Dubai Medical Journal

Research Article

Dubai Med J
DOI: 10.1159/000533470

Received: April 17, 2023
Accepted: August 3, 2023
Published online: September 14, 2023

Is There Any Risk for Metabolic Syndrome in Children and Adolescents with Psychiatric Disorders?

Öznur Bilaç[a] Akın Tahıllıoğlu[b] Burak Çakır[c] Canem Kavurma[d] Arif Önder[e] Eyüp Sabri Ercan[f]

[a]Department of Child and Adolescent Psychiatry, Manisa Celal Bayar University, Manisa, Turkey; [b]Department of Child and Adolescent Psychiatry, Çigli Regional Education Hospital, Bakırçay University, Izmir, Turkey; [c]Department of Child and Adolescent Psychiatry, Uşak Education And Research Hospital, Uşak, Turkey; [d]Department of Child and Adolescent Psychiatry, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Izmir, Turkey; [e]Department of Child and Adolescent Psychiatry, Akdeniz University, Antalya, Turkey; [f]Department of Child and Adolescent Psychiatry, Ege University, Izmir, Turkey

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Keywords
Metabolic syndrome · Weight gain · Blood pressure · Antipsychotics · Psychiatric disorder · Bipolar disorder · Children and adolescents · Quetiapine · Valproic acid

Abstract
Objective: We aimed to investigate the risk of antipsychotic drug treatment in the development of metabolic syndrome (MetS) in children and adolescents and to determine which psychiatric disorder is more associated with MetS in the pediatric population. ***Methods:*** The sample consisted of 118 children and adolescents (88 used psychotropic medication). The hemogram, fasting blood glucose, lipid profile, weight, and blood pressure levels of all the participants and information regarding medication doses of the patient group at the sixth month of the treatment process were obtained. ***Results:*** Bipolar disorder (BPD) was the only psychiatric disorder associated with MetS. Quetiapine and valproic acid were found to have increasing effects on MetS. Weight gain and the increase in systolic and diastolic blood pressure significantly increased the likelihood of MetS. Hierarchical logistic regression analyses revealed that quetiapine increased the risk of MetS through weight gain, and valproic acid increased MetS risk through systolic blood pressure. ***Conclusion:*** Especially BPD and psychotropic use in children and adolescents disrupt metabolic regulation and pose a risk for MetS. Determining the risk factors causing MetS, especially in children and adolescents, plays a significant role in preventing mortality and morbidity at advanced ages.

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Introduction

Metabolic syndrome (MetS) causes mortality because of abdominal obesity, dyslipidemia, elevated fasting glucose, and hypertension. MetS also causes severe physical health problems such as atherosclerotic cardiovascular disease, type 2 diabetes, and all-cause mortality [1–3]. It has been observed that MetS prevalence in children and adolescents has increased significantly and turned into a global priority problem [4]. While the

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Correspondence to:
Burak Çakır, burakckr35@gmail.com

prevalence of MetS in adults varies between 9.5 and 19.6%, in adolescents, it is estimated to be between 2% and 9.4% [5].

Since MetS is a widespread problem, studies are focused on psychological problems alongside the physical health problems that might be associated with this syndrome. It has been shown that especially dyslipidemia and obesity are associated with psychological characteristics such as hostility, depression, anxiety, and anger [6–8]. However, it is unclear whether the psychological characteristics or MetS began before. Each direction is biologically valid. It is known that the development and the progression of both psychopathology and metabolic dysregulation occur because of detrimental biological processes. These processes include altered autonomic and neuroendocrine stress functioning, low-grade inflammation, cellular aging, and oxidative and nitrosative damage [9, 10]. On the other hand, the unhealthy lifestyle of people with psychopathology, including smoking, physical inactivity, and alcohol use, can cause metabolic dysregulation [11].

Regardless of the psychiatric disorder, there is also a relationship between the antidepressants and MetS components. The use of tricyclic antidepressants can cause abdominal obesity above all [12]. However, the effects of selective serotonin reuptake inhibitors (SSRIs) on MetS components are unclear [13, 14]. There can be weight gain, loss, or no change in weight during the use of SSRIs, but all of these situations can cause impairments in glucose and lipid profiles. The findings of a meta-analysis indicate that there may be a normalization of overactive inflammatory processes following antidepressant treatment [15].

In recent years, there has also been an increase in the use of second-generation antipsychotics (SGAs) in pediatric patients for the treatments of schizophrenia spectrum disorders, irritable and aggressive symptoms of autism spectrum disorder, intellectual disability, tics or Tourette's disorder, mood disorders (mainly bipolar), conduct disorders (CDs), and eating disorders [16, 17]. SGAs block serotonin receptors in the cortico-limbic pathways. For this reason, they have better neurological profiles than first-generation antipsychotics [18]. Nevertheless, recent studies show their adverse effects associated with metabolic components such as weight gain/obesity, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hyperglycemia/hyperinsulinism, and hypertension [19]. Risperidone has been linked to metabolic side effects such as obesity in the patients with early-onset schizophrenia [20]. In addition, it is now known that these adverse effects are more frequent in children and adolescents than adults due to less prior SGA exposure [21].

