Pretreatment Cardiometabolic Status in Youth With Early-Onset Psychosis: Baseline Results From the TEA Trial

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ABSTRACT

Objective: To describe pretreatment cardiometabolic constitution in children and adolescents with first-episode psychosis (FEP).

Methods: Baseline cardiometabolic assessment was performed in youths aged 12–17 years with FEP entering the Tolerability and Efficacy of Antipsychotics (TEA) trial and matched healthy controls. Patients were included between June 10, 2010, and January 29, 2014. *ICD-10* was used as the diagnostic classification system. Cardiometabolic risk markers were compared between patients versus controls and antipsychotic-naive versus antipsychotic-exposed patients.

Results: Comparing 113 youths with FEP (age ± SD = 15.74 ± 1.36 years, males = 30.1%, schizophrenia-spectrum disorders = 92.9%, antipsychotic-naive: n = 57) to 60 controls, patients had higher waist circumference (WC) *z* scores (1.13 ± 1.65 vs 0.42 ± 1.27, *P* = .018), cholesterol (4.10 ± 0.71 vs 3.79 ± 0.49 mmol/L, *P* = .014), low-density lipoproteins (2.37 ± 0.56 vs 2.13 ± 0.51, *P* = .012), and non–high-density lipoproteins (2.58 ± 1.60 vs 2.52 ± 0.52, *P* = .018). More patients than controls (42.9% vs 20.3%, *P* = .019) and antipsychotic-naive than antipsychotic-exposed (51.9% vs 34.0%, *P* = .023) had a WC > 90th percentile. Hypercholesterolemia (34.0% vs 12.5%, *P* = .015) was more frequent in patients, while decreased high-density lipoprotein cholesterol was more frequent in controls (32.5% vs 19.0%, *P* = .032). Family history of type 2 diabetes mellitus was associated with increased body mass index (BMI) *z* score (*P* < .001), WC *z* score (*P* = .001), insulin (*P* = .038), and homeostatic model assessment of insulin resistance (HOMA-IR; *P* = .025). Dyslipidemia was associated with significantly increased insulin (*P* = .041), HOMA-IR (*P* = .032), and low-density lipoprotein cholesterol (*P* = .041). Previous antipsychotic exposure was not associated with increased cardiometabolic risk. Early age at onset predicted increased BMI and WC *z* scores, while diagnosis of schizophrenia and higher Clinical Global Impression-Severity score were associated with increased blood lipids.

Conclusions: Youths with FEP had significantly greater WC and lipid abnormalities than matched controls, regardless of antipsychotic exposure. In youths with FEP, elevated metabolic risk predates antipsychotic exposure.

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The shorter life expectancy in patients diagnosed with psychotic disorders, such as schizophrenia, is largely due to an increased risk of developing obesity, type 2 diabetes mellitus (T2DM),[1] and cardiovascular diseases (ie, coronary heart disease, stroke, and pulmonary embolism).[2–4] In a Swedish population-based study of 9,162 patients discharged with schizophrenia from 1973 to 1995, cardiovascular disease was the main cause of excess death in females, while in males, suicide was the primary cause.[5] The elevated risk results from combined effects of genetic factors, unhealthy diet, sedentary lifestyle, and adverse antipsychotic effects.[6–14] Compared to adults, youths with early-onset psychotic disorders have a poorer prognosis[15–17] and an increased risk of developing adverse effects from antipsychotic treatment.[4,7,8,18] In addition, early introduction of antipsychotics that may be needed for several years translates into longer lifetime exposure to their adverse effects. Although extensively studied, the mechanisms leading to antipsychotic-related weight gain and disturbed glucose and lipid metabolism are complex and incompletely understood.[7,19,20] As the number of antipsychotic prescriptions for children and adolescents increases,[21–23] there is an urgent need to better understand the factors associated with cardiovascular risk and morbidity, including factors related or unrelated to antipsychotic use.

The primary aim of this study was to compare cardiometabolic risk parameters in antipsychotic-naive youths with first-episode psychosis (FEP) to matched healthy controls in order to gain a better understanding of treatment-independent risk factors already present before antipsychotic exposure. The primary hypothesis was that youths with FEP have higher body mass index (BMI), waist circumference (WC), blood sugar, and lipids than matched healthy controls. The secondary aim was to investigate potential correlates of cardiometabolic risks in patients with FEP, including demographic variables, smoking,

Clinical Points

- Few studies have examined the pretreatment cardiovascular risk in youths with first-episode psychosis, despite the documented shorter life expectancy in patients with psychosis, which appears to be primarily due to premature cardiovascular disease risk factors and morbidity.
- Patients with first-episode psychosis accumulate cardiovascular risk factors at an early age, even prior to antipsychotic treatment, and clinicians must be vigilant to prevent early development of obesity and metabolic syndrome.

cardiovascular disease in first-degree relatives, measures of duration and severity of psychotic illness, and previous antipsychotic treatment. The secondary hypothesis was that the presence of cardiovascular disease in first-degree relatives and higher severity of psychopathology predict higher risk for metabolic disturbances.

METHODS

Study Design

The present study refers to baseline data of the Tolerability and Efficacy of Antipsychotics (TEA) trial, a 12-week, investigator-initiated, randomized, double-blind, multicenter trial of the effects of aripiprazole versus quetiapine extended-release in children and adolescents aged 12–17 years with FEP. The inclusion period ran from June 10, 2010, to January 29, 2014. Seven child and adolescent mental health centers across Denmark, covering all university clinics, participated in the trial. A brief outline of the methods is presented below; the detailed TEA trial protocol has been published.[24] The trial is registered at ClinicalTrials.gov (NCT01119014) and the European Clinical Trials Database (EudraCT; 2009-016715-38) and approved by the Danish Medicines Agency (2612-4168), Ethics Committee of Capital Region of Denmark (H-3-2009-123), and Danish Data Protection Agency (2009-41-3991).

Subjects

Physicians at the university hospital clinics referred youths aged 12–17 years old who seemed eligible for the trial, ie, who suffered from psychotic symptoms to a degree whereby antipsychotic treatment was warranted. Investigators screened eligible patients using the Positive and Negative Syndrome Scale (PANSS)[25] interview to verify the presence and severity of psychotic symptoms. Inclusion criteria were (1) children and adolescents aged 12–17 years, both sexes; (2) inpatients or outpatients; (3) meeting the diagnostic criteria for *ICD-10*[26] F20 (schizophrenia), F22 (persistent delusional disorders), F23 (acute and transient psychotic disorders), F24 (induced delusional disorders), F25 (schizoaffective disorders), F28/F29 (other/unspecified nonorganic psychosis), F30.2 (mania with psychotic symptoms), F31.2 (bipolar affective disorder, current episode manic with psychotic symptoms), F31.5 (bipolar affective disorder, current episode severe depression with psychotic symptoms), F32.3 (severe depressive episode with psychotic symptoms), or F33.3 (recurrent depressive episode, current episode severe with psychotic symptom); (4) clinical indication for antipsychotic treatment; (5) presence of psychotic symptoms scoring ≥4 on ≥1 of the following PANSS items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness/persecution), or G9 (unusual thought content) as well as a total PANSS score >60 points; (6) antipsychotic-naive or limited exposure (ie, up to 12 months in the past year for psychosis, or no more than 1 week lifetime for any nonpsychotic indication); and (7) written and signed informed consent by caretakers. Exclusion criteria included (1) compulsory treatment, ie, pharmacologic treatment or hospital admission, instituted by the treating physician against the patient's will; (2) drug-induced or organic psychosis; (3) severe chronic somatic illness or a history of severe head trauma; (4) pregnancy or lactation; (5) substance abuse fulfilling the criteria of *ICD-10* F1x.2 dependence syndrome within the last year; (6) allergy toward the investigational drugs or known lactose intolerance; and (7) lack of informed consent.

