Baseline Cardiovascular Risk Factors in Patients With Severe Mental Illness (SMI) and Second Generation Antipsychotic Use From the Fixed Dose Intervention Trial of New England Enhancing Survival in SMI (FITNESS)

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Abstract

Objective: Individuals with severe mental illness (SMI) have a shorter life expectancy compared to the general population, largely due to cardiovascular disease (CVD). In this report from the Fixed Dose Intervention Trial of New England Enhancing Survival in SMI Patients (FITNESS), we examined baseline CVD risk factors and their treatment in patients with SMI and second generation antipsychotic (SGA) use.

Methods: FITNESS enrolled 204 participants with SMI and SGA use, but without documented history of CVD or diabetes mellitus, from several clinics in the Boston, Massachusetts, area between April 29, 2015, and September 26, 2019. We measured CVD risk factors (eg, body composition, arterial blood pressure, lipid and glucose parameters, diet, and activity) and CVD medication use prior to the initiation of the trial.

Results: The mean age of participants was 37.2 (13.5) years; 40% were female. Participants frequently had cardiovascular risk factors, including obesity (40%), elevated lipid levels (58%), elevated systolic blood pressure/hypertension (60%), elevated glycosylated hemoglobin percent (25%), active smoking (36%), and sedentary lifestyle (49%). Of CVD medications, 82% of those with hypertension were not receiving antihypertensive medications, 99% of those with dyslipidemia were not receiving cholesterol medications, and 97% of those with active smoking were not receiving smoking cessation medication. Among all participants, psychiatric diagnosis was not significantly associated with body mass index and CVD risk.

Conclusions: Despite well-documented CVD morbidity and mortality among people with SMI, CVD risks in individuals with SMI and SGA are common and frequently untreated across psychiatric diagnoses.

Trial Registration: ClinicalTrials.gov identifier: NCT02188121.

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Individuals with severe mental illness (SMI) experience premature mortality compared to the general population, with cardiovascular disease (CVD) being a leading contributor.[1–6] Chronic treatment with second generation antipsychotic medications (SGAs) contributes to elevated cardiovascular risk, including the development of obesity, metabolic syndrome, and type 2 diabetes.[7–10] Additional CVD risk factors are common in individuals with SMI, including sedentary lifestyle, dietary factors, smoking, and alcohol use.[11–13] Studies in SMI also point to endogenous risk and shared pathophysiologic features between psychiatric disorders and cardiometabolic disturbances.[14–16]

Despite advances in prevention and cardiovascular care in recent decades, there is a widening mortality gap in people with SMI compared to the general population.[11,12] Safe and efficacious pharmacotherapies to reduce cardiovascular risks are available; however, studies to date

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Clinical Points

- Cardiovascular disease risks in individuals with severe mental illness (SMI) and antipsychotic medication use remain common and frequently untreated across psychiatric diagnoses.
- Patients with severe mental illness (SMI) and second generation antipsychotic use should all receive cardiometabolic monitoring and cardiovascular disease prevention care.

have shown that few individuals with SMI receive CVD prevention.[13] While national guidelines recommend regular metabolic monitoring for patients receiving SGAs, evidence suggests that screening and treatment for cardiovascular risk factors are infrequent.[13,17,18]

The Fixed Dose Intervention Trial of New England Enhancing Survival in SMI (FITNESS) was designed to improve CVD prevention in people with SMI taking an SGA. FITNESS provided CVD prevention based on SMI diagnosis and SGA use by embedding treatment within the mental health clinic with a treatment strategy of free, fixed-doses of cardiovascular medications. In this report on baseline results from FITNESS, we examined the prevalence of several CVD risk factors and the corresponding frequency that individuals received preventive cardiovascular care before starting the trial.

METHODS

Setting and Participants

The FITNESS study recruited participants from 6 sites within the Greater Boston Area: McLean Hospital (Belmont, MA), Bay Cove: Michael J. Gill Mental Health Clinic (Jamaica Plain, MA), Massachusetts Mental Health Center (Boston, MA), Massachusetts General Hospital (Boston, MA), and the Edinburgh Center (Bedford, MA). To be eligible, participants needed to be aged 18 years or older; have a severe mental illness (defined as a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder, unspecified schizophrenia spectrum, and other psychotic disorder or posttraumatic stress disorder with evidence of functional impairment, ie, an inability to work or live independently and/or being on disability income); and have received SGA therapy during the 6 months prior to enrollment. Additionally, participants needed to be clinically stable with respect to their psychiatric conditions (no psychiatric hospitalizations in the 4 weeks prior to enrollment). The exclusion criteria included having unstable/active disease, diagnosed diabetes mellitus, being unable to provide informed consent (eg, dementia, developmental disability, or other cognitive disorder), breastfeeding, being pregnant, or planning to become pregnant. Participants completed baseline assessments between April 2015 and September 2019.