There are a growing number of studies in adults with bipolar disorder (BPD) searching MetS. In one study, the prevalence of MetS was 9.1% in people 18–30 years old. This percentage is higher than the MetS prevalence (4.2%) of the average population at this age [22]. A few studies investigated specific components of MetS, and some studies searched the effects of antipsychotics [23]. Many studies have demonstrated the efficacy of SGAs on schizophrenia [24]. Some adverse effects, such as weight gain, metabolic and endocrine alterations, and cardiovascular and motor abnormalities, even after a short exposure to antipsychotic drugs, have been reported [25].

As stated above, MetS is very common in psychiatric disorders such as depression, anxiety disorders, attention-deficit/hyperactivity disorder, schizophrenia spectrum disorders, irritability and aggression in autism spectrum disorder, intellectual disability, tics or Tourette's disorder, mood disorders (mainly bipolar), CDs, and eating disorders. Many studies indicate that antipsychotic drugs used in these disorders predispose to MetS. However, the mechanisms are not fully explained. In addition, what is known in children and adolescents is much less than in adults. As far as we are concerned, there are very few studies in which diagnoses of BPD, depression, psychosis, CD, and psychotropic medication use were evaluated in terms of METs risk in children and adolescents. In addition, demonstrating which antipsychotic drugs have a higher risk for MetS in children and adolescents is vital. To find answers to these questions, we aimed to investigate the risk of antipsychotic drug treatment in the development of MetS in children and adolescents. We also aimed to determine which psychiatric disorder is more associated with MetS in the pediatric population.

Materials and Methods

The case files of the Child and Adolescent Psychiatry Outpatient Clinic within 2 years before October 2019 were retrospectively scrutinized. 118 cases who had a psychiatric evaluation with a semi-structured interview (The Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version – K-SADS-PL) and who had hemograms and other metabolic measurements were reached. 88 of 118 participants constituted the case group because they were diagnosed with a psychiatric diagnosis, used psychotropic medication regularly for 6 months (no drug changes, using the same drug during 6 months), and their measurement results at the sixth month were complete. 30 participants who applied for counseling and had no active psychopathology in the K-SADS-PL evaluation and whose hemograms and other measurements were complete constituted the control group. The K-SADS-PL is

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a highly reliable semi-structured interview to assess psychiatric diagnoses [26]. The validity and reliability evaluation of the Turkish version was conducted by Gökler et al. [27].

Age, gender, medications, height, weight, waist circumference measurements, high-density lipoprotein cholesterol (HDL-C-C) and low-density lipoprotein cholesterol levels, serum triglyceride level, systolic blood pressure (SBP) and diastolic blood pressure (DBP) values, and other data of all patients were obtained retrospectively by scanning the examination files. Routine blood tests (hemogram, liver function tests, fasting blood glucose, lipid profile, etc.) are recommended before treatment and during follow-up in the treatment guidelines of the American Academy of Child and Adolescent Psychiatry [28, 29]. In addition to the patients' blood tests and body parameters, the psychopharmacological treatment information (initial dose, maximum dose, and the generic name of the drugs used) for all the patients was obtained. Prescribed antipsychotics were risperidone, aripiprazole, olanzapine, and quetiapine; the antidepressants were fluoxetine and sertraline; the mood stabilizer was valproic acid; and the psychostimulant was methylphenidate. The MetS diagnosis in children between 10 and 16 years and adolescents over 16 years was made according to the International Diabetes Foundation (IDF) criteria, which vary among these age groups [30].

IDF Criteria of MetS for Children Aged 10–16

1. Waist circumference >90th percentile.
2. Fasting blood glucose >100 mg/dL.
3. Serum triglyceride level ≥150 mg/dL.
4. HDL-C-C <40 mg/dL.
5. SBP ≥130 mm Hg or DBP ≥85 mm Hg.

IDF Criteria of MetS Criteria for Children Aged 16 and Above

1. Waist circumference ≥80 cm (for females), ≥94 cm (for males).
2. Fasting blood glucose >100 mg/dL.
3. Serum triglyceride level ≥150 mg/dL.
4. HDL-C <50 mg/dL (for females), <40 mg/dL (for males).
5. SBP ≥130 mm Hg or DBP ≥85 mm Hg.

Statistical Analysis

The resulting data were transferred into the 22nd version of the Statistical Package for Social Science (SPSS 22.0). Quantitative variables were evaluated by the Kolmogorov-Smirnov test in terms of appropriateness for normal distribution. The two groups with and without METs were compared in terms of metabolic/body parameters with two independent sample *t*-tests if they were normally distributed; they were evaluated by the Mann-Whitney U test if they were not normally distributed. Descriptive statistics of quantitative variables have been shown as the mean ± standard deviation, and descriptive statistics of these variables were expressed as a frequency (%). Besides, the statistics of quantitative variables have been shown as the median (interquartile range) if they were not normally distributed. Comparison of categorical variables was checked using Pearson χ^2 test if less than 20% of cells have an expected count less than 5 and Fisher's exact test if more than 20% of cells have an expected count less than 5. The correlation analysis among metabolic/body parameters and medication doses was conducted using bivariate Pearson correlation analysis.

The analytic strategy of this study depended on constituting a causal relationship among medication doses, metabolic parameters, and MetS status. In line with this purpose, an imaginary triangle symbolizing the causal relationship among these variables was formed. In order to detect the most authentic relationships among these three variables, each variable at each corner was analyzed with each other with appropriate tests in hierarchically constituted three stages.