In patients fulfilling inclusion criteria, trial interventional medication was initiated by the investigators (in collaboration with the treating physician) according to the TEA protocol.[24] At week 4, participants underwent a Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL)[27] interview covering the last 8 weeks (ie, from 4 weeks prior to and 4 weeks after randomization) in order to precisely establish their specific diagnosis.

Healthy Controls

The control sample consisted of 60 psychiatrically and somatically healthy youths (as per screening with K-SADS-PL[27] [both subjects and parents], somatic history, and clinical examination at study entry), who were recruited based on a random data extraction from the Danish Centralized Civil Register (government-owned registry of all residents in Denmark, located in Copenhagen [http://sundhedsdatastyrelsen.dk/da/forskerservice]). Controls were matched 1:2 to the enrolled patients on sex, age, and parental education.[28,29]

Assessments

Before randomization, included patients underwent comprehensive physical assessments, including height, weight, WC, heart rate, and blood pressure. Thyroid stimulating hormone (TSH), fasting plasma glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides were analyzed at the laboratory facilities of each site, while all fasting plasma insulin samples were analyzed with Roche cobas e411 (Roche Professional Diagnostics, Basel, Switzerland) at the Steno Diabetes Center, Copenhagen, Denmark. The choice of insulin over glycosylated hemoglobin

A_{1c} (HbA_{1c}) reflects research indicating that the homeostatic model assessment of insulin resistance (HOMA-IR) is a more valid marker of the risk of developing diabetes and metabolic syndrome than HbA_{1c}.[30–32] TSH was assessed, as hypo- or hyperthyroidism may affect both psychopathology and metabolism. Patients and their caregivers underwent systematic interviews regarding level of parental education,[28] participants' smoking status, and use of alcohol and illicit drugs. Clinical Global Impressions (CGI) scale,[33] Global Assessment of Psychosocial Disability (GAPD),[34] and duration of untreated psychosis (DUP)[35] were determined by the investigator. Urine samples were collected and tested for presence of illicit drugs, but determination of substance abuse did not lead to exclusion unless criteria for dependency syndrome during the past year were fulfilled. The presence or absence of psychotic or somatic illnesses in first-degree relatives was examined through systematic questions covering heart disease, diabetes type 1 and 2, dyslipidemia, obesity, and other somatic disorders (eg, epilepsy or other neurologic disorders). Any preexisting somatic illness in included participants was registered. Information regarding patients' concomitant medication at the time of inclusion was collected.

Outcomes

We assessed intermediate risk factors for developing cardiovascular disease, including elevated blood pressure (BP), increased glucose, hyperinsulinemia, insulin resistance, dyslipidemia (ie, increased fasting cholesterol and/or triglycerides), and overweight/obesity.[36]

The metabolic syndrome is defined as a cluster of measurable and modifiable risk factors that significantly increases the risk of T2DM and cardiovascular disease in adults as well as in children and adolescents.[37] Supplementary eTable 1 shows the age-dependent metabolic syndrome definition by the International Diabetes Foundation (IDF).

For the purpose of this article, WC was compared to that in the general population, using age-stratified means and 90th percentiles in 5,725 adolescents from a Norwegian study,[38] as the dietary[39] and physical habits[40] of Denmark and Norway are comparable, and no recent population-based Danish standards for WC were available.

In order to determine the age- and sex-adjusted z scores for BMI $\left(\frac{weight\ [kg]}{(height\ [m])^2}\right)$ in each individual, the LMS method[41] was used, which summarizes the distribution of the dependent variable at each age interval by its median (M) and coefficient of variation (S), plus a measure of skewness based on the Box-Cox power (L) required to transform the data to normality.[42] Accordingly, the BMI was transformed to its z score by the formula:

$$z = \frac{\left(\frac{\mathrm{BMI}}{\mathrm{M}}\right)^{\mathrm{L}} - 1}{\mathrm{L} \times \mathrm{S}} \quad \text{for } \mathrm{L} \neq 0$$

The age- and sex-adjusted values (at age intervals of 0.01 years) for L, M, and S were based on data from 12,671 measurements in "*the 2014 Danish references from birth to 20 years for height, weight, and BMI.*"[43] By using these updated reference intervals, the global increase in obesity in this age group is taken into consideration, allowing for a contemporary comparison between patients and the background population. The following categorical definitions were applied: underweight: < 5th BMI percentile; normal weight: 5th–84.9th BMI percentile; overweight: 85th–94.9th BMI percentile; and obese: ≥ 95th BMI percentile.[44]

HOMA-IR was calculated using the formula $\frac{glucose\ (mmol/l) \times \frac{insulin(pmol/l)}{6.945}}{22.5}$ (μU/mL × 6.945 = pmol/L being the conversion factor between mU/L and pmol/L, data supplied by Roche Professional Diagnostics). The defined cut-offs for elevated values were HOMA-IR > 4.39,[32,45,46] insulin ≥ 138.9 pmol/L,[47] plasma cholesterol ≥ 4.40 mmol/L, LDL cholesterol ≥ 3.4 mmol/L, HDL cholesterol < 1.03 mmol/L, non-HDL cholesterol ≥ 3.4 mmol/L, and triglycerides ≥ 1.24 mmol/L.[44] Hypertension was defined as systolic BP or diastolic BP equal to or above the 90th percentile based on age, sex, and height.[48]

The IDF criteria for metabolic syndrome—(1) elevated triglycerides (≥ 1.7 mmol/L), (2) decreased HDL cholesterol (< 1.03 mmol/L in children < 16 years or males ≥ 16 years; < 1.29 mmol/L in females ≥ 16 years of age), and (3) hypertension (systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg)—were applied to the data of all participants.[37]

Statistical Analyses

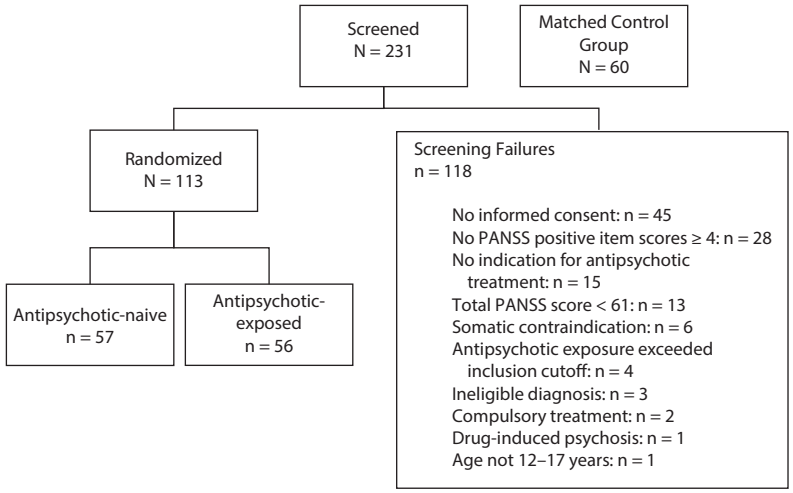
We used descriptive statistics for patient and control characteristics. A 2-sided α of .05 was considered statistically significant. For insulin, HOMA-IR, total cholesterol, HDL cholesterol, LDL cholesterol, non-HDL cholesterol, and triglycerides, only fasting samples were included. Groups compared were patients versus controls and antipsychotic-naive versus antipsychotic-exposed patients. For demographics, Mann-Whitney *U* tests and Fisher exact tests were used to compare continuous variables as appropriate. Metabolic continuous and categorical outcomes were compared using linear regression and logistic regression, respectively, with age, sex, smoking status, and level of parental education as covariates. The latter 2 covariates were included as they (1) differed between patients and controls and (2) both may have impact on food consumption. A post hoc correlation analysis of parental education and cardiometabolic outcomes was performed. SPSS version 21 (IBM Corp, released 2013, IBM SPSS Statistics for Windows, Armonk, New York) was used for statistical analyses.