Participants provided written informed consent. The study was approved by the institutional review boards (IRBs) that hold jurisdiction over the study clinic sites: the Mass General Brigham IRB and the Massachusetts Department of Mental Health IRB (DMH CORCC). The trial was registered at ClinicalTrials.gov (identifier: NCT02188121).

Baseline Assessments

Assessment of cardiovascular risk factors. We assessed for obesity (or body mass index [BMI] >27 with weight related condition), dyslipidemia (LDL-C ≥130 mg/dL, triglycerides ≥150 mg/dL or HDL-C level <50 mg/dL in females and <40 mg/dL in males), hypertension (≥130/≥80), elevated glycosylated hemoglobin percent (based on hemoglobin A1c, 5.7%–6.4%), smoking, and inactive/minimal physical activity. We collected participants' weight, height, and waist circumference. Systolic and diastolic blood pressure were measured twice, a minimum of 5 minutes apart, with a third reading indicated if the first two differed by greater than 5 mm HG. Baseline blood samples were drawn for measurement of serum glucose, complete metabolic profile, lipid profile, complete blood count, and hemoglobin A1c. Blood samples were collected non-fasting. Laboratory Corporation of America performed laboratory assays for all study sites. Diet and physical activity were assessed using the Starting the Conversation questionnaire[19] and the International Physical Activity Questionnaire.[20]

Assessment of metabolic syndrome and atherosclerotic cardiovascular disease (ASCVD) risk. Metabolic syndrome was defined according to the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III).[21] Metformin is often prescribed for antipsychotic-induced weight gain,[22] and there were 20 participants taking metformin without a diagnosis of diabetes. We counted metformin as pharmacologic treatment in the calculation of metabolic syndrome for 2 participants who had a prior medical history including prediabetes. Antihypertensives taken for other reasons (eg, anxiety, akathisia) were also not counted as pharmacologic treatment.

We calculated 10-year and lifetime atherosclerotic cardiovascular disease (ASCVD) risk with the American College of Cardiology's ASCVD Risk Estimator Plus.[23] Current 10-year ASCVD risk was obtained for participants ages 40–79 (n = 69) and lifetime risk was obtained for participants ages 20–59 (n = 185; 9 participants below the age of 20 were also included). Current 10-year ASCVD risk was categorized as follows: low risk (<5%), borderline risk (5%–7.4%), intermediate risk (7.5%–19.9%), and high risk (≥20%).

Assessment of psychiatric symptoms, cognition, and medication adherence. We assessed baseline psychiatric symptoms, cognition, and material needs (food, housing, and energy/utilities)[24] using standardized measures. We collected baseline measures of participants' views on medications (Drug Attitude Inventory), in addition to self-reported

adherence to prescribed psychiatric, antihypertensive, and lipid lowering medications.[25] Information on medications, including psychiatric and CVD medications, was collected from medical records and patient report. Chlorpromazine equivalents were calculated based on daily dose of antipsychotic medication prescribed at the time of study.[26]

Statistical Analyses

Descriptive analyses were conducted for demographic and clinical characteristics, cardiometabolic risk factors, and views on treatment. We used chi-square and *t* tests as appropriate to compare categorical and continuous variables by sex and by baseline CVD care. We determined the frequency of having multiple CVD risk factors, including obesity (or BMI >27 with weight related condition), dyslipidemia, hypertension, current smoking, and inactive/minimal physical activity. We performed linear regression analyses to evaluate variables associated with ASCVD lifetime risk and BMI, including psychiatric diagnosis and CVD medications. In addition, we carried out linear regression analyses to evaluate the association of specific antipsychotic medications (excluding asenapine, brexpiprazole, and iloperidone due to few participants taking these antipsychotics) to CVD risk factors, including BMI, LDL cholesterol, triglycerides, blood pressure, and hemoglobin A1c, and ASCVD lifetime risk. Linear regression models were adjusted for age, sex, and race, given their associations with CVD risk factors.[10] All hypothesis tests were 2-sided and conducted with a confidence level of alpha = 0.05.

