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Correlation of Metabolic Syndrome with IL-27 in the Patients with Schizophrenia

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ABSTRACT

Introduction: Growing evidence suggests that antipsychotic drugs affect the level of cytokines and metabolic syndrome parameters in schizophrenic patients. The present study aimed to investigate the serum markers of metabolic syndrome, including low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), fasting blood sugar (FBS),total cholesterol, and insulin, and interleukin-27 (IL-27) in the patients with schizophrenia and compared the levels with healthy subjects.

Methods: In this cross-sectional study, the serum level of IL-27 was measured in 45 patients with schizophrenia and 45 healthy subjects using the ELISA. In addition, the markers of metabolic syndrome were measured in Dr. Salehi Laboratory in Yasouj, Iran. Data analysis was performed in SPSS version 21.

Results: A significant increase was observed in IL-27 in the patients with schizophrenia (P= 0.043) compared to the healthy controls. Evaluation of the risk factors of metabolic syndrome in schizophrenic patients compared to the controls indicated no significant differences in the body mass index (P=0.764), systolic blood pressure (P=0.670), diastolic blood pressure (P=0.216), total cholesterol (P=0.103), TG (P=0.097), and LDL (P=0.255). However, the serum levels of HDL (P=0.012) and insulin (P=0.001) significantly decreased and increased, respectively in schizophrenic patients compared to the controls. Moreover, a strong, positive correlation was observed between the levels of insulin and LDL andIL-27, with the correlation-coefficients of 0.312 and 0.641, respectively. A negative correlation was also denoted between IL-27 and HDL with the correlation-coefficient of -0.413 (P=0.005). The associations between IL-27 and the other markers of metabolic syndrome were not considered significant.

Conclusion: According to the results, changes in IL-27 may affect the Pathophysiology of schizophrenia. Antipsychotic therapy has been reported to increase the serum levels of IL-27, which in turn exacerbate and increase the incidence of metabolic disorders.

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Introduction

Schizophrenia is a chronic, debilitative disease with the estimated prevalence rate of 1% in the world population (1, 2). Growing evidence suggests the involvement of cytokine disorders in the pathogenesis of schizophrenia (3). Extensive research has been focused on cytokines such as interferon gamma (IFN-γ), interleukin-2 (IL-2), IL-6, and tumor necrosis factor (TNF-α) in schizophrenia (3, 4). Several studies have denoted the reduced levels of IL-12 and IFN-γ, as well as the increased production of IL-4 and IL-10, in schizophrenic patients (4-6).

According to the literature, the serum levels of anti-inflammatory cytokines decrease, and the serum levels of pro-inflammatory cytokines increase after antipsychotic therapy. For instance, the levels of IL-1B, soluble receptor IL-2 (SIL-2R), IL-6, and TNF-α have been reported

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to increase in the patients with first-episode psychosis (FEP) following the initial treatment with antipsychotic drugs (e.g., clozapine and risperidone) due to the activation of M1 macrophages and Th1 cells(7). According to Müller and Schwarz (2010), the elevated response of Th2 in schizophrenia could be reversed to the primary state using antipsychotic drugs (8).

Metabolic syndrome is defined as a set of metabolic disorders, including dyslipidemia, abdominal obesity, hypertension, and increased blood sugar, all of which are associated with insulin resistance, type II diabetes (DT2), and coronary artery disease (CAD) (9, 10).According to Kim et al., the prevalence of metabolic syndrome was 34.2% in the patients with schizophrenia, and this rate was not associated with any particular antipsychotic drugs. Moreover, abdominal obesity and dyslipidemia were reported to be the predominant factors associated with metabolic syndrome in these patients (11, 12). In the first study regarding metabolic syndrome in Iran, the prevalence of the disease was estimated at 34.7% (13).