At the first stage, we aimed to establish first-stage links among metabolic/body parameters, medication doses, and MetS. As first-stage comparison analysis between the cases with and without MetS, we have run categorical (Pearson χ^2, Fisher's exact test), parametric (Independent Samples *T* Test), and nonparametric (Mann-Whitney U test) comparison tests according to the situation, whether the variables showed normal distribution or not. Pearson correlation analysis was performed to find out possible correlations between drug doses and metabolic/body measurement parameters.

At the second stage, we aimed to establish second-stage links among metabolic/body parameters, medication doses, and MetS. The variables detected as having significant links from the first-stage analysis were tested in the second-stage analysis (binary logistic regression analysis and linear regression analysis) to see if these variables would remain significantly associated with each other. In logistic regression analyses, Hosmer-Lemeshow tests indicated that all the models were appropriate for the data presented for multiple logistic regression analyses ($p > 0.05$). Also, linear regression analyses did not have any issues with multicollinearity since all the variance inflation factors for each variable were less than 3 in all the calculations.

We constituted the final model in the third stage and investigated the actual effects. In order to form the final mediational model, independent and intermediate variables that should be associated with each other and the outcome variable were determined. Afterward, the actual effects of determined drugs on MetS were examined separately in hierarchical binary logistic regression analyses before and after associated intermediate variables were controlled. A p value <0.05 was considered statistically significant for all these analyses.

Results

Out of 118 participants, 30 (25.4%) were not diagnosed with any psychiatric disorder and used no psychiatric medication. Out of 118 participants, 42 (35.6%) were diagnosed with CD, 27 (22.9%) with major depression, 13 (11%) with BPD, and 6 (5.1%) with a psychotic disorder. All the patients having a psychiatric diagnosis were using psychiatric medication. The most used treatment regimen among the patients was an "antipsychotic + antidepressant" combination with 24 cases (20.3%). The other demographics can be found in Table 1.

A significant difference was detected between the cases with and without MetS regarding psychiatric diagnosis. In patients with bipolar disorder, the percentage of instances with MetS was much greater ($\chi^2 = 10.96$, df = 4, $p = 0.04$). In addition to bivariate analyses, the variables "age, gender, psychiatric medication, and psychiatric diagnosis" were

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Table 1. Participant demographics (n = 118)

Sex	
Boy	47 (39.8)
Girl	71 (60.2)
Mother education	
Illiterate	8 (6.8)
Literate	16 (13.6)
Primary school	43 (36.4)
Secondary school	26 (22)
High school	24 (20.3)
University	1 (0.8)
Father education	
Illiterate	2 (1.7)
Literate	9 (7.6)
Primary school	34 (28.8)
Secondary school	41 (34.7)
High school	27 (22.9)
University	5 (4.2)
Maternal psychopathology	
No	75 (63.6)
Yes	43 (36.4)
Paternal psychopathology	
No	80 (67.8)
Yes	38 (32.2)
Socioeconomic status[1]	
Semi-skilled worker, uneducated, educated at the primary school level	39 (33.3)
Semi-skilled worker, uneducated, educated below high school level	45 (38.5)
Small scale businessman, white collar or skilled worker, high school graduate	26 (22.2)
University educated, professional, or in a high administrative position	7 (6)
2. TABLO	
Psychiatric diagnoses	
None	30 (25.4)
CD	42 (35.6)
BPD	13 (11)
Psychotic disorder	6 (5.1)
Major depression	27 (22.9)
Psychopharmacological medication use	
None	30 (25.4)
Antipsychotic	18 (15.3)
Antipsychotic + antidepressant	24 (20.3)
Antipsychotic + psychostimulant	1 (0.8)
Antipsychotic + antidepressant + psychostimulant	6 (5.1)
Antipsychotic + mood stabilizer + antidepressant	10 (8.5)
Antipsychotic + mood stabilizer	9 (7.6)
Antidepressant	20 (16.9)
MetS	
No	104 (88.1)
Yes	14 (11.9)
Age, years	16.00 [2]
Boys	16.00 [2]
Girls	16.00 [2]
Mother age, years	42.00 [7]
Father age[2], years	45.00 [7]
Body measures and metabolic parameters	
Weight, kg	63.57±13.67
Height[3], cm	160.53±8.64
Waist circumference[4], cm	82.13±13.94
SBP, mm Hg	110.00 [10]
DBP, mm Hg	70.00 [20]
Glucose, mg/dL	95.00 [20]
HDL, mg/dL	49.00 [14]
Triglyceride, mg/dL	85.00 [34]
Medication doses	
Risperidone, mg	
0	98 (83.1)
1	16 (13.6)
2	3 (2.5)
4	1 (0.8)
Aripiprazole, mg	
0	71 (60.29
5	21 (17.8)
10	24 (20.3)
15	2 (1.7)
Quetiapine, mg	
0	89 (75.4)
50	1 (0.8)
100	9 (7.6)
200	6 (5.1)
300	2 (1.7)
400	5 (4.2)
600	6 (5.1)
Olanzapine, mg	
0	109 (92.4)
5	6 (5.1)
10	1 (0.8)
20	2 (1.7)
Valproic acid, mg	
0	94 (79.7)
500	7 (5.9)
1,000	17 (14.4)

Data are presented as the means ± standard deviations, median [interquartile range (IQR)] or numbers (percent), as appropriate. HDL, high-density lipoprotein. [1]n = 117; [2]n = 88; [3]n = 36; [4]n = 69.

selected as independent variables via the forward Wald selection method in a full logistic regression model in which MetS status was a dependent variable. The variable of psychiatric medication was formed under five categories (none, antidepressant-only, antipsychotic-only, antipsychotic + antidepressant, antipsychotic + other). Consistent with preliminary findings from bivariate analyses, the diagnosis of BPD was found to be the only significant predictor of MetS

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($p = 0.038$, Exp(B) = 5.62, 95% CI = 1.09–28.83; Tables 2, 3). It is important to note that none of the psychiatric medication categories were associated with MetS.

