Original Investigation

# Cardiometabolic Risk in Patients With First-Episode Schizophrenia Spectrum Disorders
## Baseline Results From the RAISE-ETP Study

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**IMPORTANCE** The fact that individuals with schizophrenia have high cardiovascular morbidity and mortality is well established. However, risk status and moderators or mediators in the earliest stages of illness are less clear.

**OBJECTIVE** To assess cardiometabolic risk in first-episode schizophrenia spectrum disorders (FES) and its relationship to illness duration, antipsychotic treatment duration and type, sex, and race/ethnicity.

**DESIGN, SETTING, AND PARTICIPANTS** Baseline results of the Recovery After an Initial Schizophrenia Episode (RAISE) study, collected between July 22, 2010, and July 5, 2012, from 34 community mental health facilities without major research, teaching, or clinical FES programs. Patients were aged 15 to 40 years, had research-confirmed diagnoses of FES, and had less than 6 months of lifetime antipsychotic treatment.

**EXPOSURE** Prebaseline antipsychotic treatment was based on the community clinician's and/or patient's decision.

**MAIN OUTCOMES AND MEASURES** Body composition and fasting lipid, glucose, and insulin parameters.

**RESULTS** In 394 of 404 patients with cardiometabolic data (mean [SD] age, 23.6 [5.0] years; mean [SD] lifetime antipsychotic treatment, 47.3 [46.1] days), 48.3% were obese or overweight, 50.8% smoked, 56.5% had dyslipidemia, 39.9% had prehypertension, 10.0% had hypertension, and 13.2% had metabolic syndrome. Prediabetes (glucose based, 4.0%; hemoglobin $A_{1c}$ based, 15.4%) and diabetes (glucose based, 3.0%; hemoglobin $A_{1c}$ based, 2.9%) were less frequent. Total psychiatric illness duration correlated significantly with higher body mass index, fat mass, fat percentage, and waist circumference (all $P < .01$) but not elevated metabolic parameters (except triglycerides to HDL-C ratio [$P = .04$]). Conversely, antipsychotic treatment duration correlated significantly with higher non–HDL-C, triglycerides, and triglycerides to HDL-C ratio and lower HDL-C and systolic blood pressure (all $P \leq .01$). Olanzapine was significantly associated with higher triglycerides, insulin, and insulin resistance, whereas quetiapine fumarate was associated with significantly higher triglycerides to HDL-C ratio (all $P \leq .02$).

**CONCLUSIONS AND RELEVANCE** In patients with FES, cardiometabolic risk factors and abnormalities are present early in the illness and likely related to the underlying illness, unhealthy lifestyle, and antipsychotic medications, which interact with each other. Prevention of and early interventions for psychiatric illness and treatment with lower-risk agents, routine antipsychotic adverse effect monitoring, and smoking cessation interventions are needed from the earliest illness phases.

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Schizophrenia spectrum disorders are associated with 2- to 3-fold excess mortality[1-3] and a 10- to 30-year gap in life expectancy[4-7] that has been widening[2,8-11] compared with the general population. Whereas secondary and tertiary prevention has improved in the general population,[8,12,13] people with schizophrenia receive inadequate care for physical illnesses[12,14-17] despite available guidelines.[18] The vast majority of this group's premature mortality is related to cardiovascular illness and obesity-related cancers.[4,7,11,13,19] Reasons for the excess cardiovascular risk are complex, involving schizophrenia-related factors, poverty, unhealthy lifestyle, suboptimal medical monitoring and care, and adverse effects of treatment.[13,20,21]

Because cardiovascular risk factors may develop quickly[22-24] and overweight or obesity can lead to diabetes mellitus and coronary heart disease risk,[25] even if weight is lost later in life,[26] patients with first-episode schizophrenia spectrum disorders (FES) require attention to both psychiatric and medical health. Although antipsychotics are the cornerstone of FES treatment[27] and reduce psychiatric symptoms and overall mortality,[28,29] they can cause cardiometabolic adverse effects[20,21] that should be prevented.[30] Unfortunately, little is known about the trajectory of cardiometabolic risk as patients progress through their illness. Further, FES data are scarce and largely limited to samples assessed in controlled trials and/or academic settings.

To better characterize the cardiometabolic health of patients with FES and its relationship to sex, race/ethnicity, illness duration, and antipsychotic treatment, we report baseline data from patients with FES enrolled in a prospective treatment study at 34 real-world community mental health clinics across the United States.

## Methods

As part of the National Institute of Mental Health–funded Recovery After an Initial Schizophrenia Episode–Early Treatment Program (RAISE-ETP) study, we examined the cardiovascular health of individuals with FES. Baseline data were collected from July 22, 2010, through July 5, 2012. The study was approved by the North Shore-LIJ Health System Institutional Review Board and/or local site institutional review boards. Adults provided written informed consent; patients younger than 18 years provided written assent, with legal guardians providing written informed consent.

### Study Design

The RAISE-ETP study is a cluster-randomized comparison of NAVIGATE, an integrated program of medication treatment guided by a decision support system, individual psychotherapy, family psychoeducation, and supported employment or education vs community care determined by the clinician's or patient's choice. Sites included 34 community mental health centers without major research, teaching, or clinical first-episode programs, located in diverse communities ranging from semirural to large urban (eAppendix 1 in the Supplement).

### Patients and Treatment

The following were inclusion criteria for the patients: (1) being aged 15 to 40 years (1 patient was aged 51 years; a protocol exception was filed); (2) being diagnosed as having schizophrenia, schizophreniform disorder, schizoaffective disorder, psychotic disorder not otherwise specified, or brief psychotic disorder; (3) having less than 6 months of cumulative antipsychotic use (defining *first episode*); and (4) being proficient in English. The following were exclusion criteria: (1) being diagnosed as having bipolar disorder, major depressive disorder with psychosis, substance-induced psychotic disorder, or psychotic disorder due to a general medical condition; (2) having current neurological disorders affecting diagnosis or prognosis; and (3) having clinically significant head trauma or another serious medical condition. The inclusion and exclusion of patients are shown in **Figure 1**. Any treatment received prior to study participation or assessment was based on the community clinician's and/or patient's choice.

### Assessment

Assessments pertinent herein documented prescribed medication, demographic, psychosocial, illness duration, medical and substance use information (based on site personnel interview of the patient or informants with or without medical record review). Race and ethnicity were coded based on patient or informant information and assessed because these variables have been associated with cardiovascular risk factors and illness in the general population. Diagnoses were determined using the Structured Clinical Interview for *DSM-IV* Axis I Disorders, Patient Edition[31] by centralized, expert interviewers conducting live, 2-way video patient interviews. Tobacco smoking status was obtained with the Fagerström questionnaire.[32]