RESULTS

Demographic and Psychiatric Characteristics

The FITNESS sample is composed of 204 participants (Figure 1) with schizophrenia (14.7%), schizoaffective disorder (27.9%), bipolar disorder (44.1%), major depressive disorder (7.4%), unspecified schizophrenia spectrum and other psychotic disorder (3.9%), posttraumatic stress disorder (1.0%), and other unspecified mood and trauma-related disorders (1.0%). Participants received their mental health care at McLean Hospital (48.5%), Massachusetts Mental Health Center (23.0%), Bay Cove: Michael J. Gill Mental Health Clinic (Gill Clinic) (6.4%), Massachusetts General Hospital (5.4%), and the Edinburgh Center (2.9%) and other Boston-area sites (13.7%). Demographic and clinical characteristics of participants are shown in Table 1. The mean (SD) age of participants was 37.2 (13.5) years, and 40% were female. More males were younger (mean [SD], 34.5 [12.7] vs 41.1 [13.8]; $P = .0005$) and Black or African American (20.3% vs 8.6%; $P = .03$), and they were more likely to have a diagnosis of schizophrenia (21.4% vs 4.9%; $P = .001$). Females were more likely to have bipolar disorder (55.6% vs 36.6%; $P = .008$) and to receive antipsychotic polypharmacy (33.3% vs 16.3%; $P = .005$).

Housing instability and food and energy insecurities[24] were present in 9.8%, 24.3%, and 30.4% of the participants, respectively. Demographic characteristics by clinic site are provided in Supplementary Material and cognitive and psychiatric symptom measures among participants in Supplementary Table 1.

Cardiometabolic Risk Factors and ASCVD Risk Estimates

The mean (SD) BMI was 30.0 (7.4) (Table 2): 36% of participants had a BMI between 25.0 and 29.9 (overweight), and 40% had BMI of 30 or more (obesity). Dyslipidemia (LDL-C ≥130 mg/dL, triglycerides ≥150 mg/dL or HDL-C level <50 mg/dL in females and <40 mg/dL in males) was present in 119 (58.3%), elevated blood pressure (120–129/<80) in 15 (7.4%), and hypertension (≥130/≥80) in 107 (52.5%). Ninety-nine (49.0%) reported being inactive, and 70 (36.3%) reported active smoking (Table 2). Of these CVD risk factors, 31 (15.2%) had 1 cardiovascular risk factor, 45 (22.1%) 2 risk factors, 54 (26.5%) 3 risk factors, and 63 (30.9%) 4 or more risk factors. Females had significantly higher total cholesterol ($P = .007$), but had lower systolic blood pressure ($P = .0001$) and higher HDL cholesterol ($P = .0001$), compared to males.

Seventy-three (35.8%) met criteria for metabolic syndrome (Table 3). Females were significantly more likely to have abdominal obesity ($P = .0001$) compared to males.

ASCVD current risk estimates showed that most participants between the ages of 40–79 had low 10-year risk (69.6%); 28.9% had borderline or intermediate risk (Table 2). Of those with borderline or intermediate risk, 11 (55%) had metabolic syndrome, a risk enhancing factor.[27] In addition, most risk estimates (84.1%) were higher than calculated optimal risk estimates. Females had significantly lower 10-year risk for ASCVD ($P = .0017$) compared to males.

In linear regression analyses, lifetime ASCVD risk and BMI were not significantly associated with psychiatric diagnosis (schizophrenia, schizoaffective disorder, and primary mood disorders).