First Stage

Stage – 1a

Metabolic/body parameters and MetS have been linked.

Stage – 1b: First-Stage Links between Medication Doses and MetS

Analysis revealed that the cases with higher risperidone, aripiprazole, quetiapine, and valproic acid doses were significantly higher in the cases having MetS ($\chi^2 = 8{,}787$, $p = 0.018$; $\chi^2 = 29{,}895$, $p < 0.001$; $\chi^2 = 11{,}074$, $p = 0.042$; $\chi^2 = 11{,}075$, $p = 0.002$, respectively). No significant differences regarding risperidone, aripiprazole, and olanzapine doses were found between the cases with and without MetS ($p > 0.05$).

Stage – 1c: First-Stage Links between Metabolic/Body Parameters and Medication Doses

Bivariate Pearson correlation analyses showed that risperidone dose was positively correlated with weight, SBP, and HDL-C ($r = 0.210$, $r = 0.193$, $r = 0.193$, all $p < 0.05$, respectively). Aripiprazole dose was positively correlated with serum glucose level ($r = 0.243$, $p < 0.01$), while quetiapine was positively correlated with weight ($r = 0.233$, $p < 0.05$). Valproic acid dose showed positive correlations with weight, SBP, and serum glucose level ($r = 0.302$, $p < 0.01$; $r = 0.188$, $p < 0.05$; $r = 0.271$, $p < 0.01$, respectively). However, olanzapine dose had no association with any metabolic/body parameters.

Second Stage

Stage – 2a

Metabolic/body parameters and MetS have been linked (online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000533470)

Stage – 2b: Second-Stage Links between Medication Doses and MetS

Since quetiapine and valproic acid doses were found to be associated with MetS, risperidone, aripiprazole, and olanzapine doses were not examined in the second-stage analysis. When quetiapine and valproic acid doses were separately entered in a binary logistic regression model as independent variables and MetS as a dependent variable, both quetiapine and valproic acid were detected to be positive predictors of MetS (online suppl. Table 2)

Third Stage

After performing the analysis of two stages, drug dose (quetiapine and valproic acid) and metabolic/body parameter (weight and SBP) variables were found to be related to each other and with MetS (Figs. 1, 2). Afterward, the real effects of quetiapine and valproic acid on MetS were examined separately in two-step hierarchical binary logistic regression analyses before and after associated intermediate variables (weight for quetiapine/weight and SBP for valproic acid) were controlled (Tables 4–6; Fig. 2). Although weight was found to have an effect on MetS in the final model, the effect of quetiapine on MetS remained significant after controlling for weight ($p = 0.013$, Exp(B) = 1.004, 95% CI = 1.001–1.007). Like quetiapine, valproic acid kept its significant effect on MetS when weight and SBP were controlled ($p = 0.045$, Exp(B) = 1.002, 95% CI = 1.000–1.003).

Discussion

According to the literature, MetS affects 12.4–44.4% of children and adolescents in the general population [31, 32]. A recent meta-analysis revealed that in the overall population, the prevalence of MetS is 58% greater in individuals diagnosed with psychiatric disorders [33]. In our study, the frequency of MetS was 11.9% in the whole sample, 12.5% in the group with a psychiatric diagnosis, and 10% in the group without a psychiatric diagnosis. In addition, there was no statistical difference between the case and control groups. In a study conducted with 162 adolescents and young adults with BPD aged 18–28, the prevalence of MetS was reported to be 19.8% [34]. Another study that included 143 BPD patients aged 18 to 65 demonstrated a frequency of MetS of 29.4% [35]. In a study conducted by Mohite et al. [36] with 140 adolescents (mean age: 15.12 years) diagnosed with BPD, the frequency of MetS was estimated to be 14%. In contrast to earlier studies, our study discovered that people with BPD had a higher prevalence of MetS (38.5%). This finding might depend on the low number of cases with the diagnosis of BPD and the use of multiple drugs in these cases. Since the frequency of BPD is lower under the age of 18, and diagnosing them is not so simple, it is not surprising that the number of cases with BPD was detected lower in our study. In a meta-analysis including 18 studies, the average frequency of MetS in patients with depression was reported to be 29.7% [33]. Another study suggested that the frequency of MetS was higher among patients with depression who did not use medication than in healthy controls (37.2%) [37]. However, in our study,

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Table 2. Comparison of the cases with and without metabolic syndrome in terms of demographics, metabolic parameters, medication doses, and psychiatric diagnoses