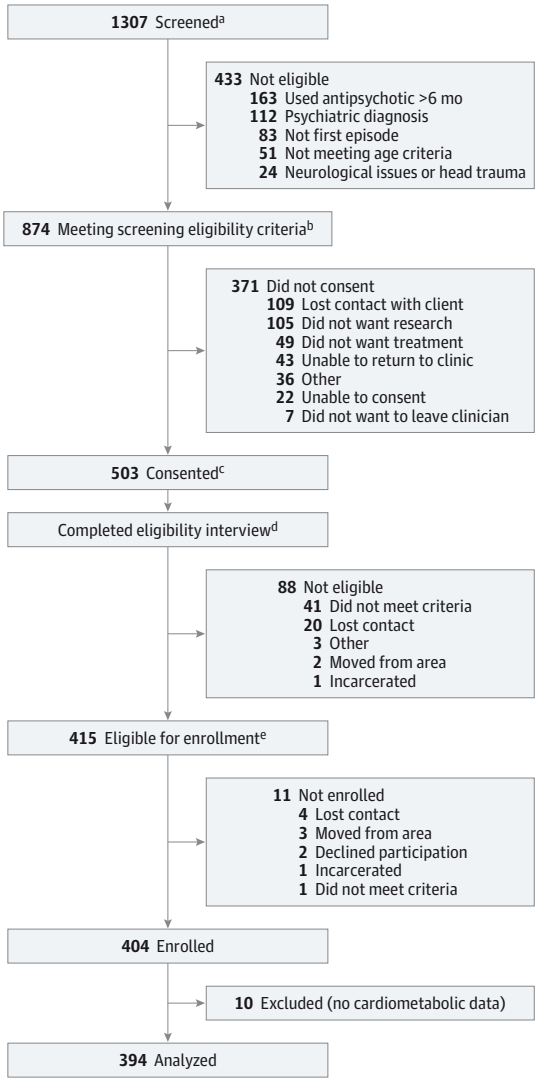
Patients underwent research assessments of height (Seca 217 stadiometer), weight plus fat mass and percentage (Tanita TBF-310GS scale), waist circumference, and systolic and diastolic blood pressure as well as fasting phlebotomy for electrolytes, liver and renal function, and levels of hemoglobin $A_{1c}$ ($HbA_{1c}$), insulin, and lipids. Fasting glucose level was assessed clinically and collected from the patients' records.

For definitions and thresholds[33-41] for body composition and cardiometabolic outcomes, see eAppendix 2 in the Supplement.

### Statistical Analysis

Except for HDL-C and $HbA_{1c}$, all metabolic parameter analyses were restricted to the 286 patients (94.1%) with fasting blood test results. Extreme outlying data were capped at 4 SDs above the mean for fasting triglycerides, glucose, and insulin in 1 individual each. One patient with type 1 insulin-dependent diabetes was excluded from the analysis of glucose, insulin, and homeostasis model assessment-estimated insulin resistance. Beyond descriptive analyses of the entire sample, categorical and continuous cardiovascular variables were compared by sex, race, ethnicity, and antipsychotic-naive vs antipsychotic-exposed status using $\chi^2$ test and *t* test or Fisher exact test as appropriate. Racial subgroups were compared using post hoc pairwise *t* test. No further adjustments for multiple comparisons were made. Because of nonnormal

Figure 1. Flow Diagram of Study Participants




[a] Potential research participants contacted by research staff.

[b] Potential participants meeting brief (preconsent) checklist.

[c] Potential participants who signed informed consent and agreed to participate in the study if eligibility criteria were met.

[d] After signing informed consent, patients submitted to diagnostic eligibility interview, during which major inclusion and exclusion criteria were assessed.

[e] For patients meeting eligibility on the diagnostic interview, enrollment into treatment occurred at the end of the baseline 2 visit, during which the final eligibility criteria were assessed.

distribution of duration of illness and antipsychotic treatment, Spearman ρ was used to assess correlations between these variables and continuous cardiometabolic variables (providing more power than categorical outcomes). Exploratory linear regression analyses of continuous cardiometabolic variables were performed to evaluate the contribution of specific second-generation antipsychotics (excluding asenapine, clozapine, and lurasidone hydrochloride [each n < 10]), first-generation antipsychotics (grouped together), antipsychotic polypharmacy, and no baseline antipsychotic treatment (entering treatment groups as binary variables). For analyses of body composition and blood pressure, linear regression models were adjusted for sex, age, race, and ethnicity. Because patients taking quetiapine fumarate had significantly higher fat percentage, all metabolic outcome models were additionally adjusted for fat percentage. Analyses were conducted with JMP version 5 statistical software (SAS Institute Inc), with α = .05 (2-sided).

## Results

### Demographic, Illness, Treatment, and Smoking Characteristics

The RAISE-ETP sample consists of 404 patients; 394 (97.5%) had 1 or more baseline assessments of body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), blood pressure, or metabolic assessment, composing the study sample (Figure 1). The mean (SD) age of patients was 23.6 (5.0) years; 73.1% of patients were male; 81.5% were non-Hispanic; and 54.6% were white (**Table 1**). Diagnoses included schizophrenia (53.8%), schizoaffective disorder (20.1%), schizophreniform disorder (16.0%), and psychotic disorder not otherwise specified or brief psychotic disorder (10.2%).

At baseline, 56.9% were referred from outpatient settings and 78.4% had at least 1 psychiatric hospitalization; 86.3% had received antipsychotics, of which 92.4% were second-generation antipsychotics (Table 1). The mean (SD) total lifetime antipsychotic treatment was 47.3 (46.1) days (95% CI, 42.7-51.9). Other psychotropic medications consisted mainly of antidepressants (32.0%), anticholinergics (17.3%), mood stabilizers (12.2%), and benzodiazepines (11.2%).

Males were significantly younger than females at first psychotic symptom onset ($P = .04$) and baseline ($P < .001$) (Table 1). More females than males had schizoaffective disorder ($P < .001$) and received antidepressants ($P = .001$) and benzodiazepines ($P = .009$). Racial groups did not differ significantly regarding sex ($P = .09$), age ($P = .59$), baseline antipsychotic treatment group ($P = .32$), or antipsychotic treatment duration ($P = .97$).

Among all patients, 50.8% smoked cigarettes; significantly more males than females smoked (55.9% vs 36.8%, respectively; $P < .001$) (**Table 2**). No patient received nicotine replacement or medication treatment for smoking (**Figure 2**).

### Body Composition

The mean (SD) BMI was 26.6 (6.7); 48.3% of patients were obese (22.1%) or overweight (26.2%) (Table 2). Females compared with males had significantly higher fat mass (mean [SD], 25.3 [16.3] vs 16.6 [13.4] kg, respectively; $P < .001$) and fat percentage (mean [SD], 32.5% [10.8%] vs 19.0% [9.5%], respectively; $P < .001$). Black patients had significantly higher fat mass than white patients (mean [SD], 21.6 [17.6] vs 18.0 [12.9] kg, respectively; $P = .03$) (**Table 3**).

### Arterial Hypertension

Among the patients, 39.9% had prehypertension and 10.0% had hypertension but only 3.6% received antihypertensive drugs