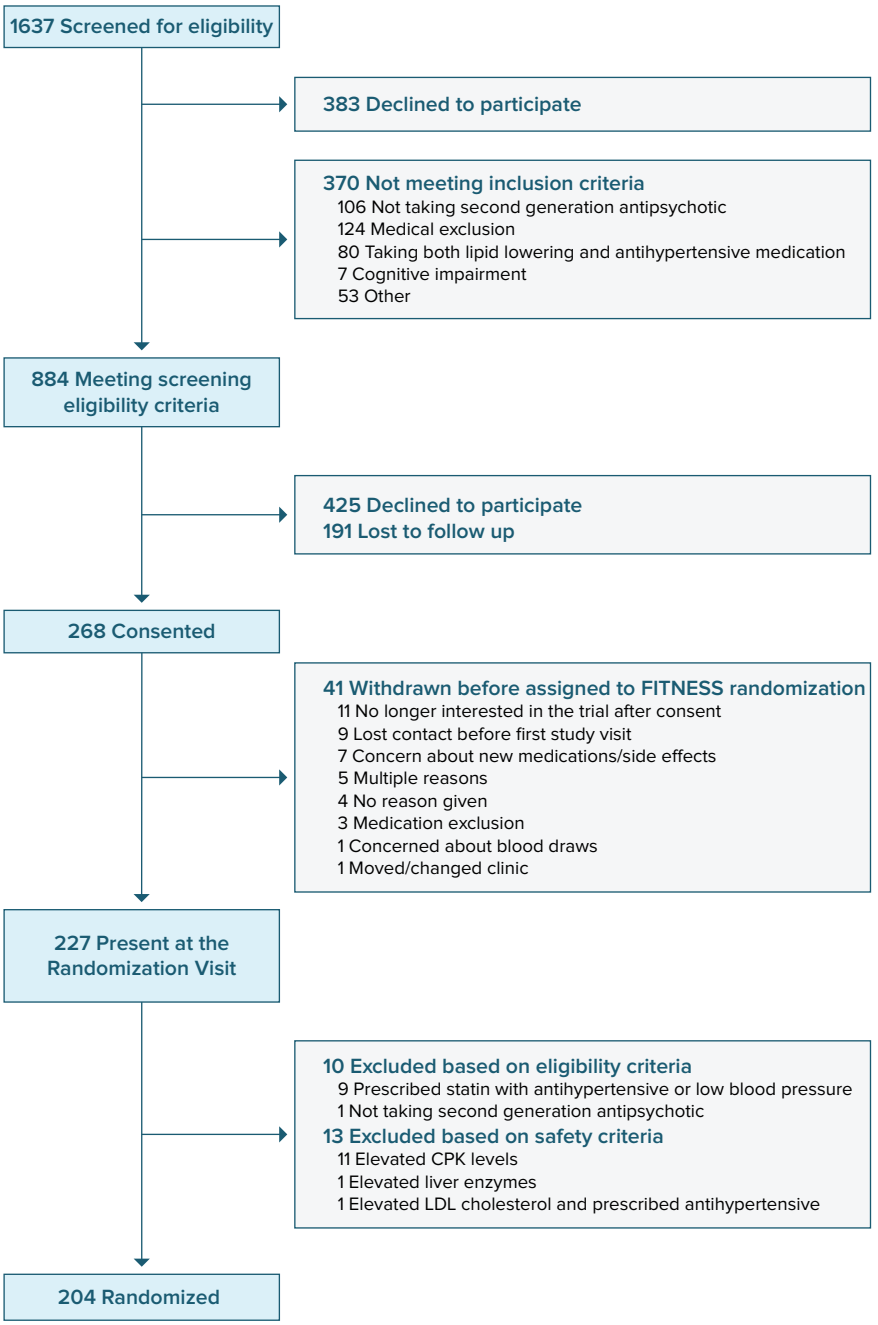
Antipsychotic Medication and CVD Risk Factors

In linear regression analyses, clozapine was significantly associated with higher triglyceride (coeff 58.28; 95% CI, 17.43, 99.13; $P = .005$) and higher hemoglobin A1c (coeff 0.16; 95% CI, 0.01, 0.30; $P = .03$) levels. Olanzapine was associated with lower systolic blood pressure (coeff −5.97, 95% CI, −10.95, −0.99; $P = .02$). We did not find any other significant associations with specific antipsychotic medications.

Baseline CVD Medications

At baseline, 24 (11.8%) were prescribed an antihypertensive, 20 (9.8%) were prescribed

Figure 1.
Flow Diagram of FITNESS Participants



Abbreviation: CPK = creatine phosphokinase.

metformin, and 4 (2.0%) were prescribed a lipid lowering medication. Only 2 (1.0%) were receiving nicotine replacement therapy. Among participants with hypertension (n = 107), 88 (82%) were not receiving any antihypertensive medication. Among those with dyslipidemia (n = 119), 118 (99.2%) were not receiving any lipid lowering medication. Among those with obesity or a BMI of 27 or greater with 1 or more weight-related conditions (n = 109), 95 (87.1%) were not receiving metformin (or weight loss medication). Among current smokers (n = 70), 68 (97.1%) were not receiving nicotine replacement therapy or other smoking cessation medication. Among those with 2 or more cardiovascular risk factors (n = 162), 123 (75.9%) were not receiving any CVD preventive medications. Furthermore, among

Table 1.

Demographic and Diagnostic Characteristics of Participants in FITNESS

	Total N = 204
Age, mean (SD), y	37.2 (13.5)
18–39 y, %	60.8
40–59 y, %	31.9
>60 y, %	7.4
Female, %	39.7
Race, %	
American Indian or Alaska Native	0.5
Asian	2.5
Native Hawaiian or Pacific Islander	0.0
Black or African American	15.7
White	68.6
More than one race	9.3
Unknown or not reported	3.4
Ethnicity, %	
Hispanic or Latino	6.4
Not Hispanic or Latino	89.2
Unknown or not reported	4.4
Diagnosis, %	
Schizophrenia	14.7
Schizoaffective disorder	27.9
Bipolar disorder	44.1
Major depressive disorder	7.4
Unspecified schizophrenia spectrum and other psychotic disorder	3.9
Posttraumatic stress disorder	1.0
Other	1.0
Psychiatric medication, %	
Quetiapine	20.6
Aripiprazole	20.1
Clozapine	17.6
Olanzapine	17.6
Risperidone	14.2
Lurasidone	8.8
Paliperidone	7.4
Ziprasidone	2.0
Asenapine	1.0
Brexpiprazole	0.0
Iloperidone	0.5
First generation antipsychotic	9.3
More than 1 antipsychotic	23.0
Mood stabilizer	64.2
Lithium	21.6
Chlorpromazine equivalent, mean (SD), mg/d	437.57 (388.9)