Inflammation and activation of the immune system are considered to be the key, emerging mechanisms that are associated with visceral obesity, DT2, and CAD (14, 15). In mice with metabolic syndrome, the synergy of IL-18 and IL-12 has been reported to promote the stimulation of Th1 cells, polarizability, IFN-γ production, and atherosclerotic plaque inception (16). Additionally, activation of the innate immune system in the adipose tissue leads to the inflammation of the adipose tissue macrophages and stimulation of toll-like receptors (TLRs); the activation of these pathways induces inflammatory cytokine production (17). Obesity also produces the M1and M2 macrophages by reducing the production of arginase and IL-10 and increasing the production of pro-inflammatory TNF-α (17). The endocrine function of the adipose tissue plays a pivotal role in energy balance, glucose homeostasis, and immune functions (18). TLR-4 ligands (e.g., fatty acids) activate NF-κB and AP-1, thereby increasing the production of pro-inflammatory cytokines (e.g., IL-6, IL-18, and TNF-α) (19).

Antipsychotics play a key role in the treatment of mental disorders. Antipsychotic drugs may cause various side-effects, including weight gain, drowsiness, loss of sex drive, increased risk of metabolic syndrome and DT2, cardiovascular complications, and severe reduction of red blood cells and other blood cells and platelets. However, second-generation (atypical) antipsychotics have been reported to have significantly fewer side-effects compared to the first generation of these drugs (20, 21).

Interleukin-27(IL-27) is a heterodimeric cytokine composed of EBI3 and p28 subunits, which are partly similar to the p40 and p35 subunits of IL-12 (1). The signaling pathways of IL-27isthrough a heterodimer receptor by JAK-STAT, the receptor of which is composed of the WSX-1 subunit and gp130 signaling subunit; these are also used by the IL-6 family of cytokines (2). WSX-1 consists of the STAT1binding site and gp130, which has four STAT3docking sites, two of which could also recruit STAT1. In lymphocytes, IL-27 activates STAT1, STAT3, and STAT5 (22).

The IL-12 cytokine family includes IL-12, IL-23, IL-27, and IL-35, which have various functions and are involved in pro-inflammatory and anti-inflammatory responses. IL-27 could synergize with IL-12 to promote Th1 differentiation, enhancing the early commitment of naive T cells to the Th1 cell lineage and increasing IL-18 and TNF-α responsiveness. Furthermore, IL-27 could produce INF-γ, suppress the formation of TGF-β-induced Tregs, limitIL-2 production, and block lineage commitment and induction of Th17 responses (23).Previous studies have also indicated that IL-27 could be directly antagonized to the spread of the Th17 cell response, limiting the selective inflammation induced by IL-17 cells in the central nervous system (24).

According to the literature, cytokines are involved in the development of metabolic disorders, such as metabolic syndrome, CAD, and DT2. In addition, significant associations have been denoted between IL-18 and obesity, body mass index (BMI), fat mass, and insulin resistance in patients with metabolic syndrome and atherosclerosis (14,25-27). On the other hand, a significant increase has been reported in IL-27 levels in patients with CAD and ischemic heart disease compared to healthy controls (25,28). There are also speculations on the potential role of IL-27 in the development of

T1D (27). However, no studies have investigated the correlation of IL-27 and metabolic syndrome in patients with schizophrenia.

The present study aimed to evaluate the association between metabolic syndrome andIL-27 in schizophrenic patients.

Material and methods

This cross-sectional study was conducted based on the data collected from medical records and contact with the relatives of 45 schizophrenic patients admitted to Behravan Hospital and Iran Hospital in Yasuj, Iran during 2015-2017. In addition to the selected patients, 45 physically healthy individuals were considered as the control group. The patients were selected based on DSM-IV-IR by a psychiatrist. All the subjects in the control group were recruited based on the Blood Transfusion Organization (BTO) samples, screened for the personal or familial history of schizophrenia, and excluded if positive. Only healthy subjects using no medications with no diagnosis of psychiatric disorders and the medical or familial history of psychiatric disease were assigned to the control group. In addition, the subjects with no major medical conditions (e.g., inflammatory and non-inflammatory diseases) were enrolled in the study.

Data were obtained on the systolic and diastolic blood pressure, weight, height, and BMI of the subjects. Waist circumference (the narrowest part of the lumbar region) was measured at the end of exhalation. Blood samples were also obtained with the participants fasting for 10-12 hours beforehand, and 10 milliliters of blood were collected during8-12 AM in two separate tubes (five milliliters in EDTA tubes and five milliliters in EDTA-free tubes). The samples were centrifuged immediately at 2,500 rpm for 10 minutes, and the plasma was frozen at the temperature of -80°C.