Table 1. Demographic, Illness, and Treatment Characteristics by Sex

| Characteristic | Total (N = 394) | Males (n = 288) | Females (n = 106) | *P* Value |
|---|---|---|---|---|
| Age, mean (SD), y | 23.6 (5.0) | 23.1 (4.4) | 25.0 (6.3) | <.001 |
| Age at first psychiatric illness, mean (SD), y | 16.9 (6.5) | 16.7 (6.2) | 17.5 (7.0) | .28 |
| Duration since onset of any first psychiatric illness, mean (SD), y | 6.7 (6.7) | 6.4 (6.3) | 7.6 (7.9) | .13 |
| Duration of untreated psychosis, median (IQR), wk | 84.6 (25.9-270.9) | 76.7 (24.9-280.9) | 105.1 (31.6-260.0) | .31 |
| Age at first psychotic symptoms, mean (SD), y | 19.0 (6.2) | 18.6 (5.5) | 20.1 (7.9) | .04 |
| Non-Hispanic ethnicity, No. (%) | 321 (81.5) | 229 (79.5) | 92 (86.8) | .10 |
| Race, No. (%) | | | | |
| White | 215 (54.6) | 165 (57.3) | 50 (47.2) | .09 |
| Black | 144 (36.6) | 96 (33.3) | 48 (45.3) | |
| Native American | 22 (5.6) | 19 (6.6) | 3 (2.8) | |
| Asian | 12 (3.1) | 7 (2.4) | 5 (4.7) | |
| Hawaiian | 1 (0.3) | 1 (0.4) | 0 | |
| Educational level, No. (%) | | | | |
| Patient (n = 393) | | | | |
| Postgraduate degree | 1 (0.3) | 0 | 1 (1.0) | .30 |
| Some postgraduate education | 9 (2.3) | 7 (2.4) | 2 (1.9) | |
| 4 y of college | 14 (3.6) | 7 (2.4) | 7 (6.7) | |
| Some secondary education | 99 (25.2) | 69 (24.0) | 30 (28.6) | |
| High school diploma | 128 (32.6) | 97 (33.7) | 31 (29.5) | |
| High school | 125 (31.8) | 95 (33.0) | 30 (28.6) | |
| Eighth grade | 12 (3.1) | 9 (3.1) | 3 (2.9) | |
| None | 5 (1.3) | 4 (1.4) | 1 (1.0) | |
| Maternal (n = 327) | | | | |
| Postgraduate degree | 17 (5.2) | 16 (6.7) | 1 (1.1) | .04 |
| Some postgraduate education | 9 (2.8) | 7 (2.9) | 2 (2.3) | |
| 4 y of college | 62 (19.0) | 44 (18.5) | 18 (20.2) | |
| Some secondary education | 75 (22.9) | 61 (25.6) | 14 (15.7) | |
| High school diploma | 106 (32.4) | 76 (31.9) | 30 (33.7) | |
| High school | 37 (11.3) | 20 (8.4) | 17 (19.1) | |
| Eighth grade | 14 (4.3) | 10 (4.2) | 4 (4.5) | |
| None | 7 (2.1) | 4 (1.7) | 3 (3.4) | |
| Primary SCID diagnosis, No. (%) | | | | |
| Schizophrenia | 212 (53.8) | 161 (55.9) | 51 (48.1) | .004 |
| Schizoaffective disorder | 79 (20.1) | 45 (15.6) | 34 (32.1) | |
| Schizophreniform disorder | 63 (16.0) | 50 (17.4) | 13 (12.3) | |
| Psychotic disorder not otherwise specified | 40 (10.2) | 32 (11.1) | 8 (7.6) | |
| Outpatient treatment setting at baseline, No. (%) | 224 (56.9) | 155 (53.8) | 69 (65.1) | .20 |
| Duration of antipsychotic treatment, mean (SD), d | 47.3 (46.1) | 46.6 (43.5) | 49.3 (52.6) | .61 |

(continued)

(Table 2 and Figure 2). Males had significantly higher systolic ($P < .001$) and diastolic ($P = .01$) blood pressure and more frequent prehypertension ($P < .001$) than females, who received more antihypertensives ($P = .047$).

## Lipid Metabolism

Altogether, 56.5% had at least 1 abnormality in low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol (HDL-C), HDL-C, or triglycerides level but only 0.5% received lipid-lowering medications (Table 2 and Figure 2). Males had lower HDL-C ($P < .001$) and higher triglycerides ($P = .03$) (Table 2). White patients compared with black patients had higher triglycerides ($P < .001$), more hypertriglyceridemia ($P = .002$) and dyslipidemia ($P < .001$), and lower HDL-C ($P < .001$) (Table 3). Hispanic patients had more dyslipidemia than non-Hispanic patients, driven by more elevated non-HDL-C (both $P = .03$) (Table 3).

Table 1. Demographic, Illness, and Treatment Characteristics by Sex (continued)

| Characteristic | Total (N = 394) | Males (n = 288) | Females (n = 106) | *P* Value |
|---|---|---|---|---|
| Antipsychotic treatment, No. (%) | | | | |
| Risperidone | 108 (27.4) | 88 (30.6) | 20 (18.9) | .17 |
| None | 54 (13.7) | 33 (11.5) | 21 (19.8) | |
| Olanzapine | 49 (12.4) | 40 (13.9) | 9 (8.5) | |
| Antipsychotic polypharmacy | 37 (9.4) | 27 (9.4) | 10 (9.4) | |
| Aripiprazole | 35 (8.9) | 21 (7.3) | 14 (13.2) | |
| Paliperidone palmitate | 34 (8.6) | 23 (8.0) | 11 (10.4) | |
| Quetiapine fumarate | 28 (7.1) | 20 (6.9) | 8 (7.6) | |
| First-generation antipsychotic | 26 (6.6) | 18 (6.3) | 8 (7.6) | |
| Ziprasidone hydrochloride | 12 (3.1) | 9 (3.1) | 3 (2.8) | |
| Lurasidone hydrochloride | 7 (1.9) | 6 (2.1) | 1 (0.9) | |
| Clozapine | 2 (0.5) | 2 (0.7) | 0 | |
| Asenapine | 2 (0.5) | 1 (0.4) | 1 (0.9) | |
| Nonantipsychotic comedication, No. (%) | | | | |
| Antidepressant | 126 (32.0) | 79 (27.4) | 47 (44.3) | .001 |
| Anticholinergic | 68 (17.3) | 53 (18.4) | 15 (14.2) | .32 |
| Antiepileptic, lithium carbonate, or lithium citrate | 48 (12.2) | 36 (12.5) | 12 (11.3) | .75 |
| Benzodiazepine | 44 (11.2) | 25 (8.7) | 19 (18.1) | .009 |
| Nonbenzodiazepine hypnotic | 20 (5.1) | 13 (4.5) | 7 (6.6) | .40 |
| Psychostimulant or atomoxetine hydrochloride | 6 (1.5) | 5 (1.7) | 1 (1.0) | >.99 |

Abbreviations: IQR, interquartile range; SCID, Structured Clinical Interview for *DSM-IV* Axis I Disorders, Patient Edition.

## Carbohydrate Metabolism

Based on fasting glucose level (available in 101 of 286 fasting patients [34.0%]), prediabetes and diabetes were present in 4.0% and 3.0% of patients, respectively (Table 2 and Figure 2). Prevalence figures for $HbA_{1c}$-defined prediabetes and diabetes were 15.4% and 2.9%, respectively. Hyperinsulinemia occurred in 12.7% of patients and insulin resistance based on the triglycerides to HDL-C ratio was present in 21.7%. Males had significantly higher insulin resistance based on the triglycerides to HDL-C ratio than females ($P = .01$), who had glucose-defined diabetes significantly more often (3 females and 0 males; $P = .04$) (Table 2). Black patients had significantly higher $HbA_{1c}$-defined prediabetes than white patients ($P < .001$), who had significantly higher triglycerides to HDL-C ratios than black patients ($P < .001$) (Table 3).

## Metabolic Syndrome

Among the patients, 13.2% had metabolic syndrome (Table 2). While males fulfilled elevated blood pressure criteria significantly more often than females ($P = .02$; although more females received antihypertensive medication counting toward this criterion), abdominal obesity was more than 3 times as common in females (45.6% in females vs 14.7% in males; $P < .001$). This finding was independent of the lower threshold for abdominal obesity in females than males (>88 vs >102 cm, respectively), as females had more abdominal obesity than males when using a threshold greater than 102 cm for both groups (25.2% vs 14.7%, respectively; $P = .002$) (Table 2). Consistent with continuous variables, significantly more white patients fulfilled hypertriglyceridemia ($P < .001$) and low HDL-C ($P = .004$) criteria than black patients (Table 3).

## Illness Duration and Cardiometabolic Risk

Abnormalities in each body composition parameter and triglycerides to HDL-C ratio were associated with longer duration of psychiatric illness (mean [SD], 6.7 [6.7] years; median, 4.3 years) (**Table 4**). No other metabolic variables were significantly associated with illness duration.

## Antipsychotic Exposure and Cardiometabolic Risk

Duration of lifetime antipsychotic treatment was associated with lower systolic blood pressure ($P = .003$) and greater abnormalities in measures of HDL-C ($P = .02$), non–HDL-C ($P = .01$), triglycerides ($P = .01$), and triglycerides to HDL-C ratio ($P = .005$) (Table 4). Although glucose level was inversely related to antipsychotic treatment duration ($P = .02$), results were based on only 99 patients with data.