those who were receiving CVD medications, hypertension was significantly more likely in participants with antihypertensive medication compared to participants without antihypertensive medication (79.2% vs 48.9%; $P = .005$). BMI was significantly higher in those receiving metformin compared to those without metformin (mean [SD], 35.2 [11.1] vs 29.5 [6.7]; $P = .001$). In linear regression analyses, prescription of a CVD medication (antihypertensive, metformin or lipid lowering medication) was significantly associated with BMI (Coeff 6.37, 95% CI, 3.96, 8.77, $P < .0001$).

Medication Adherence and Treatment Views

On self-reports of antihypertensive and lipid lowering medication adherence, all of those who completed the surveys at baseline (n = 22) reported taking these medications as prescribed. Self-reported adherence was 74.5% for psychiatric medications. On the Hogan Drug Attitude Inventory, 85.1% endorsed that staying on medications was helpful for prevention of illness.

DISCUSSION

Our results show that patients with SMI and SGA use continue to have untreated cardiovascular risk factors and that there remains an urgent need to improve CVD prevention in SMI. We found a high prevalence of baseline cardiovascular risk factors, including obesity, elevated lipid levels, elevated systolic blood pressure/hypertension, active smoking, and sedentary lifestyle. Most participants (80%) had 2 or more of these risk factors. The prevalence of obesity in our sample at 40% was similar to that found in the National Health and Nutrition Examination Survey (NHANES), conducted in the US general population around the same time period (2017–2018),[28] however, was almost twice the 23% prevalence in Massachusetts (Centers for Disease Control and Prevention, 2016).[29] The prevalence of overweight and obesity in our sample was also higher than we previously reported in a McLean Hospital sample of patients with SMI collected several years earlier (29% overweight and 33% obesity).[30] Obesity and metabolic syndrome prevalence in our sample were similar to those reported in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study[31] of patients with schizophrenia spectrum disorders, but lower than those reported in the Recovery After an Initial Schizophrenia Episode (RAISE) study[32] of patients with first episode schizophrenia, as would be expected with a younger sample in the RAISE study. Notably, we found that current smoking was approximately 2.5 times higher compared to the US general population around the same time period (2017–2018).

All of these risk factors are modifiable, and several have strong evidence-based therapies that reduce cardiovascular events and mortality in large randomized clinical trials. However, despite the high levels of elevated blood pressure and hypertension (60%) and dyslipidemia (58%), 82% of those with hypertension were not receiving antihypertensive medications and 99% of those with dyslipidemia were not receiving cholesterol medications. More than half of participants had either obesity or a BMI of 27 or greater with one or more weight-related conditions, but only 13% were prescribed metformin, shown to be effective in treating antipsychotic-induced weight gain.[22] In contrast to the

Table 2.

