metabolic parameters among nonadherent patients with chronic psychosis. Information about smoking status and antipsychotic nonadherence was obtained via auto-anamnestic and hetero-anamnestic information. PANSS data were obtained while patients were in a psychotic state during the illness requiring hospitalization. Plasma total cholesterol, LDL cholesterol, HDL cholesterol (HDL- c), triglyceride, and glucose levels were determined after a 12-hour fasting period. Compared with non-smoking antipsychotic-naïve first-episode individuals, antipsychotic-naïve smokers exhibited significantly lower depression factor scores, and significantly higher triglyceride levels and triglyceride/HDL- c ratio ($p < 0.05$). Compared with non-smoking nonadherent chronic individuals, nonadherent smokers exhibited significantly lower negative symptoms and negative factor scores, and lower HDL- c levels. Contributions of smoking to clinical and metabolic parameters ranged from ~ 3.4 % to 10 %. Our present results indicated that smoking may be associated with less severe clinical psychopathology, and with increased risk for metabolic abnormalities, among unmedicated patients with first-episode psychosis and chronic psychosis.

Keywords: medication adherence; psychotic disorders; schizophrenia; smoking

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Introduction

Among individuals with psychosis (particularly schizophrenia), the estimated prevalence of smoking is six-fold greater than in the general population [1]. Elevated smoking rates

have been reported among chronic patients receiving antipsychotic treatment, as well as patients suffering a first psychotic episode [1–3]. It is important to elucidate the potential influence of smoking on clinical psychopathology and metabolic parameters of psychosis among unmedicated patients for several reasons. Smoking is reportedly associated with nonadherence to antipsychotic medications in patients with first-episode psychosis and those with chronic psychosis [4,5]. Additionally, smoking increases the metabolism of specific antipsychotics (i.e., clozapine and olanzapine), by inducing cytochrome P450 enzyme CYP1A2 activity; therefore, smokers may be at risk of undertreatment [6-8]. Furthermore, smoking may act together with antipsychotics and/or other risk factors (i.e., unhealthy diet) to promote the development of metabolic syndrome, obesity, diabetes, and dyslipidaemia [7,9,10]. Metabolic abnormalities are a major contributor towards cardiovascular diseases, which are consistently associated with excess morbidity and mortality among individuals with psychosis [7,11].

Several studies of antipsychotic-naïve or minimally medicated patients with first-episode psychosis have examined the potential relevance of smoking in clinical psychopathology, as measured using Positive and Negative Syndrome Scale (PANSS) scores [12-15]. The results of one study indicate that smoking or severe nicotine dependence is associated with decreased severity of depressive and negative symptoms, while other findings revealed increased severity of positive symptoms among smokers compared to non-smokers [12,13]. However, reports also describe negative results regarding the relationship between smoking status or severity of nicotine dependence and the severity of specific psychotic or depressive symptoms [12-15].

Only sparse data are available regarding the potential association between smoking and metabolic parameters among unmedicated patients with psychosis. In one study among antipsychotic - naïve first -episode psychosis patients researchers investigated the potential

influence of smoking on those parameters [16]. They reported higher prevalence of hypertriglyceridemia, overweight, elevated insulin, and insulin resistance among smokers compared with non-smokers. Moreover, compared with non-smokers, smokers had higher prevalence of metabolic syndrome and showed different contributing components for metabolic syndrome.

A recent study, performed within the Recovery After an Initial Schizophrenia Episode - Early Treatment Program and including a large number of individuals with first - episode psychosis (N = 404), describes an intriguing link between smoking, poor adherence to antipsychotic medications, and clinical outcome of psychosis. Specifically, among first-episode psychotic receiving antipsychotic medication, smokers exhibited greater positive, negative, and total symptom severity, as well as a higher number of missed antipsychotic pills during the 24-month treatment, compared with non-smokers [4].

Patients who are nonadherent to antipsychotic medications may represent another model group of unmedicated psychotic patients in whom to study the effects of smoking on clinical psychopathology and metabolic parameters. A systematic review describes a high estimated prevalence (50 %) of antipsychotic medication nonadherence among patients with chronic psychosis [17,18]. However, to our knowledge, no studies have examined the potential influence of smoking on clinical psychopathology and metabolic parameters among nonadherent patients with chronic psychosis.

In this study, we aimed to investigate the contribution of smoking status to PANSS scores and metabolic syndrome-related parameters (plasma lipid and glucose concentrations and body mass index) among antipsychotic-naïve patients with first-episode psychosis and nonadherent patients with chronic psychosis. We hypothesized that an elevated smoking rate would contribute to variations of metabolic parameters and clinical psychopathology within both patient groups. We also specu-

lated that the effects of smoking on clinical and metabolic parameters might differ these two patient groups due to differences regarding previous exposure to antipsychotics and/or illness duration.