	Cases without MetS (n = 104)	Cases with MetS (n = 14)	Test statistics	p value
Age	16.00 (3)	16.00 (3)	Z = −0.664	ns[a]
Mother age	42.18±6.35	44.07±4.69	t = −1.072	ns[b]
Father age[1]	45.00 (8)	45.00 (5)	Z = −0.253	ns[a]
Weight	62.22±13.08	73.57±14.28	t = −3.014	**0.003**[b]
SBP	110.00 (20)	130.00 (13)	Z = −5.078	**<0.001**[a]
DBP	70.00 (20)	75.00 (16)	Z = −2.346	**0.019**[a]
Glucose	92.00 (20)	101.50 (13)	Z = −2.257	**0.024**[a]
HDL	49.00 (14)	45.50 (14)	Z = −1.603	ns[a]
Triglyceride	80 (31)	103.50 (80)	Z = −2.235	**0.025**[a]
Risperidone dose, mg			χ^2 = 8,787	**0.018**[d]
0	30 (100)	68 (77.3)		
1	0 (0)	16 (18.2)		
2	0 (0)	3 (3.4)		
4	0 (0)	1 (1.1)		
Aripiprazole dose, mg			χ^2 = 29,895	**<0.001**[d]
0	30 (100)	41 (46.6)		
5	0 (0)	21 (23.9)		
10	0 (0)	24 (27.3)		
15	0 (0)	2 (2.3)		
Quetiapine dose, mg			χ^2 = 11,074	**0.042**[d]
0	30 (100)	59 (67.0)		
50	0 (0)	1 (1.1)		
100	0 (0)	9 (10.2)		
200	0 (0)	6 (6.8)		
300	0 (0)	2 (2.3)		
400	0 (0)	5 (5.7)		
600	0 (0)	6 (6.8)		
Olanzapine dose, mg			χ^2 = 2,570	ns[d]
0	30 (100)	79 (89.8)		
5	0 (0)	6 (6.8)		
10	0 (0)	1 (1.1)		
20	0 (0)	2 (2.3)		
Valproic acid dose, mg			χ^2 = 11,075	**0.002**[d]
0	30 (100)	64 (72.7)		
500	0 (0)	7 (8.0)		
1,000	0 (0)	17 (19.3)		
Gender				
Boys	42 (40.4)	5 (35.7)	df = 1	ns[c]
Girls	62 (59.6)	9 (64.3)	χ^2 = 0.112	
Maternal smoking				
Smoking during pregnancy	55 (52.9)	8 (57.1)	df = 1	ns[c]
Not smoking during pregnancy	49 (47.1)	6 (42.9)	χ^2 = 0.090	
GDM				
No maternal GDM	66 (63.5)	11 (78.6)	df = 1	ns[d]
Maternal GDM +	38 (36.5)	3 (21.4)	χ^2 = 1,242	
Maternal psychopathology				
No psychiatric disorder in mother	63 (60.6)	12 (85.7)	df = 1	ns[c]
Psychiatric disorder in mother	41 (39.4)	2 (14.3)	χ^2 = 3,366	

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Table 2 (continued)

	Cases without MetS (n = 104)	Cases with MetS (n = 14)	Test statistics	p value
Paternal psychopathology				
No psychiatric disorder in father	70 (67.3)	10 (71.4)	df = 1	ns[d]
Psychiatric disorder in father	34 (32.7)	4 (28.6)	χ^2 = 0.096	
Mother education level				
Illiterate	7 (6.7)	1 (7.1)	df = 5	ns[d]
Literate	15 (14.4)	1 (7.1)		
Primary school	39 (37.5)	4 (28.6)		
Secondary school	23 (22.1)	3 (21.4)	χ^2 = 8,716	
High school	20 (19.2)	4 (28.6)		
University	0 (0)	1 (7.1)		
Father education level				
Illiterate	1 (1.0)	1 (7.1)	df = 5	ns[d]
Literate	8 (7.7)	1 (7.1)		
Primary school	33 (31.7)	1 (7.1)	χ^2 = 6,839	
Secondary school	36 (34.6)	5 (35.7)		
High school	22 (21.2)	5 (35.7)		
University	4 (3.8)	1 (7.1)		
Socioeconomic status				
Semi-skilled worker, uneducated, educated at primary school level	37 (35.9)	2 (14.3)	df = 3	ns[d]
Semi-skilled worker, uneducated, educated below high school level	40 (38.8)	5 (35.7)		
Small scale businessman, white collar or skilled worker, high school graduate	20 (19.4)	6 (42.9)	χ^2 = 4,845	
University educated, professional or in a high administrative position	6 (5.8)	1 (7.1)		
Diagnosis				
No diagnosis	27 (26.0)	3 (21.4)	df = 4	**0.040[d]**
CD	38 (36.5)	4 (28.6)		
BPD	8 (7.7)	5 (35.7)	χ^2 = 10,966	
Psychotic disorder	5 (4.8)	1 (7.1)		
Major depression	26 (25.0)	1 (7.1)		
Treatment				
No treatment	27 (26)	3 (21.4)	df = 4	ns[d]
Antipsychotic	16 (15.4)	2 (14.3)	χ^2 = 7,606	
Antidepressant	20 (19.2)	0 (0)		
Antipsychotic + antidepressant	22 (21.2)	2 (14.3)		
Antipsychotic + others	19 (18.3)	7 (50)		
Sport				
No play sport	60 (77.9)	6 (54.5)	df = 1	ns[d]
Play sport	17 (22.1)	5 (45.5)	χ^2 = 2,805	

Data are presented as the means ± standard deviations, median [interquartile range (IQR)] or numbers (percent), as appropriate. Bold values mark statistically significant differences. SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; GDM, gestational diabetes mellitus; ns, not significant. [1]n = 88. [a]Mann-Whitney U test. [b]Independent samples T test. [c]Pearson χ^2 test. [d]Fisher's exact test.