Compared with patients with any lifetime antipsychotic exposure, antipsychotic-naive patients had lower non–HDL-C levels ($P = .04$). However, more antipsychotic-naive patients were obese ($P = .01$) and had hypertension ($P = .03$), and more patients in this group fulfilled the abdominal obesity ($P = .003$) and elevated blood pressure ($P = .03$) criteria for metabolic syndrome, which was also more frequent than in the antipsychotic-exposed patients ($P = .04$) (eTable 1 in the Supplement).

Comparing baseline treatment groups, not using antipsychotics at the time of blood draw was associated with significantly lower levels of total cholesterol and low-density lipoprotein cholesterol (both $P = .03$). Moreover, higher levels of triglycerides ($P = .007$), insulin ($P = .02$), and homeostasis model assessment–estimated insulin resistance ($P < .001$) were associated with olanzapine therapy, while a higher triglycerides to HDL-C ratio was associated with quetiapine ($P = .02$) (eTable 2 in the Supplement).

Table 2. Cardiometabolic Risk Status and Treatment at Baseline by Sex

| Variable | Total (N = 394) | Males (n = 288) | Females (n = 106) | *P* Value | NHANES | |
|---|---|---|---|---|---|---|
| | | | | | Age 20-29 y | Age Mid-40s |
| Smoking, No. (%) (n = 394) | 200 (50.8) | 161 (55.9) | 39 (36.8) | <.001 | 36.7% for males, 24.9% for females[42] | |
| Body composition | | | | | | |
| BMI, mean (SD) (n = 389) | 26.6 (6.7) | 26.3 (6.0) | 27.3 (8.3) | .17 | | |
| Weight status, No. (%) (n = 389) | | | | | | |
| Underweight | 8 (2.1) | 3 (1.1) | 5 (4.8) | .02 | | |
| Normal | 193 (49.6) | 144 (50.7) | 49 (46.7) | | | |
| Overweight | 102 (26.2) | 81 (28.5) | 21 (20.0) | | | |
| Obese | 86 (22.1) | 56 (19.7) | 30 (28.6) | | 25% (ages 20-24 y)[43] | |
| Fat mass, mean (SD), kg (n = 373) | 19.0 (14.3) | 16.6 (13.4) | 25.3 (16.3) | <.001 | | |
| Fat %, mean (SD) (n = 375) | 22.7 (9.8) | 19.0 (9.5) | 32.5 (10.8) | <.001 | | |
| Waist circumference, mean (SD), cm (n = 388) | 91.1 (16.3) | 91.1 (15.6) | 91.2 (18.3) | .95 | | |
| Abdominal obesity, waist circumference >102 cm for males and females, No. (%) (n = 388) | 68 (17.5) | 42 (14.7) | 26 (25.2) | .002 | | |
| Arterial blood pressure (n = 389) | | | | | | |
| Mean (SD), mm Hg | | | | | | |
| Systolic | 117.1 (12.4) | 120.1 (12.2) | 108.6 (13.0) | <.001 | | |
| Diastolic | 75.5 (9.9) | 76.3 (9.6) | 73.4 (10.7) | .01 | | |
| Prehypertension, blood pressure 120-139/80-89 mm Hg, No. (%) | 155 (39.9) | 134 (47.0) | 21 (20.2) | <.001 | | 20.9%[44] |
| Hypertension, blood pressure ≥140/90 mm Hg, No. (%) | 39 (10.0) | 31 (10.9) | 8 (7.7) | .35 | | 49.9%[44] |
| Fasting lipid metabolism (n = 286)[a] | | | | | | |
| Total cholesterol, mean (SD), mg/dL | 173.4 (35.5) | 173.4 (37.2) | 173.3 (30.5) | .97 | | |
| Hypercholesterolemia, total cholesterol ≥200 mg/dL, No. (%) | 61 (21.0) | 46 (21.7) | 15 (19.2) | .65 | | |
| LDL-C, mean (SD), mg/dL | 100.7 (31.1) | 101.4 (32.6) | 99.9 (26.6) | .56 | | |
| Elevated LDL-C, ≥130 mg/dL, No. (%) | 49 (17.1) | 38 (18.3) | 11 (14.1) | .40 | | 27%[35] |
| Fasting and nonfasting HDL-C, mean (SD), mg/dL (n = 304) | 49.2 (12.8) | 47.4 (12.0) | 54.2 (14.6) | <.001 | | |
| Non-HDL-C, mean (SD), mg/dL | 124.0 (35.8) | 125.8 (37.8) | 119.1 (29.9) | .16 | | |
| Elevated non-HDL-C, ≥130 mg/dL, mean (SD) | 116 (40.6) | 89 (42.8) | 27 (34.6) | .21 | | |
| Triglycerides, mean (SD), mg/dL | 115.4 (77.5) | 121.7 (84.9) | 98.8 (52.9) | .03 | | |
| Hypertriglyceridemia, triglycerides ≥170 mg/dL, No. (%) | 46 (16.1) | 37 (17.8) | 9 (11.5) | .20 | | 30%[35] |
| Dyslipidemia, No. (%)[b] | 161 (56.5) | 115 (55.6) | 46 (59.0) | .60 | | 53%[35] |
| Fasting carbohydrate metabolism[a] | | | | | | |
| $HbA_{1c}$, mean (SD), % (n = 280) | 5.4 (0.7) | 5.3 (0.4) | 5.5 (1.1) | .05 | | |
| Glucose, mean (SD), mg/dL (n = 100)[c] | 86.4 (17.9) | 85.2 (13.4) | 88.6 (24.5) | .37 | | |
| Insulin, mean (SD), μIU/mL (n = 235)[c] | 11.6 (13.6) | 11.8 (14.6) | 11.1 (10.8) | .71 | | |
| Hyperinsulinemia, insulin >20 μIU/mL, No. (%) (n = 235) | 30 (12.7) | 22 (12.9) | 8 (12.3) | .91 | | |
| HOMA-IR, mean (SD) (n = 235)[c] | 3.1 (3.8) | 3.0 (3.4) | 3.2 (4.4) | .84 | | |
| Triglycerides to HDL-C ratio (n = 286) | | | | | | |
| Mean (SD) | 2.6 (2.2) | 2.9 (2.4) | 2.1 (1.6) | .01 | | |
| Ratio ≥3.5, No. (%) | 62 (21.7) | 51 (24.5) | 11 (14.1) | .06 | | |
| Prediabetes, No. (%) | | | | | | |
| Glucose based, 100-125 mg/dL (n = 101) | 4 (4.0) | 3 (4.6) | 1 (2.9) | >.99 | | |
| $HbA_{1c}$ based, 5.7%-6.4% (n = 280) | 43 (15.4) | 27 (13.4) | 16 (20.5) | .14 | | |
| Diabetes, No. (%) | | | | | | |
| Glucose based, >125 mg/dL (n = 101) | 3 (3.0) | 0 | 3 (8.6) | .04 | | |
| $HbA_{1c}$ based, >6.4% (n = 280) | 8 (2.9) | 5 (2.5) | 3 (3.9) | .69 | | |

(continued)