Subjects and Methods

For this study, we recruited a total of 171 antipsychotic-naïve first-episode patients or nonadherent chronic individuals, all Croatian citizens, who were treated at the Department of Psychiatry in the University Hospital Center Sestre milosrdnice, Zagreb between 2016 and 2021. Among these patients, 150 (87.7 %) were diagnosed with schizophrenia, 10 (5.8 %) with schizoaffective disorder, and 11 (6.5 %) with psychotic disorder not otherwise specified. Table 1 presents the patients' characteristics. Written informed consent was obtained from each patient. This study was approved by the Ethics Committee and was conducted in accordance with the ethical standards expressed in the latest version of the Declaration of Helsinki.

Antipsychotic-naïve patients had never previously been treated with antipsychotic medications. Nonadherent chronic patients were - according to auto-anamnestic and hetero-anamnestic information - noncompliant with their antipsychotic medication usage, or had been off antipsychotic depot injections for at least 1 month. Smokers were defined as individuals who smoked more than one cigarette daily for over 1 year, and non-smokers as individuals who had smoked fewer than 100 cigarettes during their lifetime [19]. The numbers of patients classified as occasional smokers and ex-smokers, and those who had been smoking for less than 1 year were too small for statistical analysis, and thus these patients were excluded from the study. Clinical diagnoses were assessed by at least two psychiatrists, according to the Diagnostic and Statistical Manual of Mental Disorders - V (DSM - V) criteria using a structured clinical interview. Age of onset was defined as the patient's age at their first hospital admission due to a psychotic episode, during which the diagnosis of psychotic disorder was established. PANSS data were recorded during a psychotic state in the illness requiring hospitalization. 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) [13,20,21].

After a 12-hour fasting period, plasma total cholesterol, LDL cholesterol (LDL - c), HDL cholesterol (HDL - c), triglyceride, and glucose levels were determined using an Olympus AU640 autoanalyzer (Olympus, Tokyo, Japan). For the Croatian population, 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; and HDL - c < 1.0 mmol/L was considered decreased [22]. BMI was calculated as weight (in kg) divided by height (m²). Patients with a BMI of 25.0 – 29.9 were considered overweight, and those with a BMI of ≥ 30.0 were considered obese [23,24].

Statistical data processing

To compare characteristics between different patient groups (antipsychotic-naïve first-episode patients *vs.* nonadherent chronic individuals, and smokers vs. non-smokers), we used one-way analysis of variance (ANOVA) or chi -square (χ^2) tests. A p value of < 0.05 was considered significant. Associations of PANSS scores and lipid profiles with smoking status that appeared statistically significant by one - way ANOVA test were further examined by multiple regression analyses. Regression analyses were controlled for the possible effects of gender, age, and BMI, as well as for number of psychotic episodes among nonadherent chronic patients [25-31]. Data analyses were performed using Statistica for Windows, version 13 (StatSoft, Inc., Tulsa, OK, USA).

Results

The recruited patients included 64 antipsychotic-naïve first-episode patients, of whom 34 (53.1 %) were smokers, and 107 nonadherent chronic individuals, of whom 58 (54.2 %) were smokers (Table 1 and Table 2). Compared with non-smoking antipsychotic-naïve individuals, the antipsychotic-naïve smokers scored significantly lower for depression factor (8.9 ± 2.5 *vs.* 10.5 ± 2.7, p = 0.043), and had significantly higher values for triglyceride levels (1.5 ± 0.8 vs. 1.0 ± 0.4, p = 0.008) and triglyceride/HDL - c ratio (1.5 ± 1.2 vs. 0.9 ± 0.5, p = 0.009). Compared with non-smoking nonadherent individuals, nonadherent smokers scored significantly lower for negative symptoms (25.6 ± 7.9 vs. 29.7 ± 6.9, p = 0.006) and negative factor (12.7 ± 5.4 vs. 15.0 ± 5.8, p = 0.038), and exhibited significantly lower HDL - c levels (1.1 ± 0.3 vs. 1.3 ± 0.4, p = 0.010) (Table 2).