RESULTS

Demographic and Clinical Characteristics

Of 231 patients screened in the 7 mental health centers, 113 patients were included in the TEA trial (for reasons for exclusion, see patient flowchart; Figure 1). Of these, 91 were recruited from the 3 centers within the Capital Region of Denmark. The screening failures consisted of 118

Figure 1. Patient Flowchart for TEA Trial



Abbreviations: PANSS = Positive and Negative Syndrome Scale, TEA = Tolerability and Efficacy of Antipsychotics.

youths (males = 37.3%, mean age ± SD = 15.31 ± 1.50 years), without significant differences in age or sex distribution between screening failures and randomized patients. All healthy controls were recruited within the Capital Region of Denmark. Of the 134 healthy controls who were willing to participate, 18 were excluded during screening, and of the remaining 116, the 60 that matched the best to patients on relevant variables were enrolled.

Participant baseline characteristics are shown in Table 1. Mean age was 15.74 ± 1.36 years for patients (34 [30.1%] males) and 15.69 ± 1.41 years for controls (18 [30.0%] males). Differences in age and sex distribution were not significant. The most frequent diagnoses among included patients were schizophrenia (*ICD-10* F20; 66.4%) and schizoaffective disorders (*ICD-10* F25; 20.4%). Mean CGI was 4.85 ± 0.73, and mean DUP was 135.71 ± 155.61 weeks. Prior to inclusion, 56 patients (49.6%) had received antipsychotic treatment for a limited period of time (median lifetime doses for each antipsychotic are listed in Table 1), while 57 patients (50.4%) were completely antipsychotic-naive. Of the included patients, 17.7% were treated with melatonin (10.7% of antipsychotic-naive patients and 25.0% of antipsychotic-exposed patients, $P = .038$), 13.3% were treated with antidepressants, 2.7% were treated with anxiolytics, and 0.9% were treated with either mood stabilizers, stimulants, or antihistamines (for sedation), without significant between-group differences. Regarding illicit drug use, 12.0% of patients tested positive for benzodiazepines (most frequently given in the psychiatric emergency room or prescribed by the general practitioner for acute symptom reduction), while 2.8% tested positive for tetrahydrocannabinol. Among patients, 96.4% reported consuming 0 to 7 servings of alcohol per week and 3.6% reported 8 to 14 servings of alcohol per week, while 2.7% did not answer the question. Among healthy controls, 98.3% reported consuming 0 to 7 servings of alcohol per week and 1.7% reported 8 to 14 servings per week ($P = .657$).

As only few controls with lower parental education level consented to participate, controls had a significantly higher level of parental education than patients ($P < .001$). As matching was performed group wise (one group for each year of age and sex), the number of controls was slightly higher than half of the number of patients.

There were no significant differences between patients and controls on presence in first-degree relatives of obesity (22.1% of patients vs 11.7% of controls), dyslipidemia (10.6% of patients vs 3.3% of controls), and type 1 diabetes mellitus (T1DM) (1.8% of patients vs 3.3% of controls), while T2DM was significantly more frequent in first-degree relatives of patients (8.0%) compared to controls (0.0%; $P = .028$).

Smoking

Patients smoked significantly more cigarettes than controls ($P < .001$) (Table 1). Among patients, 40 (35.7%) smoked cigarettes on a regular basis. The median number of cigarettes smoked per day among smokers was 10 (interquartile range [IQR], 6.0–16.5). Among controls, there was 1 smoker (1.7%), smoking 2 cigarettes a day.

Anthropometric Parameters

To test the validity of the WC measurements, we correlated the BMI *z* scores and WC *z* scores in both patients and controls and found a strong correlation between these measurements (Pearson $r = 0.746$, $P < .001$ and Pearson $r = 0.820$, $P < .001$, respectively).

Height and weight were comparable across all groups. There was no significant difference in BMI *z* scores between patients versus controls or antipsychotic-naive versus antipsychotic-exposed patients (Table 2). On the contrary, mean WC *z* scores were significantly higher in patients than in controls ($P = .018$); however, the standardized residuals for the patient group were not normally distributed as determined by Shapiro-Wilk test.

Table 1. Participant Characteristics[a]

Characteristic	All Patients (N = 113)	Antipsychotic-Naive (n = 57)	Antipsychotic-Exposed (n = 56)	Controls (n = 60)	*P* Value[b] Controls vs Patients	*P* Value[b] Antipsychotic-Exposed vs Antipsychotic-Naive
Demographic						
Age, mean ± SD, y	15.74 ± 1.36	15.87 ± 1.36	15.60 ± 1.36	15.69 ± 1.41	.857	.469
Males, n (%)	34 (30.1)	16 (28.1)	18 (32.1)	18 (30.0)	1.000	.685
Smokers, n (%)	40 (35.7)	22 (38.6)	18 (32.7)	1 (1.7)	**< .001**	.558
Cigarettes per day, median (IQR)	10.0 (6.0–16.5)	7.5 (5.0–15.0)	10.0 (6.8–20.0)	2.0 (2.0–2.0)	**< .001**	.791
TSH, mean ± SD	2.03 ± 0.97	2.01 ± 0.99	2.05 ± 0.96	2.07 ± 1.02	.889	.543
Tanner stage, mean ± SD						
Males	4.12 ± 0.91	.321	3.94 ± 1.11	3.94 ± 0.80	.321	.484
Females	4.21 ± 0.64	.110	4.28 ± 0.61	4.00 ± 0.70	.110	.407
Parents' level of education, n (%)						
Low	30 (26.5)	21 (36.8)	9 (16.1)	4 (6.7)	**< .001**	**.012**
Medium	68 (60.2)	32 (56.1)	36 (64.2)	33 (55.0)		
High	13 (11.5)	3 (5.2)	10 (17.8)	13 (21.7)		
Diseases in first-degree relatives, n (%)						
T1DM in family	2 (1.8)	1 (1.8)	1 (1.8)	2 (3.3)	.610	1.000
T2DM in family	9 (8.0)	4 (7.0)	5 (8.9)	0 (0.0)	**.028**	.742
Familial dyslipidemia	12 (10.6)	8 (14.0)	4 (7.1)	2 (3.3)	.142	.361
Familial obesity	25 (22.1)	11 (19.3)	14 (25.0)	7 (11.7)	.103	.504
Psychopathology, mean ± SD						
PANSS positive subscore	20.26 ± 3.52	20.23 ± 3.64	20.29 ± 3.44			.725
PANSS negative subscore	20.59 ± 5.29	20.28 ± 5.00	20.91 ± 5.61			.610
PANSS general subscore	37.04 ± 6.44	36.77 ± 6.10	37.32 ± 6.82			.883
PANSS total	77.89 ± 12.24	77.28 ± 11.75	78.52 ± 3.14			.726
Age at onset of psychotic symptoms, y	13.15 ± 3.06	13.13 ± 3.20	13.16 ± 2.94			.860
DUP, wk	135.71 ± 155.61	142.33 ± 154.60	128.44 ± 157.91			.396
CGI-S score	4.85 ± 0.73	4.77 ± 0.73	4.93 ± 0.73			.360
GAPD score	4.39 ± 1.10	4.28 ± 1.11	4.50 ± 1.08			.320
Diagnosis, n (%)						
Schizophrenia (F20)	75 (66.4)	40 (70.2)	35 (62.5)			.695
Delusional disorders (F22)	2 (1.8)	1 (1.8)	1 (1.8)			
Acute and transient psychotic disorders (F23)	1 (0.9)	1 (1.8)	0 (0.0)			
Schizoaffective disorders (F25)	23 (20.4)	10 (17.5)	13 (23.2)			
Other psychotic disorders (F28)	4 (3.5)	1 (1.8)	3 (5.4)			
Bipolar disorder (F31)	1 (0.9)	0 (0.0)	1 (1.8)			
Major depressive disorders (F32)	6 (5.3)	3 (5.3)	3 (5.4)			
Recurrent depressive disorder (F33)	1 (0.9)	1 (1.8)	0 (0.0)			
Antipsychotic use before inclusion						
No. of antipsychotic medications used, n (%)						
1			42 (75.0)			
2			13 (23.2)			
3			1 (1.8)			
Distribution of antipsychotic medications						
Aripiprazole, n (%)			3 (2.7)			
Aripiprazole, median cumulated lifetime dose, mg (IQR)			20.00 (15.00–35.00)			
Aripiprazole, median no. of days (IQR)			7.0 (6.0–8.0)			
Quetiapine, n (%)			9 (8.0)			
Quetiapine, median cumulated lifetime dose, mg (IQR)			250.00 (75.00–820.00)			
Quetiapine, median no. of days (IQR)			15.5 (2.5–16.0)			
Olanzapine, n (%)			23 (20.4)			
Olanzapine, median cumulated lifetime dose, mg (IQR)			45.00 (10.00–115.00)			
Olanzapine, median no. of days (IQR)			8.0 (1.0–16.0)			
Chlorprothixene,[c] n (%)			38 (33.6)			
Chlorprothixene, median cumulated lifetime dose, mg (IQR)			75.00 (25.00–180.00)			
Chlorprothixene, median no. of days (IQR)			3.0 (1.0–8.0)			