The serum concentration of IL-27 was measured in duplicate using the ELISA assay (Ebioscience, USA) in accordance with the instructions of the manufacturer. Cell blood count (CBC) was also determined using a cell counter. Five m/l of serum was also collected in a serum clot-activated container. Moreover, fasting blood sugar (FBS), total cholesterol, very low-density lipoprotein (VLDL), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and triglyceride (TG) were measured using the enzymatic method (Pars Azmoon kit, Iran), and the serum level of insulin was measured using the ELISA (Saman Tajhiz, Iran).

Data analysis was performed in SPSS version 21 using nonparametric tests, including the Mann-Whitney U test and Spearman's correlation-coefficient. In all the statistical analyses, $P \leq 0.05$ was considered significant.

Results

Table 1 shows various atypical and typical antipsychotics administered to the patients with schizophrenia. In the schizophrenic group, a significant difference was observed between men and women in terms of the number of the used medications. Accordingly, women mostly used olanzapine, while men mostly used Artane. In addition, among 45schizophrenic patients, 29 cases (64.4%) were paranoid (31.1% females and 33.3% males). The clinical characteristics of the unorganized, catatonic, non-distinctive, and other schizophrenic patients are presented in Table 1.

Table 1. Characteristics of Disease Type and Medications in Patients

Characteristics	Group	Schizophrenic Patients		Healthy Controls	
		Female (n=19)	Male (n=26)	Female (n=21)	Male (n=24)
Type of Disease	Paranoid	14	15	0	0
	Disorganized	0	5	0	0
	Catatonic	0	2	0	0
	Undifferentiated	1	1	0	0
	Rest	4	3	0	0
Medications	Clozapine	5	10	0	0
	Risperidone	8	13	0	0
	Olanzapine	15	6	0	0
	Haloperidol	6	5	0	0
	SodiumValproate	9	5	0	0
	Biperiden	4	5	0	0
	Artane	10	15	0	0
	Chlorpromazine	0	7	0	0
	Li	6	1	0	0
	Clonazepam	10	10	0	0

Among 45 schizophrenic patients, 57.7% (n=26) were male, and 42.3% (n=19) were female. In the control group, 53.3% of the patients (n=24) were male, and 46.7% (n=21) were female. According to the findings, the number of smokers (P=0.005) and frequency of the mean age (P=0.039) were higher in the schizophrenic patients. No significant differences were observed between the schizophrenic patients and control group in terms of the BMI (P=0.764), systolic blood pressure (P=0.670), and diastolic blood pressure (P=0.216).

Statistical analysis of the blood cells in the study groups is presented in Table 2. According to the information in this table, red blood cells (P=0.001) and mean corpuscular hemoglobin concentration (P=0.002) reduced more significantly in the schizophrenic patients compared to the controls. On the other hand, mean corpuscular volume (P=0.005) and mean corpuscular hemoglobin (P=0.02) increased more significantly in the schizophrenic patients compared to the controls. No significant differences were observed between the patients and controls in terms of white blood cell count, platelet count, and Hematocrit.

According to the obtained results, the serum levels of FBS, total cholesterol, TG, LDL, and VLDL were higher in the schizophrenic patients compared to the control group (P<0.05), while the difference was not considered statistically significant (P>0.05). However, the serum levels of HDL and insulin significantly decreased and increased, respectively in the schizophrenic patients compared to the control group (P=0.012 and P= 0.001, respectively) (Table 2).

Table 2. Demographic, Clinical, and Medical Characteristics of Subjects

Characteristics	Group	Schizophrenic Patients (n=45)		Control (n=45)		*P-value*
		Male (n=26)[1]	Female (n=19)	Male (n=24)	Female (n=21)	
Gender (male/female) (%)		57.7%	42.3%	53.3%	46.7%	-
Age (year) (Mean±SD)		40.96± 10.28	41.32± 9.14	35.88±11.05	38.10±11.26	0. 039
BMI (Mean±SD)		25.88± 7.17	25.1± 5.1	25.83± 3.29	23.66± 2.43	0.764
Smoker (N)		15	8	10	0	0.005
Non-smoker (N)		11	11	14	21	
Systolic Blood Pressure (Mean±SD)		12.58±1.72	11.95± 1.47	12.54±1.35	12.14±0.91	0.670
Diastolic Blood Pressure (Mean±SD)		8.08±1.12	8.16±1.25	8.25± 0.7	8.24± 0.7	0.216