Table 1. Patients' characteristics

	Antipsychotic-naïve first-episode patients (N = 64)	Nonadherent chronic patients (N = 107)	p
Age	28.3 ± 9.2	43.2 ± 14.0	< 0.001
Males/females	41/23	49/58	0.020
Age of onset	27.8 ± 9.2	28.3 ± 10.8	0.754
Smokers/nonsmokers	34/30	58/49	0.891
Number of psychotic episodes	-	4.0 ± 1.6	-
Illness duration	0.5 ± 0.9	14.9 ± 12.2	< 0.001
PANSS positive symptom score	22.9 ± 5.7	23.0 ± 6.5	0.857
PANSS negative symptom score	26.9 ± 7.8	27.4 ± 7.7	0.636
PANSS general psychopathology score	51.7 ± 10.1	50.7 ± 8.3	0.493
PANSS total symptom score	101.5 ± 20.0	101.1 ± 17.5	0.949
PANSS positive factor	13.5 ± 3.5	13.1 ± 4.3	0.532
PANSS negative factor	13.9 ± 6.2	13.7 ± 5.7	0.896
PANSS excitement factor	7.8 ± 2.5	8.7 ± 2.8	0.055
PANSS depression factor	9.6 ± 2.7	9.3 ± 2.7	0.446
PANSS cognitive factor	5.9 ± 2.4	5.9 ± 2.0	0.982
Total cholesterol (mmol/L)	4.3 ± 0.8	4.9 ± 1.2	< 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	0.990
Triglycerides (mmoL/L)	1.3 ± 0.7	1.4 ± 1.0	0.250
LDL/HDL	2.3 ± 0.9	2.7 ± 1.1	0.007
Triglycerides/HDL	1.2 ± 1.0	1.4 ± 0.3	0.459
Glucose (mmol/L)	5.1 ± 0.7	5.8 ± 1.6	0.001
Body mass index (kg/m²)	23.2 ± 3.9	25.6 ± 4.6	0.003

Differences were compared using one-way ANOVA test, with the exceptions of sex and smoking status (χ^2 test). PANSS indicates Positive and Negative Syndrome Scale

Multiple regression analyses revealed that smoking significantly predicted depression factor scores (β = –0.32, p = 0.024), triglyceride levels (β = 0.29, p = 0.018), and triglyceride/HDL - c ratio (β = 0.24, p = 0.018) among antipsychotic-naïve individuals; and significantly predicted HDL - c levels (β = −0.21, p = 0.049) and negative symptom scores (β = −0.27, p = 0.006) but not the negative factor scores (p > 0.05) among nonadherent patients. The contribution of smoking to the variability of these variables ranged from approximately 3.4% to 10 %, with the lowest contribution observed for HDL - c (R^2 change = 0.034), and the highest contribution for depressive factor scores (R^2 change = 0.099) (Table 3).

Table 2. Patients' characteristics according to smoking status

	Antipsychotic - naïve first - episode patients			Nonadherent chronic patients		
	Smokers (N = 34)	Non-smokers (N = 30)	p	Smokers (N = 58)	Non-smokers (N = 49)	p
Age	27.8 ± 6.8	28.9 ± 11.4	0.626	39.1 ± 11.5	48.3 ± 15.3	< 0.001
Sex (Males/females)	24/10	17/13	0.247	34/24	16/33	0.007
Age of onset	27.1 ± 6.7	28.6 ± 11.4	0.541	25.8 ± 8.0	31.4 ± 13.0	0.009
Number of psychotic episodes	-	-	-	3.9 ± 1.7	4.1 ± 1.5	0.401
PANSS positive symptom score	22.8 ± 5.5	22.9 ± 6.0	0.923	23.6 ± 6.4	22.4 ± 4.7	0.333
PANSS negative symptom score	25.9 ± 8.0	28.0 ± 7.5	0.304	25.6 ± 7.9	29.7 ± 6.9	0.006
PANSS general psychopathology score	50.3 ± 10.7	53.2 ± 9.4	0.254	49.6 ± 8.9	52.0 ± 7.2	0.116
PANSS total symptom score	99.0 ± 19.7	104.1 ± 20.0	0.309	98.8 ± 17.8	104.2 ± 16.6	0.107
PANSS positive factor	13.0 ± 2.4	14.1 ± 4.3	0.254	13.1 ± 4.1	13.1 ± 4.5	0.989
PANSS negative factor	13.4 ± 5.7	14.4 ± 6.7	0.608	12.7 ± 5.4	15.0 ± 5.8	0.038
PANSS excitement factor	7.6 ± 2.5	8.0 ± 2.6	0.621	8.8 ± 2.6	8.7 ± 3.2	0.758
PANSS depression factor	8.9 ± 2.5	10.5 ± 2.7	0.043	9.1 ± 2.6	9.5 ± 2.9	0.434
PANSS cognitive factor	5.9 ± 2.2	6.0 ± 2.5	0.957	6.0 ± 2.2	5.9 ± 1.9	0.832
Total cholesterol (mmol/L)	4.3 ± 0.8	4.4 ± 0.8	0.655	4.9 ± 1.3	4.9 ± 1.0	0.892
LDL cholesterol (mmol/L)	2.5 ± 0.7	2.7 ± 0.7	0.299	3.0 ± 1.0	3.1 ± 0.9	0.103
HDL cholesterol (mmol/L)	1.1 ± 0.3	1.3 ± 0.2	0.112	1.1 ± 0.3	1.3 ± 0.4	0.010
Triglycerides (mmol/L)	1.5 ± 0.8	1.0 ± 0.4	0.008	1.6 ± 1.2	1.3 ± 0.6	0.127
LDL/HDL	2.4 ± 1.1	2.2 ± 0.6	0.343	2.8 ± 1.2	2.5 ± 0.9	0.103
Triglycerides/HDL	1.5 ± 1.2	0.9 ± 0.5	0.009	1.6 ± 1.5	1.1 ± 0.7	0.082
Glucose (mmol/L)	5.1 ± 0.8	5.0 ± 0.6	0.851	5.9 ± 1.9	5.6 ± 1.0	0.394
Body mass index (kg/m²)	23.8 ± 3.9	22.7 ± 3.9	0.271	25.2 ± 4.8	25.6 ± 4.6	0.668