(continued)

Table 1 (continued). Participant Characteristics

Characteristic	All Patients (N = 113)	Antipsychotic-Naive (n = 57)	Antipsychotic-Exposed (n = 56)	Controls (n = 60)	*P* Value[b] Controls vs Patients	*P* Value[b] Antipsychotic-Exposed vs Antipsychotic-Naive
Use of other psychopharmacologic agents prior to inclusion						
Melatonin	20 (17.7)	6 (10.7)	14 (25.0)			.038
Antidepressants	15 (13.3)	9 (15.8)	6 (10.7)			.303
Anxiolytics	3 (2.7)	2 (3.5)	1 (1.8)			.507
Mood stabilizers (eg, lamotrigine)	1 (0.9)	1 (1.8)	0 (0.0)			.504
Stimulants (eg, methylphenidate)	1 (0.9)	1 (1.8)	0 (0.0)			.504
Antihistamines (eg, promethazine[d])	1 (0.9)	1 (1.8)	0 (0.0)			.504
Alcohol use, n (%)						
0–7 servings per week	106 (96.4)	52 (96.3)	54 (96.4)	59 (98.3)	.657	1.000
8–14 servings per week	4 (3.6)	2 (3.7)	2 (3.6)	1 (1.7)		
Positive drug tests, n (%)						
Tetrahydrocannabinol	3 (2.8)	1 (1.9)	2 (3.6)			.514
Cocaine	0 (0.0)	0 (0.0)	0 (0.0)			
Opioids	0 (0.0)	0 (0.0)	0 (0.0)			
Methamphetamine	0 (0.0)	0 (0.0)	0 (0.0)			
Benzodiazepine	13 (12.0)	7 (13.2)	6 (10.9)			.471
Amphetamine	0 (0.0)	0 (0.0)	0 (0.0)			

[a]Percentages are calculated for participants with valid data.
[b]Bolded values: $P < .05$.
[c]First-generation high dose antipsychotic similar to thiothixene.
[d]Promethazine used for sedation.
Abbreviations: BP = blood pressure; CGI-S = Clinical Global Impressions–Severity scale; DUP = duration of untreated psychosis; GAPD = Global Assessment of Psychosocial Disability; *ICD-10* = *International Statistical Classification of Diseases and Related Health Problems*, 10th revision; IQR = interquartile range; PANSS = Positive and Negative Syndrome Scale; SSRI = selective serotonin reuptake inhibitor; SD = standard deviation; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus, TSH = thyroid stimulating hormone.

Table 2. Cardiometabolic Parameters in Patients Versus Controls

Cardiometabolic Parameter	All Patients N	All Patients Mean ± SD	Antipsychotic-Naive n	Antipsychotic-Naive Mean ± SD	Antipsychotic-Exposed n	Antipsychotic-Exposed Mean ± SD	Controls n	Controls Mean ± SD	*P* Value[a] Controls vs Patients	*P* Value[a] Antipsychotic-Naive vs Antipsychotic-Exposed
Anthropometric assessments										
Weight, kg	113	62.22 ± 12.3	57	63.43 ± 12.77	56	60.98 ± 11.78	60	61.55 ± 10.09	.816	.173
Height, m	113	1.69 ± 0.10	57	1.70 ± 0.09	56	1.69 ± 0.1	60	1.69 ± .08	.434	.362
BMI *z* score	113	0.44 ± 1.26	57	0.51 ± 1.25	56	0.36 ± 1.27	60	0.44 ± 0.99	.771	.570
BMI percentile	113	0.60 ± 0.33	57	0.62 ± 0.32	56	0.58 ± 0.33	60	0.61 ± .27	.771	.570
WC *z* score	105	1.13 ± 1.65	52	1.41 ± 1.72	53	0.86 ± 1.54	59	0.42 ± 1.27	**.018**	.105
Heart rate and blood pressure										
Heart rate, bpm	112	70.3 ± 11.3	57	69.4 ± 11.6	55	71.2 ± 11.0	60	66.1 ± 11.0	**.012**	.663
Systolic BP, mm Hg	112	118.6 ± 12.3[b]	57	117.7 ± 11.1[b]	55	119.4 ± 13.4[b]	60	123.8 ± 12.0[c]	**.046**	.795
Diastolic BP, mm Hg	112	69.6 ± 9.2[b]	57	69.5 ± 8.2[b]	55	69.8 ± 10.2[b]	60	73.8 ± 8.4[c]	**.013**	.710
Glucose metabolism										
Glucose, mmol/L	99	4.94 ± 0.68	49	4.87 ± 0.51	50	5.00 ± 0.81	39	5.07 ± 0.30	.094	.519
Insulin, pmol/L	90	75.43 ± 58.80	46	75.91 ± 59.84	44	74.93 ± 58.37	39	72.64 ± 31.70	.087	.974
HOMA-IR	89	2.51 ± 2.92	46	2.46 ± 2.4	43	2.57 ± 3.41	38	2.41 ± 1.09	**.048**	.992
Lipids										
Total cholesterol, mmol/L	100	4.10 ± 0.71	49	4.17 ± 0.77	51	4.03 ± 0.65	40	3.79 ± 0.49	**.014**	.397
LDL cholesterol, mmol/L	100	2.37 ± 0.56	49	2.42 ± 0.61	51	2.33 ± 0.51	36	2.13 ± 0.51	**.012**	.431
HDL cholesterol, mmol/L	100	1.52 ± 1.57	49	1.51 ± 1.30	51	1.54 ± 1.81	40	1.26 ± 0.31	.138	.882
Non-HDL cholesterol, mmol/L	100	2.58 ± 1.60	49	2.67 ± 1.51	51	2.49 ± 1.70	40	2.52 ± 0.52	**.018**	.344
Triglycerides, mmol/L	99	0.96 ± 0.37	49	1.00 ± 0.42	50	0.91 ± 0.31	38	0.84 ± 0.34	.154	.510
Triglycerides/HDL ratio	99	0.76 ± 0.38	49	0.78 ± 0.41	50	0.74 ± 0.35	38	0.71 ± 0.36	.914	.707

[a]Bolded values: $P < .05$.
[b]Measured after 5 minutes of rest.
[c]Measured without consistent adherence to rest.
Abbreviations: BMI = body mass index, BP = blood pressure, bpm = beats per minute, HDL = high-density lipoprotein, HOMA-IR = homeostatic model assessment of insulin resistance, kg = kilograms, LDL = low-density lipoprotein, m = meters, SD = standard deviation, TSH = thyroid stimulating hormone, WC = waist circumference.