RBC*10^6 (Mean±SD)	5.08± 0.73	4.38± 0.38	5.39±.31	4.82±.43	0.001
WBC*10^3 (Mean±SD)	5.59± 1.3	6.56 ± 2.17	6.43±.63	5.76±1.32	0.508
Platelet Count (Mean±SD)	217.96±75.51	280.42±74.56	242.29±45.49	247.23±52.37	0.583
Hematocrit (Mean±SD)	42.28±3.70	37.95±4.17	44.07±4.13	38.6±2.89	0.429
MCV (Mean±SD)	86.20±11.66	87.96±11.09	83.89±4.70	81.46±7.12	0.005
MCH (Mean±SD)	28.50±4.56	29.60±4.50	28.97±3.21	26.75±3.55	0.02
MCHC (Mean±SD)	33.15±1.02	29.85±1.42	33.63±1.62	32.49±1.59	0.002
FBS (Mean±SD)	85.46±12.33		83.00±12.05		0.475
Total Cholesterol (Mean±SD)	208.69±34.25		183.57±40.56		0.103
TG (Mean±SD)	176.75±70.62		160.71±87.48		0.097
LDL (Mean±SD)	125.75±30.98		121.33±34.87		0.169
VLDL (Mean±SD)	27.34±9.25		25.40±8.75		0.231
HDL (Mean±SD)	37.04±7.78		40.28±6.20		0.012
Insulin (Mean±SD)	9.2±6.50 IU/ml		2.25±1.7IU/ml		0.001

[1]Data analyzed by Mann-Whitney U test

According to the finding, IL-27 significantly increased in the patients with schizophrenia (209.63±80.03) compared to the control group (175.15±54.08) (P=0.043). Additionally, the obtained results indicated that the serum level of IL-27 was higher in men compared to women in the studied groups, while no significant difference was observed in terms of gender (P≤0.05) (Figure 1).

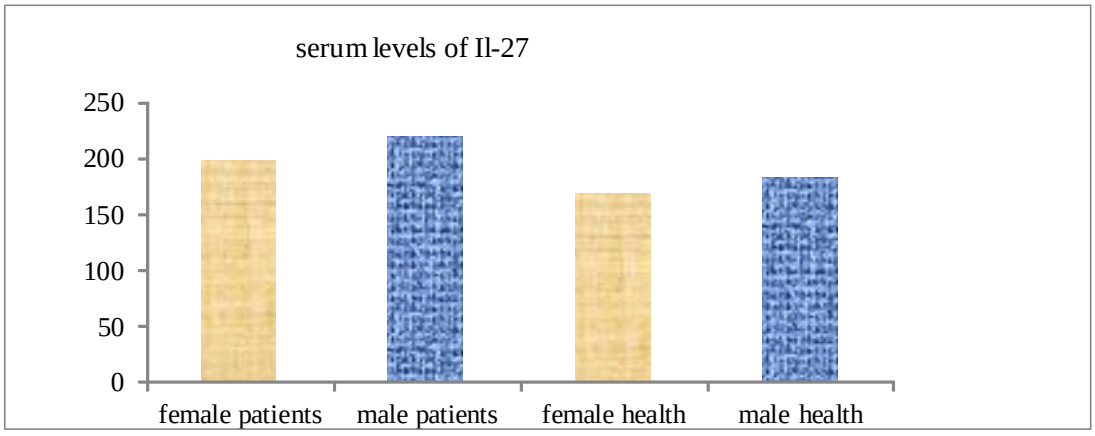

Figure 1. Comparison of Serum Level of IL-27 in Female and Male Subjects (schizophrenia patients and healthy controls)

According to the results of the present study, the prevalence of metabolic syndrome was 28.4% and 13.8% based on NCEP-ATP III in the schizophrenic patients and controls, respectively. In addition, a correlation was observed between metabolic syndrome and IL-27 levels based on Spearman's correlation-coefficient (Table 3). IL-27 also had a strong, positive correlation with LDL (r=0.641; P= 0.071), as well as a negative correlation with HDL (r=-0.413; P=0.005).Moreover, IL-27 had positive correlations with the other parameters, including insulin, FBS, TG, total cholesterol, and BMI, while the associations were not considered

significant (Table 3).