Differences were compared using one - way ANOVA test, with the exception of sex (χ^2 test)
PANSS indicates Positive and Negative Syndrome Scale

Table 3. Psychopathology data and metabolic parameters predicted by smoking[a,b]

Antipsychotic-naïve first-episode patients (N = 64)			
	b	R² change	F[c]	p
Depression factor scores	−0.32	0.099	5.43	0.024
Triglycerides	0.29	0.075	5.89	0.018
Triglycerides/HDL cholesterol ratio	0.24	0.069	5.94	0.018
Nonadherent chronic patients (N = 107)			
	b	R² change	F[c]	p
Negative symptom scores	−0.27	0.075	7.92	0.006
HDL cholesterol	−0.21	0.034	3.97	0.049

[a] Candidate predictor variables for PANSS psychopathology and lipid profiles included smoking, age, gender, and body mass index, as well as number of psychotic episodes for multi-episode psychotic patients

[b] Dependent variables included depression factor scores, triglyceride levels, triglycerides/HDL-cholesterol ratio, negative symptom scores, negative factor scores, and HDL cholesterol levels

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

Discussion

Our present data showed that age, gender, and age of disease onset were associated with smoking status among nonadherent chronic patients, with smokers more likely to be male, to be younger, and to have a lower age of disease onset. The overall smoking rate did not significantly differ between antipsychotic - naïve first-episode patients and nonadherent chronic individuals (Table 1 and Table 2). A smoking rate greater than 50 % was observed in both patient groups (Table 1 and Table 2), which is in accordance with the elevated smoking rates previously reported for first-episode and chronic psychotic subjects [3,4]. Furthermore, the earlier disease onset among nonadherent chronic smokers compared with non-smokers (Table 2) is in line with systematic review and meta-analysis results indicating that daily smoking may contribute to earlier onset of psychotic illness [4].

Compared with the corresponding non-smoking patients, antipsychotic-naïve first-episode patients who smoked exhibited a lower severity of depressive symptoms, and nonadherent chronic patients who smoked exhibited a lower severity of negative symptoms (Table 2 and Table 3). This apparent protective effect of smoking on the severity of negative and depressive symptoms among patients with psychosis is reportedly attributed to restoration of dopaminergic neurotransmission in the prefrontal cortex via nicotine's central effects on the dopaminergic system and supports the self-medication hypothesis, suggesting that the high smoking rate within the psychiatric population is due to beneficial effects of nicotine [13,32,33].

Our finding of lower depressive factor scores among antipsychotic-naïve first-episode patients who smoked is in concordance with the results of a study among minimally medicated first-episode schizophrenic individuals in the Polish population. Factor analysis for assessment of depressive symptoms revealed a lower severity of negative symptoms among minimally medicated first-episode schizophrenic patients who smoked compared with non-smokers. Furthermore, compared to non-smokers, smokers experienced a lower severity of depressive and negative symptoms [13]. On the other hand, many studies have found no evidence of an association between depressive symptoms and smoking among first-

episode psychotic patients or chronic patients under antipsychotic treatment [14,15,34-36]. Importantly, these studies have used different methods for assessing depressive symptoms, including the Calgary Depression Scale, Beck Depression Inventory, or Hospital Anxiety and Depression Scale. Several studies in first-episode psychotic patients have also not found an association between negative symptoms severity and smoking status [12,14,15].

Our current results showed lower negative symptoms scores in both antipsychotic-naïve first-episode patients and nonadherent chronic psychotic patients who smoked compared with non-smokers. However, the contribution of smoking status to negative symptoms severity was only statistically significant among the nonadherent chronic patients (Table 2 and Table 3). We speculate that the lower number of antipsychotic-naïve first-episode individuals prohibited detection of any protective effect of smoking on negative symptoms severity in that group. We further speculate that the lack of association between smoking status and negative symptoms severity in other studies might be related to variations in the dosage of antipsychotic medications. Specifically, in one Canadian study that reported negative findings, the antipsychotic dosage was slightly greater compared to in the Polish population [14]. In another recent study, British patients were treated with antipsychotics, but no data were provided regarding the type and dosage of antipsychotic medications [15]. Although it has been proposed that nicotine alleviates negative symptoms by stimulating dopamine release, the protective effects of nicotine could be weakened by the increased metabolism of antipsychotics and consequent undertreatment [37]. Studies of chronic medicated patients have yielded rather contradictory results regarding whether smoking interacts with antipsychotics in terms of negative symptoms severity [37-43]. Some findings suggest no significant differences in negative symptoms severity between smokers and non-smokers, while other findings indicate both lower and higher severity of negative symptoms in smokers compared with non-smokers [37-43].