Although no significant differences in the frequency of overweight or obese individuals or in the distribution of BMI percentile groups existed, significantly more patients (42.9%) than controls (20.3%) had WC *z* score > 90th percentile ($P < .019$). Also, more antipsychotic-naive than antipsychotic-exposed patients had WC *z* score > 90th percentile (51.9% vs 34.0%, $P = .023$) (Table 3).

Blood Pressure and Heart Rate

Both the systolic BP (118.6 ± 12.3 vs 123.8 ± 12.0 mm Hg, $P = .046$) and the diastolic BP (69.6 ± 9.2 vs 73.8 ± 8.4 mm Hg, $P = .013$) were significantly lower in patients than controls. The mean systolic and diastolic BP did not differ significantly between antipsychotic-naive and antipsychotic-exposed patients (Table 2). Further, patients had had a significantly

Table 3. Frequency of Abnormal Cardiometabolic Values in Patients Versus Controls

	All Patients		Antipsychotic-Naive		Antipsychotic-Exposed		Controls		*P* Value[a]	
Variable	N	n (%)	N	n (%)	N	n (%)	N	n (%)	Controls vs Patients	Antipsychotic-Naive vs Antipsychotic-Exposed
Body mass index percentile groups	113		57		56		60		.375	.566
Underweight		7 (6.2)		2 (3.5)		5 (8.9)		1 (1.7)		
Normal		66 (58.4)		36 (63.2)		30 (53.6)		43 (71.7)		
Overweight		19 (16.8)		9 (15.8)		10 (17.9)		9 (15.0)		
Obese		21 (18.6)		10 (17.5)		11 (19.6)		7 (11.7)		
Overweight or obese	113	40 (35.4)	57	19 (33.3)	56	21 (37.5)	60	16 (26.7)	.183	.893
Systolic and/or diastolic BP ≥ 90th percentile	113	29 (25.7)	57	17 (29.8)	56	19 (33.9)	60	36 (60.0)	.273	.755
IDF metabolic syndrome										
WC *z* score > 90th percentile	105	45 (42.9)	52	27 (51.9)	53	18 (34.0)	59	12 (20.3)	**.019**	**.023**
Triglycerides ≥ 1.7 mmol/L	99	6 (6.1)	49	4 (8.2)	50	2 (4.0)	38	1 (2.6)	.583	.709
HDL-cholesterol < 1.03 mmol/L, <1.29 in females ≥ 16 years	100	19 (19.0)	49	8 (16.3)	51	11 (21.6)	40	13 (32.5)	**.032**	.362
Systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg	112	21 (18.8)	57	10 (17.5)	55	11 (20.0)	60	17 (28.3)	.382	.614
Glucose > 5.6 mmol/L	99	7 (7.1)	49	5 (10.2)	50	2 (4.0)	39	1 (2.6)	.360	.249
Metabolic syndrome present	106	3 (2.8)	51	1 (2.0)	55	2 (3.6)	58	0 (0.0)	.997	.546
Glucose metabolism										
Glucose ≥ 6.1 mmol/L	99	2 (2.0)	49	1 (2.0)	50	1 (2.0)	38	0 (0.0)	1.000	.891
Glucose ≥ 7.0 mmol/L	99	1 (1.0)	49	0 (0.0)	50	1 (2.0)	38	0 (0.0)	1.000	.999
Insulin ≥ 138.9 pmol/L	90	7 (7.8)	46	3 (6.5)	44	4 (9.1)	39	1 (2.6)	.834	.160
Insulin resistance (HOMA-IR > 4.39)	89	9 (10.1)	46	3 (6.5)	43	6 (14.0)	39	1 (2.6)	.402	.070
Lipid abnormalities										
Total cholesterol ≥ 4.4 mmol/L	100	34 (34.0)	49	20 (40.8)	51	14 (27.5)	40	5 (12.5)	**.015**	.209
LDL cholesterol ≥ 3.4 mmol/L	100	3 (3.0)	49	1 (2.0)	51	2 (3.9)	36	0 (0.0)	.998	.688
HDL cholesterol < 1.03 mmol/L	100	19 (19.0)	49	8 (16.3)	51	11 (21.6)	40	13 (32.5)	**.032**	.362
Non-HDL cholesterol ≥ 3.4 mmol/L	100	15 (15.0)	49	10 (20.4)	51	5 (9.8)	40	1 (2.5)	.114	.111
Triglycerides ≥ 1.24 mmol/L	99	16 (16.2)	49	10 (20.4)	50	6 (12.0)	38	6 (15.8)	.312	.367
Dyslipidemia[b]	99	40 (40.4)	49	24 (49.0)	50	16 (32.0)	38	10 (26.3)	.284	.204

[a]Bolded values: $P < .05$.
[b]Dyslipidemia = total cholesterol > 4.40 mmol/L and/or triglycerides > 1.24 mmol/L.
Abbreviations: BMI = body mass index, HDL = high-density lipoprotein, HOMA-IR = homeostatic model assessment of insulin resistance, LDL = low-density lipoprotein, SD = standard deviation, WC = waist circumference.

higher heart rate than controls (70.3 ± 11.3 vs 66.1 ± 11.0 bpm, $P = .012$), while, again, the 2 patient subgroups did not differ from each other. However, for diastolic blood pressure, the standardized residuals were not normally distributed as determined by Shapiro-Wilk test.

The frequency of systolic and/or diastolic BP ≥ 90th percentile for age, sex, and height did not differ significantly between groups (Table 3).

Glucose Metabolism

Compared to patients, controls had slightly higher fasting glucose levels (4.94 ± 0.68 vs 5.07 ± 0.30 mmol/L, $P = .094$), without differences between the patient subgroups ($P = .591$) (Table 2).

There were no significant differences between patients and controls in levels of fasting insulin, but HOMA-IR was higher in patients than in controls (2.51 ± 2.92 vs 2.41 ± 1.09, $P = .048$, Table 2). There were no significant differences in prevalence of hyperglycemia, hyperinsulinemia, or insulin resistance between the groups (Table 3). Two patients and no controls had fasting glucose ≥ 6.1 mmol/L ($P = 1.000$), and 1 patient and no controls had fasting glucose ≥ 7.0 mmol/L ($P = 1.000$); thus, 1 patient fulfilled the criteria for T2DM. No patients or controls had T1DM at time of inclusion.