Table 2. Cardiometabolic Risk Status and Treatment at Baseline by Sex (continued)

| Variable | Total (N = 394) | Males (n = 288) | Females (n = 106) | *P* Value | NHANES Age 20-29 y | NHANES Age Mid-40s |
|---|---|---|---|---|---|---|
| Metabolic syndrome and individual criteria, No. (%) | | | | | | |
| Metabolic syndrome, fasting glucose ≥100 mg/dL per ATP III (n = 257) | 34 (13.2) | 21 (11.2) | 13 (18.6) | .12 | 6.7%[41, d] | 21.8%[41,d] |
| Low HDL-C, <40 mg/dL in males and <50 mg/dL in females (n = 305) | 91 (29.8) | 61 (27.4) | 30 (35.6) | .12 | | 37.1%[41] |
| Abdominal obesity, waist circumference >102 cm in males and >88 cm in females (n = 388) | 89 (22.9) | 42 (14.7) | 47 (45.6) | <.001 | | 38.6%[41] |
| Elevated blood pressure, ≥130/80 mm Hg, or antihypertensive treatment (n = 389) | 92 (23.7) | 76 (26.7) | 16 (15.4) | .02 | | 34.0%[41] |
| Elevated triglycerides, ≥150 mg/dL (n = 286) | 62 (21.7) | 50 (24.0) | 12 (15.4) | .11 | | 30.0%[41] |
| Hyperglycemia, glucose ≥100 mg/dL (n = 101) | 7 (7.0) | 3 (4.6) | 4 (11.4) | .69 | | 12.6%[41,d] |
| Cardiometabolic treatment medication, No. (%) | | | | | | |
| Antihypertensive | 14 (3.6) | 7 (2.4) | 7 (6.6) | .047 | | |
| Antidiabetic | 3 (0.8) | 1 (0.4) | 2 (1.9) | .18 | | |
| Lipid lowering | 2 (0.5) | 2 (0.7) | 0 | >.99 | | |

Abbreviations: ATP III, Adult Treatment Panel III; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); $HbA_{1c}$, hemoglobin $A_{1c}$; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment–estimated insulin resistance; LDL-C, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey.

SI conversion factors: To convert fat mass to pounds, divide by 0.45; to convert total cholesterol, LDL-C, HDL-C, and non–HDL-C to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113; to convert $HbA_{1c}$ from percentage of total hemoglobin to proportion of total hemoglobin, multiply by 0.01; to convert glucose to millimoles per liter, multiply by 0.0555; and to convert insulin to picomoles per liter, multiply by 6.945.

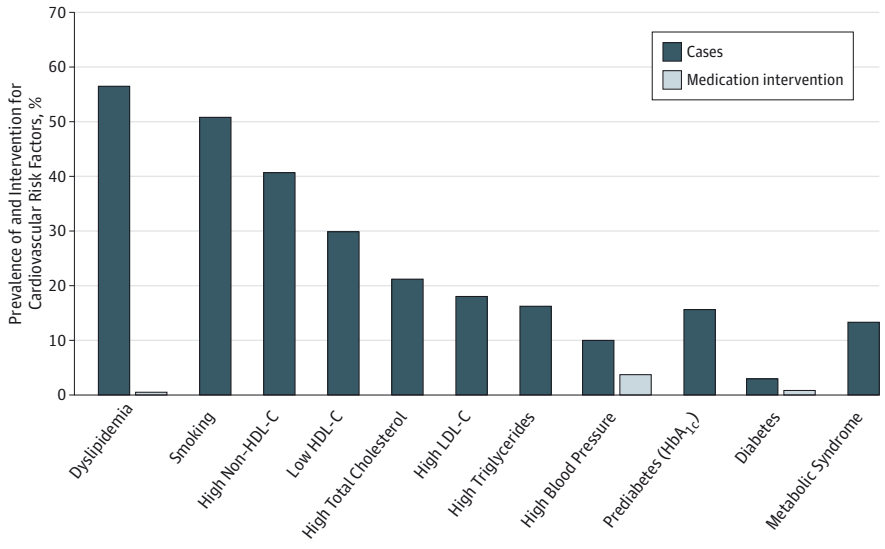
[a] Because HDL-C and $HbA_{1c}$ are not affected by time from last food ingestion, their data include nonfasting patients.

[b] Defined as an elevated LDL-C level (≥130 mg/dL), non–HDL-C level (≥130 mg/dL), or triglycerides level (≥150 mg/dL) or a low HDL-C level (<40 mg/dL in males and <50 mg/dL in females).

[c] One patient with type 1 insulin-dependent diabetes was excluded from the analysis of glucose, insulin, and HOMA-IR levels.

[d] The NHANES definition of metabolic syndrome uses a fasting glucose level of 110 mg/dL or higher as the glucose abnormality criterion instead of the currently used metabolic syndrome definition with a fasting glucose threshold of 100 mg/dL or higher.

Figure 2. Prevalence of Smoking, Lipid Abnormalities, Hypertension, Diabetes, and Metabolic Syndrome and Respective Medication Treatment for the Conditions




Dyslipidemia indicates an elevated low-density lipoprotein cholesterol (LDL-C) level (≥130 mg/dL; to convert to millimoles per liter, multiply by 0.0259), an elevated non–high-density lipoprotein cholesterol (HDL-C) level (≥130 mg/dL; to convert to millimoles per liter, multiply by 0.0259), an elevated triglycerides level (≥150 mg/dL; to convert to millimoles per liter, multiply by 0.0113), or a low HDL-C level (<40 mg/dL in males and <50 mg/dL in females; to convert to millimoles per liter, multiply by 0.0259). $HbA_{1c}$ indicates hemoglobin $A_{1c}$.

## Discussion

Despite the young age of this study sample of 394 patients with FES, an average of only 47 days of lifetime antipsychotic exposure, and overweight and obesity figures comparable to those for similarly aged US population members,[43] there was a clear pattern of increased smoking[42] and several metabolic risk indices[41,44] compared with similarly aged persons in the general US population. Moreover, dyslipidemia was as frequent

Table 3. Cardiometabolic Risk Status and Treatment at Baseline by Race and Ethnicity