Negative results regarding the association between positive symptoms severity and smoking could potentially be attributed to ethnic differences (Table 2) [12]. Distributions of polymorphisms in genes that may be risk variants for nicotine dependence and/or psychosis susceptibility, including cholinergic and dopaminergic neurotransmission genes, reportedly vary across different ethnicities [44,45]. A study of antipsychotic-naïve first-episode schizophrenia patients from the Chinese population provided no evidence for an association between negative symptoms and smoking status, in contrast to a Polish study [12,13]. Notably, the Chinese study reported higher positive symptoms severity among smokers compared with non-smokers and is the only investigation among first-episode psychotic patients to reveals that smoking status might contribute to positive symptoms severity [12]. Studies among chronic patients under antipsychotic treatment also suggest that smoking may have both protective and risk effects on the severity of positive symptoms [39-41,43], but the data less consistently support the possibility that smoking may modulate positive symptoms severity.

Our present results also revealed significantly higher triglyceride levels and triglycerides/HDL -c ratio among antipsychotic-naïve first-episode patients who smoked, and significantly lower HDL -c levels among nonadherent chronic psychotic patients who smoked (Table 2 and Table 3). These findings are concordant with prior reports of the effects of smoking on lipid profiles in the general population as well as with prior report among antipsychotic - naïve first - episode psychosis patients from the Chinese population, indicating a higher prevalence of hypertriglyceridemia plus several other metabolic syndrome - related parameters among smokers compared with non-smokers [16,46,47]. However, our results are in contrast with the findings of two studies investigating the potential relationship between smoking status and plasma lipid profiles among chronic medicated schizophrenia patients. Those two studies revealed no significant association between smoking and any lipid levels, including total cholesterol, LDL - c, HDL - c, and tri-

glycerides [48,49]. Discrepancies in the results found between medicated and unmedicated patients suggest that antipsychotic medications might mask the effect of smoking on plasma lipids [48]. Furthermore, although nonadherent chronic individuals were off antipsychotic treatment at the time of assessment, it cannot be excluded that prior antipsychotic treatment had cumulative effects on lipid profiles during the variable illness duration.

Unhealthy diet is another possible modulator of lipid profiles, particularly among patients with longer illness duration [10]. Many studies indicate that patients with schizophrenia have a dietary pattern characterized by a low consumption of fibre, folate, polyunsaturated fatty acids, and monounsaturated fatty acids, and high intake of saturated fat and calories [9,50-52]. Smoking has been also linked to unhealthy dietary pattern in schizophrenia, with smokers reportedly more likely to consume salt and saturated fat, and less likely to follow a high-fibre and low-caloric diet [10,50,53].

Intriguingly, both patient groups showed elevated smoking rates (Table 1 and Table 2), but the metabolic parameters were not substantially deteriorated. In fact, with the exception of slightly higher LDL - c levels and BMI values among nonadherent chronic psychotic patients, all parameters were within the reference range (Table 1) [22-24]. Furthermore, the observed smoking-associated variations of triglyceride levels among antipsychotic-naïve first-episode patients, and of HDL - c concentration among nonadherent chronic patients, did not exceed normal plasma triglyceride or HDL - c levels (Table 2). These findings may be related to the low mean age of our patients - particularly of the first-episode psychotic patients - which makes it likely that they had only been smoking for a short period (Table 1). Moreover, it is plausible that the severity of nicotine dependence might be of greater relevance in determining metabolic parameters than smoking status alone. For instance, one study revealed that patients with more severe nicotine dependence (i.e., higher number of cigarette packs smoked per day) exhibited significantly higher plasma total cholesterol and

were more likely to use other substances (e.g., cocaine and alcohol) compared to less-dependent smokers [54]. The latter observation is important because heavy drinking (particularly liquor drinking) is reportedly associated with an increased risk of metabolic syndrome through influences on its components [55]. Notably, that study did not include non-smokers, which impedes interpretation of the results in the context of other studies examining the relationship between lipids and smoking.