Lipid Metabolism

Compared to controls, patients had significantly higher total, LDL cholesterol, and non–HDL cholesterol levels than controls (total cholesterol: 4.10 ± 0.71 vs 3.79 ± 0.49 mmol/L, $P = .014$; LDL cholesterol: 2.37 ± 0.56 vs 2.13 ± 0.51 mmol/L, $P = .012$; non-HDL cholesterol: 2.58 ± 1.60 vs 2.52 ± 0.52 mmol/L, $P = .018$) (Table 2). However, for LDL and non-HDL cholesterol, the standardized residuals were not normally distributed as determined by Shapiro-Wilk test.

Table 4. Psychopathological Predictors of Anthropometric and Metabolic Outcomes[a]

Predictor	BMI *z* Score	WC *z* Score	Glucose	Insulin	HOMA-IR	Cholesterol	LDL Cholesterol	Non-HDL Cholesterol	HDL Cholesterol	TG	TG/HDL Ratio
Diagnosed with schizophrenia (F20)	$F_{1, 111} = 0.002$ $P = .968$	$F_{1, 103} = 0.007$ $P = .931$	$F_{1, 97} = 0.082$ $P = .775$	$F_{1, 88} = 0.080$ $P = .778$	$F_{1, 87} = 0.111$ $P = .740$	**$F_{1, 98} = 8.651$ $P = .004$**	$F_{1, 98} = 2.142$ $P = .147$	$F_{1, 96} = 3.209$ $P = .076$	**$F_{1, 98} = 4.043$ $P = .047$**	**$F_{1, 97} = 6.124$ $P = .015$**	$F_{1, 97} = 0.320$ $P = .859$
Age at onset of psychotic symptoms	**$F_{1, 107} = 10.308$ $P = .002$**	**$F_{1, 99} = 18.650$ $P < .001$**	$F_{1, 93} = 0.561$ $P = .456$	$F_{1, 85} = 1.096$ $P = .298$	$F_{1, 84} = 1.452$ $P = .232$	$F_{1, 94} = 0.170$ $P = .681$	$F_{1, 94} = 0.492$ $P = .485$	$F_{1, 92} = 0.476$ $P = .492$	$F_{1, 94} = 0.889$ $P = .348$	$F_{1, 94} = 0.318$ $P = 0.574$	$F_{1, 94} = 0.108$ $P = .743$
PANSS positive score	$F_{1, 111} = 3.645$ $P = .059$	$F_{1, 103} = 0.505$ $P = .479$	$F_{1, 97} = 0.918$ $P = .340$	$F_{1, 88} = 0.449$ $P = .505$	$F_{1, 87} = 0.371$ $P = .544$	$F_{1, 98} = 1.169$ $P = .282$	$F_{1, 98} = 0.365$ $P = .547$	$F_{1, 96} = 0.236$ $P = .628$	$F_{1, 98} = 0.591$ $P = .444$	$F_{1, 97} = 0.199$ $P = .657$	$F_{1, 97} = 0.065$ $P = .799$
PANSS negative score	$F_{1, 111} = 0.001$ $P = .972$	$F_{1, 103} = 0.093$ $P = .761$	$F_{1, 97} = 0.375$ $P = .541$	$F_{1, 88} = 0.171$ $P = .680$	$F_{1, 87} = 0.010$ $P = .922$	$F_{1, 98} = 0.965$ $P = .328$	$F_{1, 98} = 1.292$ $P = .258$	$F_{1, 96} = 1.315$ $P = .254$	$F_{1, 98} = 0.004$ $P = .947$	$F_{1, 97} = 0.020$ $P = .888$	$F_{1, 97} = 0.014$ $P = .906$
PANSS total score	$F_{1, 111} = 0.686$ $P = .409$	$F_{1, 103} = 0.002$ $P = .962$	$F_{1, 97} = 0.157$ $P = .693$	$F_{1, 88} = 0.039$ $P = .844$	$F_{1, 87} = 0.242$ $P = .624$	$F_{1, 98} = 0.095$ $P = .758$	$F_{1, 98} = 0.368$ $P = .545$	$F_{1, 96} = 0.570$ $P = .452$	$F_{1, 98} = 0.168$ $P = .683$	$F_{1, 97} = 0.011$ $P = .915$	$F_{1, 97} = 0.129$ $P = .720$
CGI-S score	$F_{1, 111} = 0.318$ $P = .574$	$F_{1, 103} = 0.811$ $P = .370$	$F_{1, 97} = 0.331$ $P = .567$	$F_{1, 88} = 0.094$ $P = .759$	$F_{1, 87} = 0.207$ $P = .650$	**$F_{1, 98} = 7.294$ $P = .008$**	**$F_{1, 98} = 4.752$ $P = .032$**	**$F_{1, 96} = 6.953$ $P = .010$**	$F_{1, 98} = 0.077$ $P = .782$	$F_{1, 97} = 1.458$ $P = .230$	$F_{1, 97} = 0.333$ $P = .565$
Level of parental education	$F_{1, 109} = 0.151$ $P = .698$	$F_{1, 101} = 0.610$ $P = .437$	$F_{1, 96} = 0.615$ $P = .435$	**$F_{1, 87} = 4.930$ $P = .029$**	$F_{1, 86} = 3.622$ $P = .060$	$F_{1, 97} = 0.791$ $P = .376$	$F_{1, 97} = 0.002$ $P = .696$	$F_{1, 95} = 0.076$ $P = .784$	$F_{1, 97} = 0.332$ $P = .566$	$F_{1, 96} = 1.296$ $P = .258$	$F_{1, 96} = 0.096$ $P = .758$

[a]Bolded values: $P < .05$.
Abbreviations: BMI = body mass index, BP = blood pressure, HDL = high-density lipoprotein, CGI-S = Clinical Global Impressions–Severity scale, HOMA-IR = homeostatic model assessment of insulin resistance, LDL = low-density lipoprotein, PANSS = Positive and Negative Syndrome Scale, TG = triglycerides, WC = waist circumference.

Again, antipsychotic-naive versus antipsychotic-exposed patients did not differ on lipid levels (Table 2).

Finally, evaluating categorical outcomes, the prevalence of total cholesterol ≥ 4.40 mmol/L was higher in patients than in controls (34.0% vs 12.5%, $P = .015$ [Table 3]), while decreased HDL cholesterol was less frequent in patients than controls (19.0% vs 32.5%, $P = .032$).

Metabolic Syndrome

There were no significant differences between the prevalence of metabolic syndrome in the patient (2.8%) versus control (0.0%) groups or the antipsychotic-naive (2.0%) and antipsychotic-exposed (3.6%) subgroups (Table 3 and supplementary eTable 2).

Effect of Schizophrenia Diagnosis

No difference in patient characteristics, DUP, PANSS, or GAPD scores was found between patients diagnosed with schizophrenia versus patients with other psychosis diagnoses. Being diagnosed with schizophrenia was associated with lower total cholesterol (3.96 ± 0.68 vs 4.38 ± 0.69 mmol/L, $P = .004$) and lower triglycerides (0.90 ± 0.34 vs 1.07 ± 0.39, $P = .015$), but also lower HDL cholesterol (1.38 ± 1.13 vs 1.80 ± 2.18 mmol/L, $P = .047$), than in patients with other diagnoses (Table 4).

Correlates of Anthropometric and Metabolic Parameters

Using linear regression analyses, we found significant associations between younger age at onset of psychotic symptoms in patients and both higher BMI ($P = .002$) and higher WC ($P < .001$) *z* scores. Also, CGI–severity score was positively and significantly associated with total cholesterol ($P = .008$), LDL cholesterol ($P = .032$), and non-HDL cholesterol ($P = .010$) (Table 4).