| Variable | Race | | | | | Ethnicity | | |
|---|---|---|---|---|---|---|---|---|
| | White (n = 215) | Black (n = 144) | Native American (n = 22) | Asian (n = 12) | *P* Value | Non-Hispanic (n = 321) | Hispanic (n = 73) | *P* Value |
| Smoking, No. (%) (n = 393) | 117 (54.4) | 70 (48.6) | 9 (40.9) | 4 (33.3) | .29 | 172 (53.6) | 28 (38.4) | .02 |
| Body composition | | | | | | | | |
| BMI, mean (SD) (n = 389) | 26.2 (6.2) | 27.5 (7.4) | 26.2 (6.7) | 23.0 (3.6) | .08 | 26.7 (6.8) | 26.1 (6.2) | .52 |
| Weight status, No. (%) (n = 389) | | | | | | | | |
| Underweight | 5 (2.4) | 1 (0.7) | 1 (4.6) | 1 (8.3) | .25 | 8 (2.5) | 0 | .20 |
| Normal | 102 (47.9) | 71 (50.4) | 12 (54.6) | 7 (58.3) | | 151 (47.9) | 42 (59.2) | |
| Overweight | 61 (28.6) | 31 (22.0) | 6 (27.3) | 4 (33.3) | | 85 (26.7) | 17 (23.9) | |
| Obese | 45 (21.1) | 38 (27.0) | 3 (13.6) | 0 | | 74 (23.3) | 12 (16.9) | |
| Fat mass, mean (SD), kg (n = 373) | 18.0 (12.9) | 21.6 (17.6) | 16.3 (13.6) | 12.4 (5.8) | .04[a] | 19.5 (15.6) | 16.6 (9.9) | .14 |
| Fat %, mean (SD) (n = 375) | 21.8 (10.9) | 24.6 (12.7) | 20.6 (9.9) | 18.9 (6.9) | .07 | 22.8 (11.8) | 22.1 (10.2) | .68 |
| Waist circumference, mean (SD), cm (n = 387) | 91.3 (14.3) | 92.2 (19.0) | 89.3 (17.8) | 79.1 (8.3) | .06 | 91.5 (16.8) | 89.3 (13.7) | .28 |
| Arterial blood pressure (n = 388) | | | | | | | | |
| Mean (SD), mm Hg | | | | | | | | |
| Systolic | 116.4 (12.7) | 118.6 (14.2) | 115.5 (14.9) | 115.4 (14.2) | .43 | 117.6 (13.2) | 114.6 (14.1) | .09 |
| Diastolic | 74.9 (9.5) | 77.1 (10.6) | 72.3 (9.6) | 72.6 (8.1) | .06 | 75.9 (9.5) | 73.8 (11.5) | .11 |
| Prehypertension, blood pressure 120-139/80-89 mm Hg, No. (%) | 90 (42.3) | 50 (35.2) | 10 (47.6) | 5 (41.7) | .51 | 128 (40.4) | 27 (37.5) | .65 |
| Hypertension, blood pressure ≥140/90 mm Hg, No. (%) | 19 (8.9) | 20 (14.1) | 0 | 0 | .09 | 31 (9.8) | 8 (11.1) | .73 |
| Fasting lipid metabolism (n = 286)[b] | | | | | | | | |
| Total cholesterol, mean (SD), mg/dL | 175.3 (35.7) | 171.3 (35.8) | 171.7 (36.6) | 172.6 (25.6) | .84 | 172.7 (34.8) | 175.8 (37.7) | .55 |
| Hypercholesterolemia, total cholesterol ≥200 mg/dL, No. (%) | 36 (23.2) | 19 (17.8) | 5 (27.8) | 1 (11.1) | .54 | 46 (20.4) | 15 (23.4) | .59 |
| LDL-C, mean (SD), mg/dL | 102.8 (30.3) | 99.3 (34.0) | 97.2 (26.2) | 93.0 (12.9) | .65 | 100.2 (31.2) | 102.7 (31.0) | .58 |
| Elevated LDL-C, ≥130 mg/dL, No. (%) | 30 (19.9) | 15 (14.0) | 4 (23.5) | 0 | .28 | 38 (17.1) | 11 (17.5) | .95 |
| Fasting and nonfasting HDL-C, mean (SD), mg/dL (n = 303) | 46.3 (11.8) | 53.0 (13.7) | 50.2 (15.7) | 53.1 (10.4) | <.001[c] | 49.7 (12.9) | 47.5 (13.9) | .24 |
| Non-HDL-C, mean (SD), mg/dL | 128.9 (36.2) | 118.3 (36.1) | 120.6 (33.1) | 119.4 (23.3) | .12 | 122.9 (35.9) | 127.8 (35.8) | .34 |
| Elevated non-HDL-C, ≥130 mg/dL, mean (SD) | 72 (47.4) | 35 (32.7) | 5 (29.4) | 4 (44.4) | .09 | 83 (37.2) | 33 (52.4) | .03 |
| Triglycerides, mean (SD), mg/dL | 133.2 (89.1) | 90.1 (55.5) | 111.7 (59.9) | 126.7 (66.3) | <.001[d] | 112.0 (72.3) | 122.7 (67.8) | .29 |
| Hypertriglyceridemia, triglycerides ≥170 mg/dL, No. (%) | 35 (22.9) | 9 (8.4) | 1 (5.9) | 2 (22.2) | .01 | 37 (16.5) | 10 (15.9) | .90 |
| Dyslipidemia, No. (%)[e] | 100 (66.2) | 48 (44.9) | 8 (47.1) | 5 (55.6) | .006 | 118 (53.2) | 43 (68.3) | .03 |
| Fasting carbohydrate metabolism[b] | | | | | | | | |
| $HbA_{1c}$, mean (SD), % (n = 279) | 5.3 (0.8) | 5.5 (0.4) | 5.4 (0.5) | 5.3 (0.2) | .26 | 5.4 (0.7) | 5.3 (0.3) | .83 |
| Glucose, mean (SD), mg/dL (n = 100)[f] | 87.4 (14.9) | 85.4 (13.7) | 83.6 (14.2) | 68.7 (8.6) | .17 | 86.0 (14.9) | 83.9 (11.4) | .60 |
| Insulin, mean (SD), μIU/mL (n = 234)[f] | 10.8 (11.5) | 12.8 (15.0) | 18.1 (28.7) | 8.4 (5.4) | .23 | 11.9 (13.5) | 12.1 (18.0) | .94 |
| Hyperinsulinemia, insulin >20 μIU/mL, No. (%) (n = 234) | 13 (10.9) | 14 (15.4) | 3 (18.8) | 0 | .46 | 25 (13.4) | 5 (10.2) | .64 |
| HOMA-IR, mean (SD) (n = 234)[f] | 3.7 (5.8) | 3.1 (4.4) | 4.8 (5.6) | 0.9 (0.6) | .70 | 3.4 (5.2) | 3.5 (4.6) | .93 |
| Triglycerides to HDL-C ratio (n = 285) | | | | | | | | |
| Mean (SD) | 3.1 (2.3) | 2.0 (1.8) | 2.4 (1.6) | 2.5 (1.6) | <.001[d] | 2.6 (2.1) | 2.9 (1.9) | .32 |
| Ratio ≥3.5, No. (%) | 46 (30.3) | 11 (10.3) | 2 (11.8) | 3 (33.3) | <.001 | 47 (21.1) | 15 (23.8) | .64 |
| Prediabetes, No. (%) | | | | | | | | |
| Glucose based, 100-125 mg/dL (n = 101) | 3 (7.1) | 1 (2.2) | 0 | 0 | .60 | 3 (3.7) | 1 (5.9) | .54 |
| $HbA_{1c}$ based, 5.7%-6.4% (n = 280) | 12 (8.1) | 31 (29.3) | 1 (5.6) | 0 | <.001 | 36 (16.3) | 8 (13.3) | .58 |
| Diabetes, No. (%) | | | | | | | | |
| Glucose based, >125 mg/dL (n = 101) | 2 (4.6) | 1 (2.2) | 0 | 0 | .85 | 3 (3.6) | 0 | >.99 |
| $HbA_{1c}$ based, >6.4% (n = 280) | 3 (2.0) | 5 (4.7) | 1 (5.6) | 0 | .57 | 8 (3.6) | 1 (1.7) | .54 |

(continued)

Table 3. Cardiometabolic Risk Status and Treatment at Baseline by Race and Ethnicity (continued)

| Variable | Race | | | | | Ethnicity | | |
|---|---|---|---|---|---|---|---|---|
| | White (n = 215) | Black (n = 144) | Native American (n = 22) | Asian (n = 12) | *P* Value | Non-Hispanic (n = 321) | Hispanic (n = 73) | *P* Value |
| Metabolic syndrome and individual criteria, No. (%) | | | | | | | | |
| Metabolic syndrome, fasting glucose ≥100 mg/dL per ATP III (n = 258) | 24 (17.9) | 8 (8.1) | 2 (13.3) | 0 | .11 | 30 (14.5) | 4 (8.0) | .22 |
| Low HDL-C, <40 mg/dL in males and <50 mg/dL in females (n = 304) | 61 (37.4) | 25 (21.9) | 5 (27.8) | 0 | .008 | 69 (28.8) | 22 (33.9) | .43 |
| Abdominal obesity, waist circumference >102 cm in males and >88 cm in females (n = 387) | 49 (22.9) | 37 (26.6) | 3 (13.6) | 0 | .13 | 77 (24.3) | 12 (16.7) | .16 |
| Elevated blood pressure, ≥130/80 mm Hg, or antihypertensive treatment (n = 388) | 45 (21.1) | 41 (28.9) | 5 (23.8) | 1 (8.3) | .22 | 77 (24.3) | 15 (20.8) | .53 |
| Elevated triglycerides, ≥150 mg/dL (n = 285) | 47 (30.7) | 11 (10.3) | 2 (11.8) | 3 (33.3) | <.001 | 50 (22.3) | 13 (20.6) | .78 |
| Hyperglycemia, glucose ≥100 mg/dL (n = 101) | 5 (11.4) | 2 (4.4) | 0 | 0 | .45 | 6 (7.1) | 1 (5.9) | >.99 |
| Cardiometabolic treatment medication, No. (%) | | | | | | | | |
| Antihypertensive | 6 (2.8) | 8 (5.6) | 0 | 0 | .35 | 13 (4.1) | 1 (1.4) | .48 |
| Antidiabetic | 1 (0.5) | 2 (1.4) | 0 | 0 | .74 | 3 (0.9) | 0 | >.99 |
| Lipid lowering | 1 (0.5) | 1 (0.7) | 0 | 0 | .96 | 2 (0.6) | 0 | >.99 |

Abbreviations: ATP III, Adult Treatment Panel III; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); $HbA_{1c}$, hemoglobin $A_{1c}$; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment–estimated insulin resistance; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert fat mass to pounds, divide by 0.45; to convert total cholesterol, LDL-C, HDL-C, and non–HDL-C to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113; to convert $HbA_{1c}$ from percentage of total hemoglobin to proportion of total hemoglobin, multiply by 0.01; to convert glucose to millimoles per liter, multiply by 0.0555; and to convert insulin to picomoles per liter, multiply by 6.945.