Table 3. Correlations between Demographic Variables and IL-27 Level

Variable		BMI	LDL	Insulin	FBS	HDL	TG	Total Cholesterol	Smoking Habits
IL-27	P-value	0.616	.071	0.364	0.785	.005	0.331	0.518	0.187
(pg/ml)	r	0.077	0.641	0.312	.042	-0.413	0.148	.099	-0.219

*Data analyzed by Spearman's correlation-coefficient

Discussion

The foremost finding of the present study was the significant increase in the serum IL-27 of the schizophrenia patients compared to the healthy controls. In schizophrenic patients, the immune parameters associated with Th1 tend to decrease *in-vitro* and *in-vivo* (23). Furthermore, it has been suggested that these patients have an imbalance between the Th1 and Th2 cells, which could shift the immune system toward the increased Th2 response (29). IL-27 is produced by Th1 cell cytokines, and few studies have been conducted in this regard. For instance, Muller and Schwartz have claimed that type two immune response in schizophrenic patients increases and could be reversed to the initial state with antipsychotic therapy (30).Our findings are inconsistent with the results obtained by Milica Borovcanin, which indicated that IL-27 level had no significant difference after antipsychotic the rapyin schizophrenic patients (31).

Atypical antipsychotics are associated with increased inflammatory responses, and several studies have reported that the injection of clozapine and risperidone *in-vivo* could significantly increase the levels of inflammatory cytokines, such a TNF-α, IL-6, and IL-18 (32, 33). In this regard, Muller reported the increased levels of $CD4^+$, $CD45^+$, and RO cells (i.e., the main sources of TNF-α production) during antipsychotic therapy in various patient groups (34).Lack of IL-27 signaling leads to the increased number of the IL-17 produced by$CD4^+$T cells in the central nervous system, thereby exacerbating the disease and suggesting that IL-27 contributes to the improvement of immunity (34).According to some studies, IL27 could significantly suppress the inflammatory response induced by Th1 cells and decrease the production of INF-γ (22, 35).

According to the NCEP-ATP III criteria, approximately25% of the population in the United States and 10% of the population in France have metabolic syndrome (36). The prevalence of metabolic syndrome in the study is consistent with the findings of Kim and Teixeira (12, 36). In this regard, Kim et al. have reported the prevalence of metabolic syndrome to be34.2%, and abdominal obesity and dyslipidemia were considered to be the predominant factors contributing to metabolic syndrome in schizophrenic patients (12). Moreover, Teixeira reported that the prevalence rate of metabolic syndrome in 170 schizophrenic and schizoaffective patients was 31.8% (36).

The second major finding of the current research was that the serum levels of HDL and insulin significantly decreased and increased, respectively in the schizophrenic patients compared to the controls, while the other parameters associated with metabolic syndrome showed no significant differences. In another study, Casey et al. investigated the effects of aripiprazole (n=505) and olanzapine (n= 505) on the diagnosis and intensification of metabolic syndrome. According to the findings, after 16 weeks of therapy, aripiprazole(8.5%) and olanzapine (14.4%) exacerbated the disease, and one year after treatment with aripiprazole(10%) and olanzapine (20.5%) metabolic syndrome was observed to deteriorate as well (37).

According to the study conducted by Mitchell, metabolic disorders and obesity (52.7% versus 26.6%), TG (41.1% versus 16.9%), hypertension (39.7%versus 24.3%), diabetes (12.8%versus 2.1%), and hyperglycemia (27.8%versus 6.4%) increased in the treated and untreated patients with schizophrenia, while the increase in the treated patients was reported to be more significant compared to the untreated patients (38).

According to the results of the present study, as well as the previous studies in this regard, disruption in lipids metabolism is associated with antipsychotic therapy. Clozapine and

olanzapine have strong, positive correlations with high levels of total cholesterol, LDL, and TG, as well as strong, negative correlations with high levels of HDL (39). Henderson et al. conducted a study for 10yearson the patients using clozapine, denoting a significant increase in the serum levels of TG, while no association was observed with total cholesterol (40). On the other hand, the findings of Koro et al. based on the data of more than 18,000 schizophrenic patients revealed that the use of olanzapine is associated with a five-fold increase in the development of lipid disorders in schizophrenia patients compared to the control group (41).