Mann-Whitney *U* tests were run to assess if BMI and WC *z* scores as well as lipid and glucose metabolism parameters were higher in patients whose first-degree relatives (ie, biological parents or siblings) suffered from dyslipidemia, T1DM, or T2DM or from overweight or obesity (Table 5). There were no significant differences in sex distribution, mean age, Tanner stage, or cigarette consumption between groups in these 4 categories (ie, when comparing groups without familial obesity vs with familial obesity, without T1DM vs with T1DM, without T2DM vs with T2DM, and without dyslipidemia vs with dyslipidemia). In the patient group, we found that obesity in first-degree relatives was associated with both a higher mean patient BMI *z* score ($P = .003$) and WC *z* score ($P = .034$) and that T2DM in first-degree relatives was associated with both higher patient BMI *z* score ($P < .001$) and WC *z* score ($P = .001$), as well as with higher patient insulin ($P = .038$) and HOMA-IR ($P = .025$). In the patient group, there was also an association between dyslipidemia in first-degree relatives and higher patient LDL cholesterol ($P = .041$), higher patient insulin ($P = .041$), and HOMA-IR ($P = .032$) and between T1DM in first-degree relatives and *higher* patient HDL cholesterol ($P = .029$).

No controls had first-degree relatives with known T2DM. Obesity in first-degree relatives of controls was associated with increased control BMI *z* score ($P = .009$) and insulin ($P = .024$). T1DM in first-degree relatives of controls was associated with lower control WC *z* score ($P = .005$).

There was no statistically significant difference in any metabolic parameters between patients with first-degree relatives with (n = 9) and without (n = 104) a history of psychotic illness.

Table 5. Associations Between Somatic Conditions in First-Degree Relatives and Metabolic Disturbances in Participants[a]

Somatic Condition in First-Degree Relatives—Patients								
	Obesity (n = 25)		T1DM (n = 2)		T2DM (n = 9)		Dyslipidemia (n = 12)	
Variable	*U*	*P*	*U*	*P*	*U*	*P*	*U*	*P*
BMI *z* score	**1,525.000**	**.003**	28.000	.071	**845.000**	**<.001**	631.000	.816
WC *z* score	**1,216.000**	**.034**	48.000	.229	**712.000**	**.001**	563.500	.627
Glucose	118.500	.504	49.500	.268	429.000	.769	451.500	.717
Insulin	915.500	.068	13.000	.311	**519.000**	**.038**	**516.500**	**.041**
HOMA-IR	891.500	.086	9.000	.225	**525.000**	**.025**	**517.500**	**.032**
Total cholesterol	1,089.500	.151	149.500	.233	464.000	.511	661.000	.058
LDL cholesterol	1,067.000	.210	126.000	.524	499.500	.277	**674.500**	**.041**
Non-HDL cholesterol	1,010.500	.426	125.500	.524	493.500	.311	598.000	.231
HDL cholesterol	962.500	.682	**180.500**	**.029**	377.500	.699	537.000	.599
Triglycerides	988.000	.472	114.000	.693	452.500	.563	563.000	.379
TG/HDL ratio	872.000	.819	92.000	.911	458.000	.519	494.000	.911
Somatic Condition in First-Degree Relatives—Controls								
	Obesity (n = 5)		T1DM (n = 2)		T2DM (n = 0)		Dyslipidemia (n = 2)	
	U	*P*	*U*	*P*			*U*	*P*
BMI *z* score	**138.000**	**.009**	57.000	.983	…	…	101.000	.081
WC *z* score	209.500	.211	**2.000**	**.005**	…	…	49.000	.339
Glucose	77.000	.760	40.500	.826	…	…	56.000	.270
Insulin	**138.000**	**.024**	17.500	.243	…	…	29.000	.513
HOMA-IR	123.000	.084	21.000	.376	…	…	27.000	.579
Total cholesterol	104.500	.498	43.000	.785	…	…	44.500	.697
LDL cholesterol	111.500	.122	38.500	.762	…	…	53.000	.229
Non-HDL cholesterol	116.000	.261	46.000	.656	…	…	53.500	.369
HDL cholesterol	72.000	.551	31.500	.697	…	…	26.500	.503
Triglycerides	75.500	.769	36.500	1.000	…	…	42.000	.728
TG/HDL ratio	91.000	.738	37.500	.922	…	…	41.000	.774

[a]Bolded values: $P < .05$.
Abbreviations: BMI = body mass index, BP = blood pressure, HDL = high-density lipoprotein, HOMA-IR = homeostatic model assessment of insulin resistance, LDL = low-density lipoprotein, T1DM = type 1 diabetes, T2DM = type 2 diabetes, TG = triglycerides, WC = waist circumference.

Finally, in a post hoc analysis, we found that lower level of parental education in healthy controls was significantly correlated with higher BMI *z* score (Pearson *r*: –0.321, $P = .012$), WC *z* score (Pearson *r*: –0.263, $P = .040$), triglyceride level (Pearson *r*: 0.399, $P = .013$), and triglyceride/HDL ratio (Pearson *r*: 0.347, $P = .018$), but these correlations were not seen in the patient group.

DISCUSSION

To our knowledge, this is the first study in which cardiometabolic risk status was assessed in antipsychotic-naive or briefly exposed, early-onset, first-episode psychotic children and adolescents and compared to concurrently enrolled, matched healthy controls. Psychotic patients had higher WC *z* scores and increased lipids (total cholesterol and LDL cholesterol) than the healthy controls, despite almost identical BMI *z* score values. While the frequency of overweight and obesity based on BMI percentiles did not differ between patients and controls, the frequency of WC equal to or above the 90th percentile—the cutoff for abdominal obesity for the metabolic syndrome—was doubled in patients compared to controls.

Taken together, our data indicate a higher occurrence of abdominal obesity and specific lipid, but not glucose metabolism, abnormalities in children and adolescents with psychotic disorders in the initial phase. Our results contrast with findings from a prior systematic review in adults with FEP,[49] in which authors found no difference in cardiometabolic risk between patients and healthy controls before treatment initiation. Nevertheless, the authors found indications of a higher waist-to-hip ratio and more intra-abdominal fat relative to BMI in premedicated patients compared to controls, but that such differences did not reach significance, probably due to a lack of adequate matching with controls.[49] On the other hand, our findings converge with other studies in adults,[50,51] which link the presence of severe mental illness to an increased risk of cardiovascular risk factors, even before antipsychotic treatment is initiated. Our data support the hypothesis that the risk of developing chronic metabolic disturbances in youths with psychotic disorders is elevated even at a pretreatment stage. When antipsychotic medication effects are added, the risk is further heightened.[3,6–14,49,52,53] Similarly, baseline results from 394 patients with FEP aged 15 to 40 years (mean ± SD age = 23.6 ± 5.0 years) from the US Recovery After an Initial Schizophrenia Episode–Early Treatment Program (RAISE-ETP) study[47] showed a percentage of overweight or obesity of 48.3%. This prevalence did not differ from that of the general US population of similar age, yet despite only 47 days of lifetime antipsychotic exposure, several other metabolic abnormalities were observed compared to the

general population controls. Nevertheless, in that sample, higher anthropometric measures were associated with overall psychotic illness duration, and antipsychotic exposure duration was associated with metabolic risk. On average, patients from the TEA trial had higher sex- and age-adjusted BMI and WC *z* scores than the background population.[43] Our results do not allow us to speculate whether the reasons underlying this increased cardiometabolic risk is due to genetic factors or diet and lifestyle patterns, but most likely, both contribute to the observed differences.

Although seemingly counterintuitive, the finding that antipsychotic-naive and antipsychotic-exposed patients did not differ across almost all anthropometric and metabolic assessments is likely due to the very short mean exposure (median 6 days; IQR, 1–12) to antipsychotics.