[a] Greater for black patients than for white and Asian patients (*P* < .05, post hoc pairwise *t* test).

[b] Because HDL-C and $HbA_{1c}$ are not affected by time from last food ingestion, their data include nonfasting patients.

[c] Lower for white patients than for black patients (*P* < .05, post hoc pairwise *t* test).

[d] Greater for white patients than for black patients (*P* < .05, post hoc pairwise *t* test).

[e] Defined as an elevated LDL-C level (≥130 mg/dL), non–HDL-C level (≥130 mg/dL), or triglycerides level (≥150 mg/dL) or a low HDL-C level (<40 mg/dL in males and <50 mg/dL in females).

[f] One patient with type 1 insulin-dependent diabetes was excluded from the analysis of glucose, insulin, and HOMA-IR levels.

as in adults 15 to 20 years older in the general US population.[35] Further, body composition–related risk markers were significantly associated with longer total psychiatric illness duration, whereas metabolic risk markers were significantly associated with the overall very short mean lifetime antipsychotic treatment duration. Finally, relevant for treatment choice and recommendations for patients with FES, significantly higher continuous metabolic risk factor values were associated with olanzapine and less so with quetiapine.

Altogether, about half the patients with FES smoked tobacco or had dyslipidemia, 39.9% had prehypertension, 10.0% were hypertensive, and a substantial minority (13.2%) had metabolic syndrome. Furthermore, while 3.0% were already diabetic, as many as 15.4% had $HbA_{1c}$-defined prediabetes, which has an 8-year risk for diabetes comparable to fasting glucose–defined prediabetes.[45] Smoking was dramatically more frequent in our study's patients than in young US adults in 2009 to 2011[42] (males: 55.9% vs 36.7%, respectively; females: 36.8% vs 24.9%, respectively). Further, compared with 20- to 29-year-olds in the general US population,[43] metabolic syndrome was more prevalent in patients with FES (7.0% vs 13.2%, respectively; +89%), although obesity was similarly common as in US adults aged 20 to 24 years.[43] Because that National Health and Nutrition Examination Survey metabolic syndrome definition used a fasting glucose level of 110 mg/dL or higher (to convert to millimoles per liter, multiply by 0.0555)[41] instead of the now-used threshold of 100 mg/dL or higher[40] as the glucose abnormality criterion, some of the observed difference may be influenced by this methodological difference. Additionally, the 56.5% dyslipidemia prevalence in patients with FES was at least as high as the 53% figure reported for US adults averaging 20 years older.[35] Prehypertension (systolic/diastolic blood pressure of 120-139/80-89 mm Hg) was present in 39.9%, which was much more frequent than in 17 794 participants in the 1999 to 2006 National Health and Nutrition Examination Survey (20.9%), whose average age was 20 years older,[44] even if some of this difference may have been due to the higher hypertension frequency in the older general population sample. Although values in this first-episode US sample were generally somewhat higher than those reported in 3 European first-episode samples,[46-48] the findings converge in that the body weight and metabolic indices were

Table 4. Correlations Between Mean Continuous Cardiometabolic Health Parameters and Lifetime Durations of Psychiatric Illness and Antipsychotic Treatment

| Variable | Total Psychiatric Illness Duration | | | Cumulative Antipsychotic Treatment Duration | | |
|---|---|---|---|---|---|---|
| | No. | Spearman ρ[a] | *P* Value | No. | Spearman ρ[a] | *P* Value |
| Body composition | | | | | | |
| BMI | 383 | 0.149 | .003 | 388 | 0.047 | .36 |
| Fat mass | 368 | 0.157 | .002 | 373 | 0.044 | .40 |
| Fat % | 370 | 0.156 | .003 | 373 | 0.004 | .93 |
| Waist circumference | 383 | 0.138 | .007 | 388 | −0.011 | .98 |
| Blood pressure | | | | | | |
| Systolic | 384 | 0.008 | .88 | 389 | −0.152 | .003 |
| Diastolic | 384 | 0.053 | .30 | 389 | −0.057 | .27 |
| Fasting blood lipids[b] | | | | | | |
| Total cholesterol | 283 | 0.097 | .10 | 286 | 0.099 | .10 |
| LDL-C | 282 | 0.076 | .21 | 285 | 0.089 | .14 |
| HDL-C | 301 | −0.065 | .26 | 304 | −0.129 | .02 |
| Non-HDL-C | 283 | 0.107 | .07 | 286 | 0.151 | .01 |
| Triglycerides | 283 | 0.115 | .05 | 286 | 0.149 | .01 |
| Triglycerides to HDL-C ratio | 281 | 0.125 | .04 | 286 | 0.167 | .005 |
| Fasting carbohydrate metabolism[b] | | | | | | |
| $HbA_{1c}$ | 277 | −0.061 | .31 | 278 | −0.064 | .29 |
| Glucose | 99 | 0.162 | .11 | 100 | −0.230 | .02 |
| Insulin | 234 | 0.030 | .64 | 235 | −0.021 | .76 |
| HOMA-IR | 89 | 0.158 | .14 | 90 | −0.159 | .13 |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); $HbA_{1c}$, hemoglobin $A_{1c}$; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment–estimated insulin resistance; LDL-C, low-density lipoprotein cholesterol.

[a] Positive Spearman ρ indicates a direct relationship; negative Spearman ρ, an inverse relationship.

[b] Because HDL-C and $HbA_{1c}$ are not affected by time from last food ingestion, their data include nonfasting patients.

similar to those of the respective general population norms prior to treatment and that cardiometabolic abnormalities started to emerge early during antipsychotic exposure.

In our sample, body composition parameters, but not metabolic parameters (except for the triglycerides to HDL-C ratio), were significantly associated with longer psychiatric illness duration, indicating potential adverse changes in diet, exercise, and/or socioeconomic status related to psychiatric conditions such as depression and emerging psychosis. However, despite very short antipsychotic exposure, there was a significant effect of antipsychotic treatment duration on disturbed lipid metabolism and lipid-based proxy measures of early insulin resistance,[37] but not on body composition or carbohydrate metabolism indices. The latter may take longer to be significantly dysregulated by antipsychotics, especially in young patients, with the possible exception of olanzapine and clozapine.[19-21,23] Furthermore, longer antipsychotic treatment was associated with lower systolic blood pressure, consistent with the α-adrenergic blockade of many antipsychotics.[49]

The relative contributions of schizophrenia, unhealthy lifestyle, psychotropic treatment, and insufficient medical care to elevated cardiovascular risk and mortality have been debated.[1-13,15-17,20-25] Comparing antipsychotic-naive patients with nonnaive patients yielded only a few differences, including higher frequencies of obesity, hypertension, and metabolic syndrome (driven by more patients meeting abdominal obesity and elevated blood pressure criteria) but less elevated non–HDL-C (a major risk factor for cardiovascular illness) in the antipsychotic-naive group than in patients with lifetime antipsychotic exposure. These preliminary data are partially driven by the hypotensive effect of antipsychotics and the unexpectedly higher obesity rate in the antipsychotic-naive group. Our results are limited by the relatively small antipsychotic-naive sample and varying degrees of exposure in the nonnaive group. Taken together, these data support the view that cardiometabolic burden is partly due to psychiatric or psychotic illness and unhealthy lifestyle but accelerates after antipsychotics are initiated and taken for longer periods.[20-24]

The finding that higher levels of triglycerides, insulin, and insulin resistance were associated with olanzapine treatment is consistent with a large body of evidence regarding the cardiometabolic risk of olanzapine.[20,21,24,50-53] That this effect was observable this early is alarming and supports the Schizophrenia Patient Outcomes Research Team's recommendation that clozapine and olanzapine should not be given as first-line treatment in FES.[54] The finding that a higher triglycerides to HDL-C ratio, a marker of insulin resistance, was associated with quetiapine treatment is concerning. Together with other data suggesting a marked and early adverse lipid signal with quetiapine despite similar weight

gain as risperidone,[19-21,23,50] its first-line use in first-episode psychosis may need to be reevaluated.