The exact action mechanism of atypical antipsychotics in causing diabetes and other metabolic disorders remains unknown although the use of these drugs has been reported to increase the risk of such disorders (21). In this regard, the findings of Ryan Mc et al. indicated that the mean fasting plasma glucose (95.8 versus 88.2 mg/dl; P<0.03) and insulin (9.8 versus 7.7 u/ml; P<0.05) significantly increased in schizophrenic patients compared to the control group (42). In the present study, the insulin level in the patients with schizophrenia was significantly higher compared to the controls (P=0.001), while its actual cause and mechanism remained unclear.

In the current research, the correlation-coefficients between the markers of metabolic syndrome and IL-27 concentration demonstrated that IL-27 concentration had the most significant, positive correlation with LDL (0.641) and the least significant, negative correlation with HDL (-0.413). However, a significant difference was observed between HDL and IL-27 serum levels (P=0.005).Furthermore, the correlations between IL-27 concentration and metabolic syndrome markers were not considered significant, including total cholesterol (r=0.099, P=0.518), TG (r=0.148, P=0.331), FBS (r=0.042, P=0.785), systolic blood pressure (r=0.133, P=0.460), diastolic blood pressure (r=0.019, P=0.902), insulin (r=0.312, P=0.364), and BMI (r=0.77, P=0.616).

According to a study by Wen Jin (2012), the level of IL-27 in the patients with CAD was significantly higher compared to the control group (P= 0.01). Additionally, a positive, significant correlation was reported between oxidized LDL and IL-27(r=0.61, P=0.001). Moreover, their findings indicated that oxidized LDL could cause dendritic cells to produce IL-27(25). Therefore, IL-27 may accelerate the development and progression of CAD and metabolic diseases through inducing Th1 differentiation and the production of pro-inflammatory cytokines.

The adipose tissue is responsible for the production of inflammatory cytokines, especially the IL-12 family cytokines (IL-12, IL-23, IL-27, and IL-35). Therefore, it is likely that these cytokines increase the incidence of chronic inflammation in the patients with TD2, metabolic syndrome, and CAD. In this regard, Crespo-Facorro et al. evaluated the effects of atypical antipsychotics on the production of IL-12 in schizophrenic patients, and their findings indicated that treatment of schizophrenia patients for the first time was accompanied by the increase production of IL-12 compared to the healthy subjects. Moreover, the level of IL-12 increased significantly after six weeks of treatment (43).In another study in this regard, Heesun Nam reported that the expression of *p28*and *EBI-3* genes (IL-27 subunits) was significantly higher in the white adipose tissue of genetically obese and diet-induced obese mice (26).Therefore, the increased level of IL-27 in the schizophrenic patients in the present study could be due to the increased levels of the markers of metabolic syndrome, and the side-effects of antipsychotics might also have contributed to the higher levels of these markers.

On the other hand, our findings demonstrated that TG, BMI, total cholesterol, and IL-27 were higher in men (both patients and healthy subjects) compared to women (both patients and healthy subjects). The difference in the level of IL-27 between men and women could be attributed to the interference of the sexual hormones affecting the immunological mechanisms (44). These mechanisms are responsible for gender differences in terms of fat distribution in the body that could be caused by the differences in the mobility, oxidation, and storage of fatty acids between men and women (45).

Conclusion

Growing evidence suggests that

antipsychotic drugs affect the levels of cytokines and metabolic syndrome markers in schizophrenia. According to the results, the serum level of IL-27 was higher in the schizophrenic patients compared to the healthy controls. It seems that treatment antipsychotic therapy increases the serum level of IL-27, as well as the risk of the incidence and exacerbation of metabolic disorders, diabetes, metabolic syndrome, appetite problems, insulin resistance, lipid oxidation, visceral obesity, and CAD in these patients. Therefore, cytokines could be used as valuable biomarkers in schizophrenia. It is recommended that further investigations be conducted in order to clarify these associations.

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