The limitations of our present study are mostly related to the small sample size and the assessment of non-adherence and smoking status by self-report. Furthermore, we did not determine nicotine dependence using more specific methods (e.g., the Fagerstrom test, "pack-year" smoking history, etc.). Additionally, our sample lacked data regarding the patients' dietary habits, which might also have influenced metabolic parameters [56,57]. A strength of our study is that it was the first study to investigate the effects of smoking among nonadherent patients with chronic psychosis.

In conclusion, our present results support previous findings that smoking may be associated with less severe depressive and negative symptoms in unmedicated patients with psychosis, although a statistically significant association between negative symptoms severity and smoking status was detected only among nonadherent chronic patients. These findings support the results of a previous study of minimally medicated first-episode individuals of Caucasian (Polish) origin [13]. The similar findings may be related to the similar ethnic origin of patients in our study and those in the Polish study, but may also be related to the medication status: we recruited antipsychotic-naïve first-episode patients, and the first-episode patients in the Polish study had only minimal exposure to antipsychotics. Moreover, our results demonstrate that smoking contributes to increased plasma lipid levels among antipsychotic-naïve first-episode patients and nonadherent chronic individuals. These findings support prior report among antipsychotic-naïve first-episode psychosis patients from the Chinese population. However, they dif-

fer from the results of studies among schizophrenic patients under antipsychotics treatment, revealing no significant contribution of smoking status to plasma lipid levels [48,49].

Importantly, smoking increases the metabolism of antipsychotic medications and is associated with higher illness severity and medication non-adherence among first - episode psychotic patients initiating antipsychotic treatment [6-8,17]. Thus, its association with less severe clinical psychopathology among unmedicated individuals should not lead clinicians to prescribe lower doses of antipsychotic medications. Furthermore, our observations of higher plasma triglycerides, higher triglyceride/HDL - c ratio, and lower HDL - c levels among unmedicated individuals who smoked supports the possibility that smokers might be at additional risk for dyslipidaemia before initiating antipsychotic therapy, which should also be considered when prescribing antipsychotics.

References

1. de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. Schizophr Res. 2005;76:135-57.

2. Myles N, Newall HD, Curtis J, Nielssen O, Shiers D, Large M. Tobacco use before, at, and after first-episode psychosis: a systematic meta-analysis. J Clin Psychiatry. 2012;73:468-75.

3. Gurillo P, Jauhar S, Murray RM, MacCabe JH. Does tobacco use cause psychosis? Systematic review and meta-analysis. Lancet Psychiatry. 2015;2:718-25.

4. Oluwoye O, Monroe-DeVita M, Burduli E, Chwastiak L, McPherson S, McClellan JM, et al. Impact of tobacco, alcohol and cannabis use on treatment outcomes among patients experiencing first episode psychosis: data from the national RAISE-ETP study. Early Interv Psychiatry. 2019;13:142-6.

5. Kane JM, Kishimoto T, Correll CU. Non-adherence to medication in patients with psychotic disorders: epidemiology, contributing factors and management strategies. World Psychiatry. 2013;12:216-26.

6. Tsuda Y, Saruwatari J, Yasui-Furukori N. Meta-analysis: the effects of smoking on the disposition of two commonly used antipsychotic agents, olanzapine and clozapine. BMJ Open. 2014;4:e004216.

7. Šagud M, Vuksan-Ćusa B, Jakšić N, Mihaljević-Peleš A, Rojnić Kuzman M, Pivac N. Smoking in schizophrenia: an updated review. Psychiatr Danub. 2018;30:S216-23.

8. Wagner E, McMahon L, Falkai P, Hasan A, Siskind D. Impact of smoking behavior on clozapine blood levels - a systematic review and meta-analysis. Acta Psychiatr Scand. 2020;142:456-66.

9. Riordan HJ, Antonini P, Murphy MF. Atypical antypsychotics and metabolic syndrome in patients with schizophrenia: risk factors, monitoring and healthcare implications. Am Health Drug Benefits. 2011;4:292-302.

10. Dipasquale S, Pariante CM, Dazzan P, Aguglia E, McGuire P, Mondelli V. The dietary pattern of patients with schizophrenia. J Psychiatr Res. 2013;47:197-207.

11. Seow LSE, Chong SA, Wang P, Shafie S, Ong HL, Subramaniam M. Metabolic syndrome and cardiovascular risk among institutionalized patients with schizophrenia receiving long term tertiary care. Compr Psychiatry. 2017;74:196-203.

12. Zhang XY, Chen DC, Xiu MH, Haile CN, He SC, Luo X, et al. Cigarette smoking, psychopathology and cognitive function in first-episode drug-naive patients with schizophrenia: a case-control study. Psychol Med. 2013;43:1651-60.

13. Misiak B, Kiejna A, Frydecka D. Assessment of cigarette smoking status with respect to symptomatic manifestation in first-episode schizophrenia patients. Compr Psychiatry. 2015;58:146-51.