the frequency of MetS in the group with depression was found to be 3.7%. This result is different from the literature and may be due to the fact that neurovegetative symptoms are less common in children and adolescents. Children and adolescents are more likely to present with irritable depression [38]. Studies also report that

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Table 3. Binary logistic regression analysis examining the relationship among MetS and age, gender, psychiatric mediation, and psychiatric diagnoses via *forward Wald method*

	B	Exp (B)	95% CI for Exp (B)	Sig
Diagnosis (reference cat.: no diagnosis)				0.070
CD	−0.054	0.977	0.196–4.582	0.947
BPD	1.727	5.625	1.097–28.836	**0.038**
Psychotic disorder	0.588	1.800	0.154–20.987	0.639
Major depression	−1.061	0.346	0.034–3.545	0.371
Constant	−2.197	0.111		<0.001

Dependent variable: MetS status. Nagelkerke R^2 = 0.138. Bold values mark statistically significant differences.

depression may cause MetS in adult patients through neurovegetative symptoms such as hyperphagia, hypersomnia, and anergia [39].

In a systematic meta-analysis, Mitchell et al. [40] reported that the prevalence of MetS was 9.8% in patients with first-episode schizophrenia who did not receive treatment and 9.9% when both treated and non-treated schizophrenia groups were taken into account. A study from Turkey reported that the rate of MetS was 35.5% in the patients with first-episode psychosis (mean age: 29.1), whereas it was 12.2% in the healthy group [41]. In our study, in which the sample age group was younger compared to this study, the rate of MetS in patients with first-episode psychosis was found to be 16.6%. Furthermore, there is no literature on the prevalence of MetS in children and adolescents with CD and psychosis. In our study, the frequency of MetS in the patients with CD was found to be 9.5% and was lower than the rates in both the general sample and the healthy group. The previous studies in the literature have been conducted in patient groups with one disease and mostly with patients older than 18 years. It should be noted that the conflicting results between the literature and our study might be associated with multiple drug usage in some patients in our sample group.

It is frequently reported in the literature that there is an increase in the prevalence of MetS at young ages, especially in the presence of severe psychiatric diseases. In addition, it is also stated that the use of psychotropic drugs also carries the risk of weight gain and metabolic dysregulation that may cause MetS [42]. The increase in childhood manifestations of BPD and childhood schizophrenia and the positive contribution of SGA drugs on attention, memory, and cognitive system without the high incidence of extrapyramidal system side effects of first-generation antipsychotics led to an increase in the use of SGAs [43]. However, SGAs are associated with extensive weight gain, and they are also the ones associated with the greatest metabolic alterations, with weight gain reported in up to 72% of all antipsychotic-receiving patients [44].

Clozapine and olanzapine are reported to cause weight gain by dysregulating adipose tissue homeostasis [45]. However, some studies have reported metabolic alterations even without weight gain [46]. The antipsychotic medications quetiapine and clozapine have the worst impact on the circulatory system in children and adolescents, aripiprazole and ziprasidone have the lowest risk of metabolic side effects, and olanzapine is the antipsychotic drug most connected with weight gain and diabetes [47]. According to Patel et al. [48], among pediatric psychiatric patients who took antipsychotic medication for at least a month, the incidence of high triglyceride and low HDL-C levels was 23%, and the incidence of any blood lipid level deterioration was 51%. It was shown that olanzapine, quetiapine, and risperidone treatments increased triglyceride levels, whereas aripiprazole and olanzapine treatments increased low density lipoprotein-C cholesterol levels in a trial with 4,140 children and adolescents (mean age: 10.4 years) [49]. Atypical antipsychotic drugs have been found to increase the susceptibility to MetS in studies of children and adolescents [50]. It has been reported that combined treatment with mood stabilizers, especially valproate, increases the risk of MetS [43]. The results of our study indicate that the increase in weight and SBP and DBP predicted MetS. We also found that risperidone, valproic acid, and quetiapine caused MetS by increasing weight; risperidone and valproic acid by increasing SBP; and aripiprazole and valproic acid by increasing blood glucose level. Although it has been reported that the use of olanzapine causes