With few exceptions, compared with meta-analytically pooled patients with FES enrolled in previous studies,[55] this real-world community sample had similar cardiometabolic risk frequencies. Notable exceptions in our sample compared with the other studies include higher rates of fasting glucose-defined diabetes (2.9% vs 1.3%, respectively; +120%) and low HDL-C (29.8% vs 21.9%, respectively; +36%). The frequency of smoking in this FES sample (50.8%) was also similar to that of prior FES samples[55] but only modestly lower than in the most recent population-based studies of patients of any age with schizophrenia (59.1%).[56] Of concern regarding future diabetes risk, the $HbA_{1c}$-based prediabetes frequency (15.4%) was already 70% of that observed in patients with chronic schizophrenia (21.6%) who were 16 years older.[57]

Importantly, the relatively high prevalences of hypertension, diabetes, and especially smoking and lipid abnormalities are in stark contrast to the lack of related medical treatment in most patients. The underrecognition and undertreatment of cardiometabolic risk factors, especially lipid abnormalities, are consistent with previous reports among patients with chronic schizophrenia[12,14-16] and antipsychotic-treated patients[58-60] and are likely modifiable reasons for premature mortality in schizophrenia.[1-11] Furthermore, smoking causes diseases that disproportionately affect people with schizophrenia, including cardiovascular disease, diabetes, cancers, and pulmonary diseases, and may be a much stronger driver of cardiovascular morbidity and mortality than obesity.[61-65] Smoking cessation improves health outcomes at any age, but quitting early provides the most benefit.[66] Together with the fact that no patients with FES received nicotine replacement or medical interventions for smoking, these findings suggest that early education, engagement, and smoking cessation treatments are needed for patients with FES.[66]

We observed several significant sex differences. Consistent with the general population,[67] females had greater fat mass, higher fat percentage, more abdominal obesity, and more glucose-based diabetes. Despite this, also as in the general population, males had higher smoking rates, systolic and diastolic blood pressure, prehypertension rates, triglycerides levels, and triglycerides to HDL-C ratios and lower HDL-C levels. Notably, we confirmed higher abdominal obesity rates in females even when using the same waist circumference threshold as in males. Abdominal obesity was similarly more prevalent in females in the chronic schizophrenia population of the Clinical Antipsychotic Trials of Intervention Effectiveness study.[68] As in our sample, sex differences in metabolic syndrome were also not present among young people in the National Health and Nutrition Examination Survey general population survey but emerged among older people,[67] particularly among black and Hispanic patients.

Given that adiposity is a stronger predictor of cardiovascular risk than BMI (which was similar between males and females in our sample), females with FES may be a particularly high-risk cardiometabolic group. Nevertheless, arterial hypertension and an increased triglycerides to HDL-C ratio, an early indicator of insulin resistance,[37] which were more prevalent in males, are also cardiovascular risk factors. Thus, prospective studies are needed to assess how these different risk factors affect cardiovascular morbidity and mortality over time, especially because antipsychotic treatment and potential changes in healthy behaviors and socioeconomic status due to chronic psychiatric illness further increase the risk.

No significant differences emerged between Hispanic and non-Hispanic patients except that, consistent with general population data,[69,70] more non-Hispanic than Hispanic patients with FES smoked, while Hispanic patients with FES more often had an elevated non–HDL-C level and dyslipidemia. However, several relevant racial differences emerged. Consistent with the general population,[71-74] despite greater fat mass, black patients had significantly lower triglycerides levels and triglycerides to HDL-C ratios than white patients. Contrary to the triglycerides level and also similar to the general population,[75-77] black patients had $HbA_{1c}$-defined prediabetes significantly more often than white patients. A greater frequency of $HbA_{1c}$-defined prediabetes, which is a sign of impaired postprandial glycemic control, is alarming as retinopathy starts at even lower $HbA_{1c}$ levels in black individuals than in white individuals.[78]

Taken together, our findings highlight major opportunities for improvement in health care planning and delivery for people with schizophrenia. Our data underscore that warnings by the US Food and Drug Administration regarding diabetes risk of antipsychotics plus need for health monitoring and subsequent national and international guidelines[18] have been insufficient to positively affect the health disparity for patients with schizophrenia even at the beginning of their treatment.[12,14] Instead, there is a need for policy changes that promote the implementation of integrated care, health homes, and accountable care organizations wherein coordinated attention to both physical and mental health care needs will lead to improved health and reduced expenditure.[6]

Several limitations warrant attention. First, only 50 participants were antipsychotic naive, making comparisons with previously exposed patients preliminary. Second, the naturalistic nature of antipsychotic treatment and multiple analyses without adjustment for multiple testing limit our ability to assign causality to differences in cardiometabolic risk between medication groups. In fact, differences in medications' adverse effects may have been masked by clinicians' selective treatment of higher-risk (overweight or obese) patients with lower-risk antipsychotics, eg, aripiprazole and ziprasidone hydrochloride. Moreover, glucose level was not part of the initial research assessments and was therefore available for only a subgroup. Furthermore, fat mass, fat percentage, and insulin resistance were assessed with generalizable clinical measures and not gold-standard techniques, and we did not assess exercise or diet. Additionally, racial groups other than white or black patients were small, as were some of the individual antipsychotic treatment groups. Finally, data on the exact history of type and sequence of antipsychotic treatment prior to the baseline antipsychotic were not complete enough to allow such analyses. Nevertheless, this is a large study of patients with FES who had limited lifetime antipsychotic ex-

posure and were recruited from 34 community treatment sites in 21 states, which yielded results on cardiometabolic health that are reflective of general clinical practice settings in the United States. The limited number of eligible patients refusing participation increases generalizability of the findings. That 78.4% of RAISE-ETP patients had at least 1 hospitalization is likely due to the well-known problem that patients remained untreated in the community and only received psychiatric attention when symptoms became severe enough to warrant hospitalization, and although unfortunate, this rate generalizes to a broader US population. Furthermore, despite naturalistic treatment, individual antipsychotic groups did not significantly differ in duration of prior antipsychotic treatment, BMI, fat mass, or waist circumference, reducing the potential bias on laboratory measures and blood pressure.

## Conclusions

Early in psychotic illness and after a mean of only 6.7 weeks of antipsychotic exposure, lipid abnormalities and insulin resistance markers were elevated and significantly related to lifetime and individual antipsychotic exposure. These results reinforce the importance of assessing all patients for cardiometabolic risk prior to and throughout treatment, choosing low-risk antipsychotics, and managing cardiometabolic adverse effects that emerge in the care of patients with FES.[12,20,21,79] Further research is needed to assess the trajectory of cardiometabolic risk, underlying mechanisms, and mediating variables, including preferred treatment choices for FES and/or cardiometabolic risk factors.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