Cardiometabolic Risk Factors in Study Participants

Variable	Total N = 204	Female N = 81	Male N = 123
BMI[a]			
Mean (SD), kg/m^2	30.0 (7.4)	31.2 (8.4)	29.25 (6.5)
Distribution, no. %			
<18.5	0 (0)	0 (0)	0 (0)
18.5–24.9	49 (24.3)	20 (25.0)	29 (23.8)
25.0–29.9	72 (35.6)	25 (31.3)	47 (38.5)
30.0–34.9	38 (18.8)	13 (16.3)	25 (20.5)
35.0–39.9	24 (11.9)	10 (12.5)	14 (11.5)
≥40	19 (9.4)	12 (15.0)	7 (5.7)
Waist circumference, mean (SD), cm[b]	99.0 (16.2)	100.5 (18.5)	98.0 (14.5)
Systolic blood pressure			
Mean (SD), mm Hg***	117.3 (13.7)	112.2 (13.7)	120.7 (12.6)
Distribution, no. %			
<120	121 (59.3)	60 (74.1)	61 (49.6)
120–129	51 (25.0)	12 (14.8)	39 (31.7)
130–139	21 (10.3)	7 (8.6)	14 (11.4)
≥140	11 (5.4)	2 (2.5)	9 (7.3)
Diastolic blood pressure			
Mean (SD), mm Hg	80.9 (10.6)	81.3 (10.6)	80.6 (10.6)
Distribution, no. %			
<80	96 (47.1)	39 (48.1)	57 (46.3)
80–89	70 (34.3)	27 (33.3)	43 (35.0)
≥90	38 (18.6)	15 (18.5)	23 (18.7)
Glucose, mean (SD), mg/dL	98.2 (17.6)	97.1 (17.8)	98.9 (17.5)
Hemoglobin A1c			
Mean (SD), %	5.4 (0.4)	5.4 (0.4)	5.4 (0.4)
Distribution, no. %			
<5.7	152 (74.5)	60 (74.1)	92 (74.8)
5.7–6.4	50 (24.5)	20 (24.7)	30 (24.4)
≥6.5	2 (1.0)	1 (1.2)	1 (0.8)
Total cholesterol, mean (SD), mg/dL**	185.8 (39.0)	194.8 (40.3)	179.8 (37.2)
HDL cholesterol, mean (SD), mg/dL***	53.3 (19.2)	60.7 (22.5)	48.5 (15.0)
LDL cholesterol, mean (SD), mg/dL	103.6 (33.7)	105.9 (34.1)	102.1 (33.5)
Distribution, no. %			
<100	102 (47.9)	39 (48.1)	63 (51.2)
100–129	64 (30.0)	28 (34.6)	36 (29.3)
130–159	22 (10.3)	8 (9.9)	14 (11.4)
160–189	12 (5.6)	3 (3.7)	9 (7.3)
≥190	4 (1.9)	3 (3.7)	1 (0.8)
Triglycerides, mean (SD), mg/dL	149.3 (108.3)	146.8 (111.3)	150.9 (106.6)
Starting the Conversation: Diet[c], summary score, mean (SD)	7.3 (2.9)	7.5 (2.8)	7.2 (2.9)
International Physical Activity Questionnaire, no. %			
Inactive	99 (49.0)	43 (54.4)	56 (45.5)
Minimally active	37 (18.3)	16 (20.3)	21 (17.1)
HEPA	66 (32.7)	20 (25.3)	46 (37.4)
Current smoking, no. %	70 (36.3)	30 (37.5)	40 (35.4)
Nicotine replacement medication, no. %	2 (1.0)	0 (0.0)	2 (1.6)
Alcohol use, no. %			
None	84 (41.2)	41 (50.6)	43 (35.0)
1–3×/mo	44 (21.6)	15 (18.5)	29 (23.6)
1×/wk	23 (11.3)	5 (6.2)	18 (14.6)
2–4×/wk	22 (10.8)	9 (11.1)	13 (10.6)
More than 5–6 times/wk	12 (5.9)	5 (6.2)	7 (5.7)
Cardiometabolic medication, no. %			
Antidiabetic	20 (9.8)	6 (7.4)	14 (11.4)
Antihypertensive	24 (11.8)	9 (11.1)	15 (12.2)
Lipid lowering	4 (2.0)	0 (0.0)	4 (3.3)

(continued)

Table 2 (continued).

Variable	Total N = 204	Female N = 81	Male N = 123
ASCVD risk estimates[d]			
Current 10-year risk, % (SD)**	4.8 (5.4)	3.15 (5.0)	7.2 (5.0)
Low-risk (<5%), no. %	48 (69.6)	36 (90.0)	12 (41.4)
Borderline risk (5–7.4%)	5 (7.2)	1 (2.5)	4 (13.8)
Intermediate risk (7.5–19.9%)	15 (21.7)	2 (5.0)	13 (44.8)
High risk (≥20%)	1 (1.4)	1 (2.5)	0 (0.0)
Lifetime risk, % (SD)*	39.4 (14.7)	36.4 (10.3)	41.4 (16.7)

[a]One participant declined to be weighed and one participant was wheelchair bound and could not be weighed.
[b]Five participants declined waist measurement and 1 participant was wheelchair bound and could not do measurement.
[c]Higher summary score indicates increase in atherogenic dietary patterns.
[d]Current 10-year ASCVD risk was obtained for 69 participants ages 40–79 and lifetime risk was obtained for 185 participants ages 20–59.
*$P < .05$, **$P < .01$, ***$P < .001$.
Abbreviations: ASCVD = atherosclerotic cardiovascular disease, BMI = body mass index, HEPA = health enhancing physical activity.

Table 3.