The post hoc analysis revealed that in the healthy control group, BMI and WC *z* scores were both inversely correlated with parents' level of education. This finding coincides with results from a Greek study of 1,125 children, in which higher adherence to a healthy diet was associated with lower likelihood of overweight/obesity, but only among children with at least 1 parent with higher education.[54] This association was not seen in the patients group. It may be that in patients, the protective effect of parental education is "trumped" by effect of the psychotic disorder.

We also found that early onset of psychotic symptoms predicted both higher BMI and WC *z* scores, indicating that psychotic symptoms at an early age may interfere with the adaption of healthy eating habits after the growth spurt in early adolescence. This finding could also explain the dissonance between the effect of parental education in patients and controls. However, these hypotheses are speculative and require further investigation. Also, higher CGI-S scores correlated to higher total cholesterol, LDL cholesterol, and non-HDL cholesterol, suggesting that the severity of the psychotic disorders has a negative impact on the patient's ability to maintain a healthy diet. Nevertheless, the latter 2 results could also support the notion that the same genetic loading contributing to the development of psychosis might also be linked to the development of metabolic disturbances. Other studies have demonstrated that psychotic symptoms are related to higher risk of somatic health problems,[55] including diabetes.[56] Finally, smoking was also much more prevalent in the patient group (35.7%) than among healthy controls (1.7%), consistent with data from a Norwegian study[57] comparing substance abuse and smoking in adolescents with mental disorders to the background population. The healthy controls in our sample, however, had a relatively low frequency of tobacco use. According to a recent study[58] of childhood health in Denmark, around 5% of adolescents aged 15 years are daily smokers.

Finally, in patients, obesity and T2DM in first-degree relatives were both associated with increased BMI *z* score and WC *z* score, while T2DM and dyslipidemia in first-degree relatives were associated with increased insulin and HOMA-IR, and dyslipidemia was associated with increased LDL cholesterol. Whether or not these associations are due to shared genetic risk or shared environment/behavior requires further study. Nevertheless, these results underscore the importance of thoroughly evaluating the family history when choosing and administering antipsychotics in youths.

This study has several limitations. First, the number of patients and healthy controls is relatively modest. Even though the TEA trial is one of the largest head-to-head randomized trials of antipsychotics conducted in youths, the power estimation is based on the primary efficacy outcome measure, ie, change in PANSS positive symptoms. Second, we cannot fully ascertain the representativeness of the enrolled sample. Also, due to very limited access to information on the non-included patients, we could not compare our sample to the screening failures beyond age and gender. Although we had a high percentage of females in our sample, there was no difference in sex distribution compared to the patients not enrolled in the study, and a similar proportion of females among FEP patients was also found in a recent Danish register study[59] of early onset schizophrenia. Further, the difference between healthy controls and patients in parental education reflects that some degree of selection bias was unavoidable (only 14% of 957 healthy controls invited by letter consented to participate). Third, we did not have information on diet and exercise in patients and controls, which could have enriched analysis and interpretation of cardiometabolic status in FEP. Fourth, half of the patient sample had antipsychotic exposure prior to the baseline assessment. Using only truly antipsychotic-naive patients would have increased the power of the study but would have required a twice as long recruitment period. Also, including both antipsychotic-naive and antipsychotic-exposed patients allowed us to compare the 2 groups. Fifth, the small number of healthy controls who had first-degree relatives with metabolic/cardiovascular diseases limits the possibility to draw conclusions for the comparison between patients and controls. And finally, the very high rates of BP ≥90th percentile in healthy controls prompted us to check for any systematic error. While all patients had BP measured after 5 minutes of rest, we found that this resting period had not been rigorously implemented during the assessment of healthy controls. This discrepancy may explain the unexpectedly high BP findings seen in this group and invalidate the result.

Despite these limitations, the strengths of the present study include the comparison of patients with first-episode early-onset psychosis to a concurrently ascertained matched healthy control group, all with complete baseline data, a stringent prospective cardiometabolic risk assessment, and availability of family history data of cardiometabolic diseases. The use of very recent and precise population data as the basis for the *z* score data allows for a contemporary comparison with the background population.

In summary, our findings demonstrate that children and adolescents with psychosis already have elevated abdominal obesity and lipid abnormalities prior to antipsychotic initiation. Therefore, clinicians must carefully consider the potential for inducing weight gain and dyslipidemia when selecting antipsychotic treatment. During treatment, routine

monitoring of anthropometric and metabolic parameters is essential. Furthermore, interventions to minimize the impact of offending medications, either through exercise, dose reduction, dietary changes, or use of medications with counteracting potentials, such as metformin[60–62] or melatonin,[63–65] as well as interventions to prevent or stop smoking, are essential to reduce the long-term risk of cardiovascular disease in patients with early-onset psychosis.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Pre-Treatment Cardiometabolic Status in Youth With Early-Onset Psychosis: Baseline Results From the TEA Trial

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List of Supplementary Material for the article

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1: Definition of metabolic syndrome in children and adolescents by the International Diabetes Federation

Metabolic Syndrome is present if there is obesity plus two or more other criteria are fulfilled					
Age group (years)	Obesity (waist circumference)	Triglycerides	HDL-cholesterol	Blood pressure	Glucose
6 to <10	≥ 90th percentile	Metabolic syndrome cannot be diagnosed, but further measurements should be made if there is a family history of metabolic syndrome, T2DM, dyslipidemia, cardiovascular disease, hypertension and/or obesity.			
10 to <16	≥ 90th percentile or adult cut-off if lower	≥ 1.7 mmol/L (≥ 150 mg/dL)	< 1.03 mmol/L (< 40 mg/dL)	Systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg	FPG ≥ 5.6 mmol/L (100 mg/dL) or known T2DM
≥ 16 (adult criteria)	WC ≥ 94cm for Europid males and ≥ 80cm for Europid females, with ethnic-specific values for other groups	≥ 1.7 mmol/L (≥ 150 mg/dL) or specific treatment for high triglycerides	< 1.03mmol/L (< 40 mg/dL) in males and < 1.29mmol/L (< 50 mg/dL) in females, or specific treatment for low HDL	Systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension	FPG ≥ 5.6 mmol/L (100 mg/dL) or known T2DM

BP: Blood Pressure; cm: centimeters; FPG, Fasting Plasma Glucose; HDL, High Density Lipoprotein; mg/dL, milligrams per deciliter; mmol/L: milliomoles per liter; T2DM, Type 2 Diabetes Mellitus; WC, Waist Circumference.

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	Age, years	Gender	Alcohol	Cigarettes per day	Systolic BP, mmHg	Diastolic BP, mmHg	Heart Rate, bpm	Weight, kg	Height, m	WC, cm	BMI, kg/m^2	BMI z-score	WC z-score	Tanner stage	LDL-cholesterol mmol/L	HDL-cholesterol mmol/L	Triglycerides mmol/L	Glucose mmol/L	Insulin pmol/l
1	15	M	0	0	152	95	82	82.7	1.84	88.0	24.4	1.4	2.3	4	1.90	.70	1.07	5.5	27.0
2	14	M	0	7	145	76	60	79.7	1.82	90.0	24.1	1.5	2.8	4	1.80	.80	1.00	5.1	17.0
3	15	F	0	10	118	55	78	79.3	1.65	97.0	29.1	2.7	5.3	5	2.50	.90	1.60	6.4	403.4

BMI: Body Mass Index; BP: Blood Pressure; bpm: beats per minute; cm: centimeters; HDL: High-Density Lipoprotein; kg: kilograms; LDL: Low-Density Lipoprotein; m: meters; TG: Triglycerides; WC: Waist Circumference