Differential Effects of an Intervention to Reduce Cardiovascular Risk for Patients With Bipolar Disorder, Schizoaffective Disorder, or Schizophrenia: A Randomized Clinical Trial

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ABSTRACT

Objective: To measure the impact of a clinical decision support (CDS) tool on total modifiable cardiovascular risk at 12 months separately for outpatients with 3 subtypes of serious mental illness (SMI) identified via *ICD-9* and *ICD-10* codes: bipolar disorder, schizoaffective disorder, and schizophrenia.

Methods: This cluster-randomized pragmatic clinical trial was active from March 2016 to September 2018; data were analyzed from April 2021 to September 2022. Clinicians and patients from 78 primary care clinics participated. All 8,922 adult patients aged 18–75 years with diagnosed SMI, at least 1 cardiovascular risk factor not at goal, and an index and follow-up visit during the study period were included. The CDS tool provided a summary of modifiable cardiovascular risk and personalized treatment recommendations.

Results: Intervention patients had 4% relative reduction in total modifiable cardiovascular risk at 12 months compared to controls (relative risk ratio = 0.96; 95% CI, 0.94 to 0.98), with similar intervention benefits for all 3 SMI subtypes. At index, 10-year cardiovascular risk was higher for patients with schizophrenia (mean [SD] = 11.3% [9.2%]) than for patients with bipolar disorder (8.5% [8.9%]) or schizoaffective disorder (9.4% [8.1%]), while 30-year cardiovascular risk was highest for patients with schizoaffective disorder (44% with 2 or more major cardiovascular risk factors, compared to 40% for patients with schizophrenia and 37% for patients with bipolar disorder). Smoking was highly prevalent (47%), and mean (SD) BMI was 32.7 (7.9).

Conclusions: This CDS intervention produced a clinically and statistically significant 4% relative reduction in total modifiable cardiovascular risk for intervention patients versus controls at 12 months, an effect observed across all 3 SMI subtypes and attributable to the aggregate impact of small changes in multiple cardiovascular risk factors.

Trial Registration: ClinicalTrials.gov Identifier: NCT02451670.

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Cardiovascular disease (CVD) is the leading cause of death for people with schizophrenia, schizoaffective disorder, or bipolar disorder, often collectively termed *serious mental illness* (SMI).[1] The elevated risk of CVD is thought to be driven in part by higher prevalence rates and relative risks (RRs) of dyslipidemia (RR = 5.0), smoking (RR = 2.0–3.0), diabetes (RR = 2.0), and obesity (RR = 1.5–2.0).[2,3] Additionally, medications used to treat SMI can cause weight gain, insulin resistance, and impaired lipid metabolism.[4-6] Despite this, cardiovascular risk is often not recognized or treated for patients with SMI, leading to disparities in care and adverse cardiovascular outcomes that contribute to lifespans that are 10–15 years shorter for people with SMI compared to the general population.[1,7–14]

Although elevated cardiovascular risk for people with SMI is well established, few studies have directly compared cardiovascular risk across SMI subtypes. As such, the differential risk profile of CVD and specific modifiable cardiovascular risk factors across SMI subtypes are not well understood. A 2017 meta-analysis[15] of data from 3.2 million patients with SMI and 113.4 million controls found that schizophrenia and bipolar disorder were associated with higher risk of CVD (schizophrenia hazard ratio [HR] = 1.95; 95% CI, 1.41 to 2.70; bipolar HR = 1.57; 95% CI, 1.28 to 1.93) and CVD-related death (schizophrenia HR = 2.45; 95% CI, 1.64 to 3.65; bipolar HR = 1.65; 95% CI, 1.10 to 2.47), while schizophrenia was associated with higher risk of coronary heart disease (HR = 1.59; 95% CI, 1.08 to 2.35). These results were pooled from multiple studies; to date, few cardiovascular intervention studies have reported differential effects by SMI subtype.