Metabolic Syndrome and Criteria in Study Participants

	Total N = 204	Female N = 81	Male N = 123
Metabolic syndrome, NCEP ATP III, no. %	73 (35.8)	32 (39.5)	41 (33.3)
Waist circumference, male >102 cm, female >88 cm, no. %* **	92 (46.5)	53 (67.1)	39 (32.8)
Blood pressure mm Hg, ≥130/85 or pharmacologic treatment, no. %	89 (43.6)	33 (40.7)	56 (45.5)
HDL (mg/dL)[a], male <40, female <50 or pharmacologic treatment, no. %	64 (31.4)	27 (33.3)	37 (30.1)
Triglycerides[a] (mg/dL), ≥150 or pharmacologic treatment, no. %	72 (35.3)	26 (32.1)	46 (37.4)
Glucose (mg/dL)[a], ≥100 or pharmacologic treatment, no. %	73 (35.8)	24 (29.6)	49 (39.8)

[a]Glucose, triglyceride, and HDL values were obtained non-fasting.
***$P < .001$.
Abbreviation: NCEP ATP III = National Cholesterol Education Program's Adult Treatment Panel III.

high prevalence of smoking (36%), 97% of those with active smoking were not receiving nicotine replacement therapy or other smoking cessation medication. While many of the participants were young, ASCVD 10-year risk estimates nevertheless showed that close to 30% had borderline or intermediate 10-year risk. These data show both undertreatment of risk factors and lack of CVD preventive therapy in individuals with SMI, largely consistent with prior reports in individuals with chronic psychiatric disorders and antipsychotic use.[13] Our findings suggest that CVD risks remain elevated without improvement over time in the SMI population. This is all the more striking as 35% of participants were receiving SGAs with highest risk for metabolic side effects (clozapine and olanzapine).[8,10] Guidelines on metabolic monitoring with antipsychotic use and available lifestyle and medication interventions have not been sufficient to advance CVD prevention in this population.

Psychiatric diagnosis and specific SGA use were not associated with lifetime ASCVD risk or BMI, indicating that patients with SMI would benefit from CVD prevention across psychiatric diagnoses. Consistent with clozapine's high risk for metabolic side effects,[10] we found that clozapine use was associated with higher triglyceride and hemoglobin A1c levels. Unexpectedly, we also found that olanzapine was associated with lower systolic blood pressure. While there are differences in antipsychotic medication effects on metabolic parameters,[10] which may guide prescription choices, our findings support that the prescription of any SGA should prompt CVD prevention.

There are several reasons that may explain the undertreatment of CVD risk factors in individuals with SMI. First, despite national guidelines, regular metabolic monitoring in individuals with SMI is infrequent[13,17,18] and clinicians may thus not have offered CVD preventative therapies. In addition, individuals with SMI often view their psychiatric care as their clinical home, but psychiatric clinicians may not routinely prescribe CVD medications such as antihypertensive and lipid lowering medications in their practice and fragmentation of care makes referrals to other clinicians difficult.[33] Second, CVD treatment may have been offered, for example smoking cessation medication, but the

treatment could have been declined by patients. Third, stigma associated with SMI and provider-bias towards patient adherence may have influenced the decision of healthcare professionals not to prescribe CVD preventative therapy medications or to carry out recommended cardiometabolic monitoring.[34] Finally, lifestyle interventions may have been offered, rather than pharmacologic treatments, but we did not collect information on whether these interventions had been provided. Considering these possible reasons for lack of CVD prevention, the FITNESS trial sought to test a treatment strategy of embedding a simplified, fixed dose, initial treatment strategy for CVD prevention within the mental health clinic, offered to all patients with SMI taking an SGA. A simplified fixed dose regimen may be a useful tool for increasing both feasibility of implementation for mental health clinics and adherence.[35–37]

We found that most patients who enrolled in the trial had favorable attitudes about medication and prevention. As participants reported high levels of adherence to their current CVD and psychiatric medications, our results would indicate that improving the initiation of cardiovascular risk reduction in this high-risk population could reduce morbidity and mortality. However, substantial evidence suggests that patient adherence to CVD medication therapy is poor in many settings[18,38,39] and needs to be addressed in the implementation of CVD prevention. While in the FITNESS trial, we addressed challenges with adherence by simplifying medication regimens with fixed doses and by integrating prevention into the mental health clinic, other methods for increasing adherence can be considered, including promoting greater health care provider-patient interaction and clinic-wide strategies for monitoring adherence.[39,40] Ultimately, optimizing adherence to CVD prevention will likely require a multi-faceted approach to address factors that could be impacting adherence (eg, socioeconomic factors, health care system factors, medication regimens, or other patient-related factors).[39]

Even with successful implementation of pharmacologic interventions, lifestyle interventions are important adjunctive treatments and some have been shown to improve CVD risk in individuals with SMI.[40,41] In a recent study, the Severe Mental Illness Lifestyle Evaluation (SMILE) study,[40] significant weight loss was observed with lifestyle interventions combined with assertive community treatment (ACT) approaches. These findings suggest that lifestyle interventions (eg, promoting better nutrition and regular physical activity) should be integrated into the mental health clinic and psychiatric clinicians' practices.