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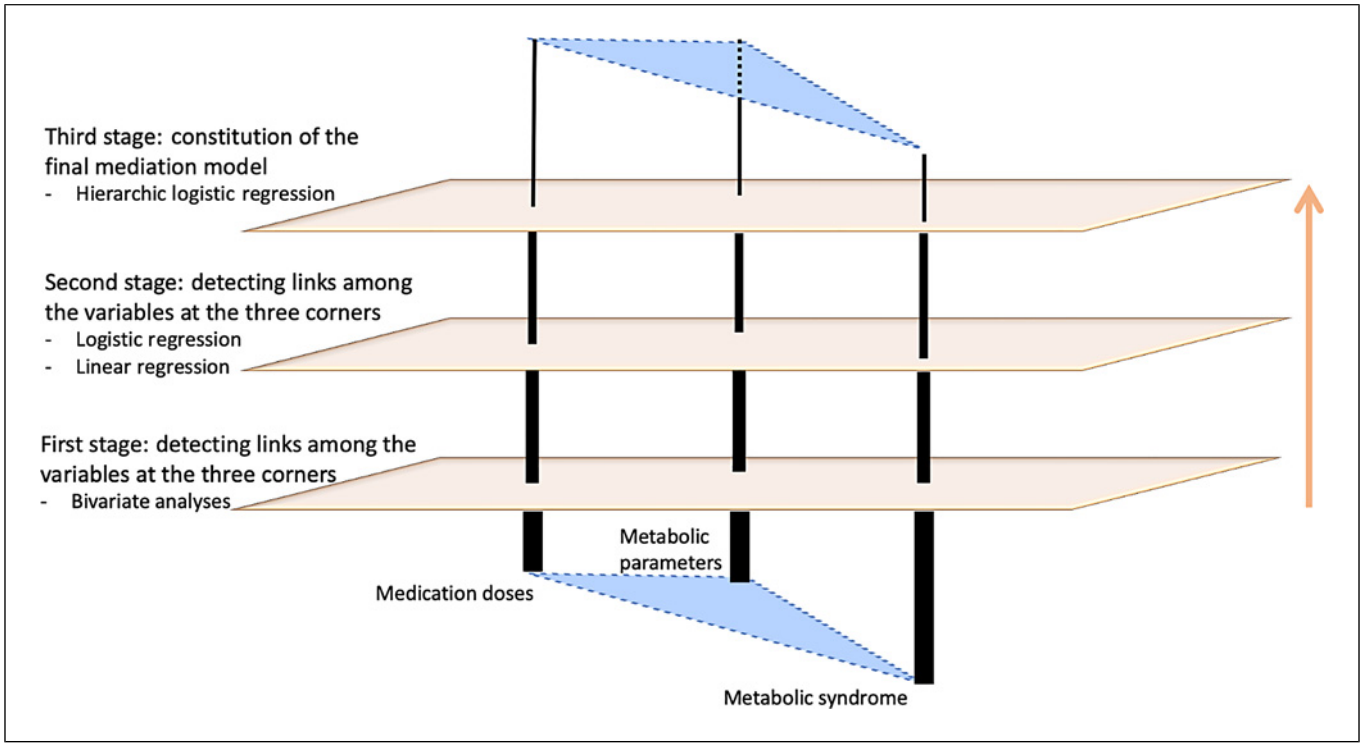


Fig. 1. Analytic strategy.

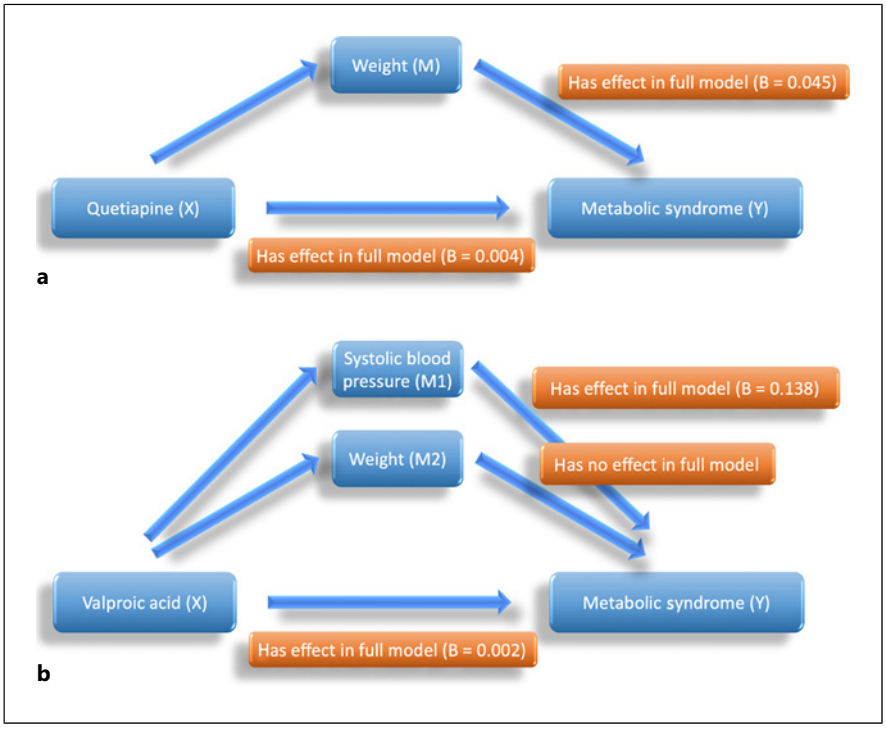


Fig. 2. Final mediation model. **a** Quetiapine is the independent (X) variable, weight is the intermediate (M) variable, MetS is the outcome (Y) variable. **b** Valproic acid is the independent (X) variable, weight and SBP are the intermediate (M) variables, MetS is the outcome (Y) variable.