14. Grossman M, Bowie CR, Lepage M, Malla AK, Joober R, Iyer SN. Smoking status and its relationship to demographic and clinical characteristics in first episode psychosis. J Psychiatr Res. 2017;85:83-90.

15. Lally J, Spaducci G, Gardner-Sood P, Atakan Z, Greenwood K, Di Forti M, et al. Tobacco smoking and nicotine dependence in first episode and established psychosis. Asian J Psychiatr. 2019;43:125-31.

16. Li Z, Wang S, Chen Y, Wu X, Gu Y, Lang X, et al. Smoking affects the patterns of metabolic disorders and metabolic syndrome in patients with first-episode drug-naive schizophrenia: a large sample study based on the Chinese han population. Int J Neuropsychopharmacol. 2021;24:798-807.

17. Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. J Clin Psychiatry. 2002;63:892-909.

18. Haddad PM, Brain C, Scott J. Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. Patient Relat Outcome Meas. 2014;5:43-62.

19. Guo S, Chen DF, Zhou DF, Sun HQ, Wu GY, Haile CN, et al. Association of functional catechol O-methyl transferase (COMT) Val108Met polymorphism with smoking severity and age of smoking initiation in Chinese male smokers. Psychopharmacology (Berl). 2007;190:449-56.

20. Wallwork RS, Fortgang R, Hashimoto R, Weinberger DR, Dickinson D. Searching for a consensus five-factor model of

the Positive and Negative Syndrome Scale for schizophrenia. Schizophr Res. 2012;137:246-50.

21. Jiang J, See YM, Subramaniam M, Lee J. Investigation of cigarette smoking among male schizophrenia patients. PLoS One. 2013;8:e71343.

22. Bergovec M, Reiner Z, Milicić D, Vrazić H. Differences in risk factors for coronary heart disease in patients from continental and Mediterranean regions of Croatia. Wien Klin Wochenschr. 2008;120:684-92.

23. Fister K, Vuletić S, Kern J. Paving the way for personalised behaviourally based prevention of obesity: systematic search of the literature. Coll Antropol. 2012;36:201-10.

24. Milanović SM, Ivanković D, Uhernik AI, Fister K, Peternel R, Vuletić S. Obesity-new threat to croatian longevity. Coll Antropol. 2012;36:113-6.

25. Canuso CM, Pandina G. Gender and schizophrenia. Psychopharmacol Bull. 2007;40:178-90.

26. Ochoa S, Usall J, Cobo J, Labad X, Kulkarni J. Gender differences in schizophrenia and first-episode psychosis: a comprehensive literature review. Schizophr Res Treatment. 2012;2012:916198.

27. Karim S, Overshott R, Burns A. Older people with chronic schizophrenia. Aging Ment Health. 2005;9:315-24.

28. Li Q, Chen D, Liu T, Walss-Bass C, de Quevedo JL, Soares JC, et al. Sex Differences in body mass index and obesity in Chinese patients with chronic schizophrenia. J Clin Psychopharmacol. 2016;36:643-8.

29. Li Q, Du X, Zhang Y, Yin G, Zhang G, Walss-Bass C, et al. The prevalence, risk factors and clinical correlates of obesity in Chinese patients with schizophrenia. Psychiatry Res. 2017;251:131-6.

30. An H, Du X, Huang X, Qi L, Jia Q, Yin G, et al. Obesity, altered oxidative stress, and clinical correlates in chronic schizophrenia patients. Transl Psychiatry. 2018;8:258.

31. Tian Y, Liu D, Wang D, Wang J, Xu H, Dai Q, et al. Obesity in Chinese patients with chronic schizophrenia: prevalence, clinical correlates and relationship with cognitive deficits. Schizophr Res. 2019;215:270-6.

32. Šagud M, Mihaljević-Peleš A, Mück-Šeler D, Pivac N, Vuksan-Ćusa B, Brataljenović T, et al. Smoking and schizophrenia. Psychiatr Danub. 2009;21:371-5.

33. Fluharty M, Taylor AE, Grabski M, Munafò MR. The Association of cigarette smoking with depression and anxiety: a systematic review. Nicotine Tob Res. 2017;19:3-13.

34. Kao YC, Liu YP, Cheng TH, Chou MK. Cigarette smoking in outpatients with chronic schizophrenia in Taiwan: relationships to socio-demographic and clinical characteristics. Psychiatry Res. 2011;190:193-9.

35. Meszaros ZS, Dimmock JA, Ploutz-Snyder RJ, Abdul-Malak Y, Leontieva L, Canfield K, et al. Predictors of smoking severity in patients with schizophrenia and alcohol use disorders. Am J Addict. 2011;20:462-7.

36. Kotov R, Guey LT, Bromet EJ, Schwartz JE. Smoking in schizophrenia: diagnostic specificity, symptom correlates, and illness severity. Schizophr Bull. 2010;36:173-81.