Of note, 17% of participants in the trial were using alcohol more than once per week. Habitual alcohol use is associated with higher risk for CVD,[42] particularly higher levels of alcohol use. Clinicians should consider alcohol use in their assessment for CVD risk and offer counseling on this risk and evidence-based therapies for alcohol use disorder,[43] if present, such as naltrexone and acamprosate.

There are limitations of this cross-sectional analysis to consider. Participants with potential contraindications to statins or angiotensin receptor blockers were excluded, which may have limited our sample. In addition, receiving both an antihypertensive and a lipid lowering medication was exclusionary for the FITNESS trial, and thus we could not consider patients who may be taking this combination of CVD medications. Our sample was also composed of individuals who were willing to enroll in a clinical trial and may have been predisposed to higher adherence to medication. Moreover, future studies should extend beyond cross-sectional analysis and conduct long term follow-up after initial assessment, eg, 10 years, to allow assessment of actual vs predicted risk of cardiovascular events. Finally, though we collected information on patients' current alcohol and nicotine use, we did not collect information on whether patients met criteria for alcohol use disorders or other substance use disorders, which would be informative, particularly with regards to alcohol use disorder and CVD risk.

Overall, we found that CVD risks in individuals with SMI and SGA remain common and frequently untreated or undertreated. Alternative approaches are necessary to carry out CVD prevention for all SGA use across psychiatric diagnoses. The high prevalence of obesity in youth and use of SGA in child and adolescent psychiatry highlights this need.[44,45] Early intervention efforts and programs to prevent and treat psychiatric disorders present an opportunity to address cardiometabolic risk at an earlier stage.

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Supplementary Material

Article Title: Baseline Cardiovascular Risk Factors in Patients With Severe Mental Illness (SMI) and Second Generation Antipsychotic Use From the Fixed Dose Intervention Trial of New England Enhancing Survival in SMI (FITNESS)

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

This Supplementary Material has been provided by the authors 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 material

Demographics and material need insecurities by study site

Across study sites, ages ranged from 33.2-45.6 years old and there were 33.3%-54.5% females and 45.5%-69.2% males. There were 0.0-2.1% of participants across study sites who identified as American Indian or Alaska Native, 0.0-4.0% Asian, 0.0% Native Hawaiian or Pacific Islander, 0.0-76.9% Black or African American, 15.4%-100.0% White, 0.0-17.0% More than one race, and 0.0%-7.7% Unknown or not reported across study sites. There were 0.0%-16.7% of participants across study sites who identified as Hispanic or Latino, 78.7%-100.0% not Hispanic or Latino, and 0.0%-8.5% Unknown or not reported. Across study sites, 0.0%-19.5% of participants reported housing instability, 10.9%-58.3% food insecurity, and 0.0%-41.7% energy insecurity.

Supplementary Table 1: Baseline cognitive and psychiatric symptom measures in FITNESS participants

	Total N=204	Female N=81	Male N=123
Brief Assessment of Cognition in Schizophrenia (BACS), Total score[a]	234.7 (52.0)	240.1 (51.1)	231.3 (52.5)
North American Adult Reading Test (NAART), FSIQ	110.8 (9.9)	111.8 (10.5)	110.1 (9.5)
Young Mania Rating Scale (YMRS), Total Score	5.2 (5.7)	5.1 (5.9)	5.2 (5.5)
Montgomery-Asberg Depression Rating Scale (MADRS), Total Score	12.7 (9.6)	13.8 (10.1)	12.0 (9.2)
Scale for the Assessment of Positive Symptoms (SAPS), Total Score	10.1 (12.7)	7.8 (10.7)	11.4 (13.6)
Scale for the Assessment of Negative Symptoms (SANS), Total Score	16.4 (13.8)	13.9 (12.8)	17.9 (14.2)
Positive and Negative Syndrome Scale (PANSS), Total Score	45.1 (9.9)	43.9 (10.3)	45.9 (9.7)
Scale to assess Unawareness of Mental Disorder (SUMD), General Items Summary Score	8.5 (5.7)	7.4 (5.3)	9.2 (5.9)
Multnomah Community Ability Scale (MCAS), Total Score	47.3 (8.1)	47.2 (9.5)	47.4 (7.1)
World Health Organization Disability Assessment Scale (WHODAS), General Disability Score	0.9 (0.6)	0.9 (0.5)	0.9 (0.6)

[a] Values are expressed as mean (SD).