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Table 4. Bivariate pearson correlation matrix

Pearson correlation	Risperidon dose	Aripiprazole dose	Quetiapine dose	Olanzapine dose	Valproic acid dose	Weight	SBP	DBP	Glucose	HDL	Triglyceride
Risperidon dose	–										
Aripiprazole dose	−0.147	–									
Quetiapine dose	0.101	0.050	–								
Olanzapine dose	0.038	0.014	0.356**	–							
Valproic acid dose	0.290**	0.260**	0.574**	0.151	–						
Weight	0.210*	−0.128	0.233*	0.007	0.302**	–					
SBP	0.193*	0.130	0.138	0.038	0.188*	0.320**	–				
DBP	0.143	0.015	0.028	0.046	0.151	0.213*	0.451**	–			
Glucose	0.026	0.243**	0.093	0.020	0.271**	0.117	0.057	−0.015	–		
HDL	0.193*	−0.132	−0.075	−0.014	−0.042	−0.003	0.023	0.024	−0.063	–	
Triglyceride	0.079	−0.014	−0.092	−0.101	0.136	0.172	−0.029	−0.037	0.265**	−0.128	–

SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein. *$p < 0.05$. **$p < 0.01$.

weight gain in children [47], a statistically significant relationship was not found in our study, probably due to the low-dose use of olanzapine and the small number of participants using olanzapine. Ko et al. [51] reported that the use of multiple antipsychotics was significantly associated with high MetS frequency; however, only aripiprazole had no effect on the increase in MetS prevalence in their study including 1,103 schizophrenia patients. Kemp et al. [52] stated that there was no significant difference between aripiprazole and placebo use in terms of MetS development in their study with 125 bipolar patients. As can be seen, literature knowledge regarding the effect of psychotropic medication use on MetS in children and adolescents is not clear today. In the current study, when the variables age, gender, psychiatric medication, and psychiatric diagnosis were examined in a single model whose dependent variable is MetS, it was found that having a diagnosis of BPD predicted MetS in particular. Despite methodological discrepancies, a study by Mohite et al. [36] points out that BPD increases the risk of MetS in individuals under the age of 18 compared to healthy controls. The findings of our study show consistency with this study. In our regression model, no medication category (antidepressants-only, antipsychotics-only, antidepressants + antipsychotics, and antipsychotics + others) predicted an increased risk for MetS. One of the reasons for this finding, which contradicts the literature, may be related to the fact that the duration of drug use and the duration of the disease in children and adolescents are not as long as in adults. However, the literature also says that SSRIs have no clear evidence for an increased risk for MetS [13, 14]. Consistently, the antidepressants used in our study were fluoxetine and sertraline which are SSRIs and did not have a significant association with MetS.

Limitations

Although this study presents important findings, it should be evaluated in the context of some limitations. Since the present study was retrospective, only the cases whose data were completely present in their files were included in the study. Therefore, the study sample consisted of a small sample group. An important limitation is that it is not known whether the patients were diagnosed with MetS before treatment. Likewise, initial measurements according to MetS IDF criteria before drug treatment were not present in the files, which leads to poor reliability of results. Also, each medication in this study did not compare the controlled doses based on the evidence, and the number of subjects making the comparison was not controlled as

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Table 5. Hierarchic binary logistic regression analysis examining the effect of quetiapine and weight on MetS

	B	Exp (B)	95% CI for Exp (B)	Sig	Nagelkerke R^2
Step 1					
Quetiapine dose	0.004	1.004	1.002–1.007	**0.001**	0.152
Constant	−2.515	0.081		<0.001	
Step 2					
Quetiapine dose	0.004	1.004	1.001–1.007	**0.013**	0.219
Weight	0.045	1.046	1.002–1.092	**0.038**	
Constant	−5.494	0.004		<0.001	

Dependent variable: MetS status. Bold values mark statistically significant differences.

Table 6. Hierarchic binary logistic regression analysis examining the effect of valproic acid, weight, and SBP on MetS

	B	Exp (B)	95% CI for Exp (B)	Sig	Nagelkerke R^2
Step 1					
Valproic acid dose	0.002	1.002	1.001–1.003	**0.001**	0.161
Constant	−2.618	0.073		<0.001	
Step 2					
Valproic acid dose	0.002	1.002	1.000–1.003	**0.045**	0.479
Weight	0.024	1.024	0.970–1.080	0.387	
SBP	0.138	1.148	1.060–1.244	**0.001**	
Constant	−20.794	0.000		<0.001	

Dependent variable: MetS status. SBP, systolic blood pressure. Bold values mark statistically significant differences.

a reason of a retrospective study. Besides, there was no information as to whether the father and mother had MetS. From both genetic and environmental perspectives, whether or not parents had MetS is extremely important. Lastly, we could not collect treatment duration information for each case. Hence, treatment duration could not be controlled in the analyses.

Conclusion

We found that especially BPD and psychotropic use in children and adolescents disrupt metabolic regulation and pose a risk for MetS. It is important to determine the risk factors causing MetS, especially in children and adolescents, in order to prevent mortality and morbidity at advanced ages. Close monitoring seems to be necessary in terms of the risk of MetS, especially in children and adolescents with psychiatric disorders and psychotropic drug use. In addition, long-term follow-up studies with larger samples are needed in this field.

Statement of Ethics

Our research complies with the guidelines for human studies and includes evidence that the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. In the manuscript, authors state that subjects have given their written informed consent and that the study protocol was approved by the institute's committee on human research. This study was initiated after obtaining ethical committee approval from Akdeniz University Faculty of Medicine Clinical Research Ethics Committee, date: November 06, 2019, decision no: 1,052.

Conflict of Interest Statement

E.S.E. is on the advisory board for Sanofi Turkey. He is also involved in the speaker bureaus of Sanofi Turkey and ARIS. The other authors declare that they have no conflicts of interest.

Funding Sources

This research received no external funding.

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Author Contributions

Ö.B.: organization-data collection. A.T.: statistic. B.Ç.: data collection-arrangement. C.K.: data collection. A.Ö.: data collection-ethic process. E.S.E.: organization.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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