37. Xu YM, Chen HH, Li F, Deng F, Liu XB, Yang HC, et al. Prevalence and correlates of cigarette smoking among Chinese schizophrenia inpatients receiving antipsychotic mono-therapy. PLoS One. 2014;9:e88478.

38. Aguilar MC, Gurpegui M, Diaz FJ, de Leon J. Nicotine dependence and symptoms in schizophrenia: naturalistic study of complex interactions. Br J Psychiatry. 2005;186:215-21.

39. Zhang XY, Tan YL, Zhou DF, Haile CN, Wu GY, Cao LY, et al. Nicotine dependence, symptoms and oxidative stress in male patients with schizophrenia. Neuropsychopharmacology. 2007;32:2020-4.

40. Zhang XY, Xiu MH, Chen DC, Yang FD, Wu GY, Lu L, et al. Nicotine dependence and serum BDNF levels in male patients with schizophrenia. Psychopharmacology (Berl). 2010;212:301-7.

41. Zhang XY, Liang J, Chen DC, Xiu MH, He J, Cheng W, et al. Cigarette smoking in male patients with chronic schizophrenia in a Chinese population: prevalence and relationship to clinical phenotypes. PLoS One. 2012;7:e30937.

42. Ekinci O, Ekinci A. Cigarette smoking in patients with schizophrenia in Turkey: relationships to psychopathology, socio-demographic and clinical characteristics. Düşünen Adam J Psychiatr Neurolog Sci. 2012;25:321-9.

43. Iasevoli F, Balletta R, Gilardi V, Giordano S, de Bartolomeis A. Tobacco smoking in treatment-resistant schizophrenia patients is associated with impaired cognitive functioning, more severe negative symptoms, and poorer social adjustment. Neuropsychiatr Dis Treat. 2013;9:1113-20.

44. Dai D, Wang Y, Yuan J, Zhou X, Jiang D, Li J, et al. Meta-analyses of 10 polymorphisms associated with the risk of schizophrenia. Biomed Rep. 2014;2:729-36.

45. Wiers CE, Towb PC, Hodgkinson CA, Shen PH, Freeman C, Miller G, et al. Association of genetic ancestry with striatal dopamine D2/D3 receptor availability. Mol Psychiatry. 2018;23:1711-6.

46. Jain RB, Ducatman A. Associations between smoking and lipid/lipoprotein concentrations among US adults aged ≥20 years. J Circ Biomark. 2018;7:1849454418779310.

47. Chimura Y, Daimon T, Wakabayashi I. Proneness to high blood lipid-related indices in female smokers. Lipids Health Dis. 2019;18:13.

48. An HM, Tan YL, Tan SP, Shi J, Wang ZR, Yang FD, et al. Smoking and serum lipid profiles in schizophrenia. Neurosci Bull. 2016;32:383-8.

49. Nadalin S, Rebić J, Ružić K, Perčić E, Šendula Jengić V, Buretić-Tomljanović A. Could smoking increase the risk for metabolic syndrome among patients with schizophrenia in a Croatian population? Medicina Fluminensis. 2018;54:52-8.

50. McCreadie RG. Diet, smoking and cardiovascular risk in people with schizophrenia. Br J Psychiatry. 2003;183:534-9.

51. Henderson DC, Borba CP, Daley TB, Boxill R, Nguyen DD, Culhane MA, et al. Dietary intake profile of patients with schizophrenia. Ann Clin Psychiatry. 2006;18:99-105.

52. Amani R. Is dietary pattern of schizophrenia patients different from healthy subjects? BMC Psychiatry. 2007;7:15.

53. Bobes J, Arango C, Garcia-Garcia M, Rejas J. Healthy lifestyle habits and 10-year cardiovascular risk in schizophrenia spectrum disorders: An analysis of the impact of smoking tobacco in the CLAMORS schizophrenia cohort. Schizophr Res. 2010;119:101-9.

54. Wehring HJ, Liu F, McMahon RP, Mackowick KM, Love RC, Dixon L, et al. Clinical characteristics of heavy and non-heavy smokers with schizophrenia. Schizophr Res. 2012;138:285-9.

55. Baik I, Shin C. Prospective study of alcohol consumption and metabolic syndrome. Am J Clin Nutr. 2008;87:1455-63.

56. Russell WR, Baka A, Björck I, Delzenne N, Gao D, Griffiths HR, et al. Impact of diet composition on blood glucose regulation. Crit Rev Food Sci Nutr. 2016;56:541-90.

57. DiNicolantonio JJ, O'Keefe JH. Effects of dietary fats on blood lipids: a review of direct comparison trials. Open Heart. 2018;5:e000871.

Nadalin, Peitl, Karlović, Huskić, Zatković, Buretić-Tomljanović