We conducted a cluster-randomized trial of a clinical decision support (CDS) tool aimed at promoting recognition and treatment of elevated cardiovascular risk for people with SMI in outpatient primary care clinics.[16] This article describes differences in baseline cardiovascular risk and treatment outcomes for 3 patient subtypes with SMI: bipolar disorder, schizophrenia, and schizoaffective disorder.

METHODS

Study Setting

Clinicians and patients from 78 primary care clinics from the Essentia Health, HealthPartners, and Park Nicollet integrated health care systems in Minnesota, North Dakota, and Wisconsin participated in this clinic-randomized pragmatic trial (ClinicalTrials.

Clinical Points

- Cardiovascular disease is the leading cause of death for people with serious mental illness (SMI), but few studies present baseline risk or the impact of an intervention by SMI subtype.
- Estimated cardiovascular risk varies across SMI subtype, with 10-year risk highest in those with schizophrenia and 30-year risk highest in those with schizoaffective disorder.
- For patients of all ages with risk factors not at goal, clinical decision support interventions can decrease cardiovascular risk for patients with all subtypes of SMI.

gov identifier: NCT02451670).[16,17] Health systems are hereafter referred to as Sites A, B, and C for anonymity. Enrollment started on March 2, 2016, at Site A, October 18, 2016, at Site B, and March 15, 2017, at Site C, and ended on September 19, 2017, with patients followed through September 19, 2018. Institutional Review Boards at each health care system reviewed, approved, and monitored the study.

Clinic Randomization

Via covariate constrained randomization, primary care clinics were randomly assigned to receive or not receive CDS tool access.[18,19] Covariates varied by site to balance factors most likely to impact the intervention or its implementation. At Site A, clinics were stratified by the proportion of Medicaid-insured patients, the presence of onsite behavioral health services, and number of patients with SMI. At Site B, clinics were stratified by urbanicity, proportion of patients who smoked, and proportion of patients under age 30 years. At Site C, clinics were stratified by proportion of Medicaid-insured patients, proportion of patients achieving optimal vascular care, and number of patients with SMI.

Study Participants

Adults (aged 18–75 years) with SMI who were not pregnant, had at least 1 modifiable cardiovascular risk factor not at goal, and had at least 1 post-index visit at a randomized clinic during the intervention period were eligible. Patients in nursing homes or hospice, diagnosed with cancer, or requesting exclusion from research were excluded. Patients were assigned to the primary care clinic of their index visit. SMI was defined as having 1 inpatient or 2 outpatient diagnoses during the 2 years prior to index (bipolar disorder [*ICD-9*: 296.00–296.89, 301.11; *ICD-10*: F30.1–F31.9], schizoaffective disorder [*ICD-9*: 295.6; *ICD-10*: F25.0–F25.9], and schizophrenia [*ICD-9*: 295.0–295.5, 295.8–295.9, 297.1, 297.3, 298.8, 298.9, 301.22; *ICD-10*: F20.0–F24, F28–F29]). Patients with multiple SMI subtype diagnoses were considered to have schizoaffective disorder. The Institutional Review Boards granted waivers of written informed consent for CDS use because it presented evidence-based care recommendations to help clinicians achieve guideline-consistent care.

Intervention

An electronic health record (EHR) alert prompted rooming staff to print a 1-page handout for study-eligible patients and their clinicians. The CDS was not visible to control clinicians or patients. The handouts summarized and prioritized modifiable cardiovascular risk factors for each patient: blood pressure (BP), lipids, glycated hemoglobin (A1c), smoking status, and body mass index (BMI). The CDS estimated 10-year (for patients 40–75 years old) and 30-year (for patients 18–59 years old) risk of a myocardial infarction or stroke for cardiovascular risk factor control based on risk prediction equations from the American College of Cardiology (ACC)/American Heart Association (AHA),[20,21] the Framingham Study,[22] and the United Kingdom Prospective Diabetes Study (UKPDS).[23,24] The handouts also provided patient-specific treatment recommendations.

Data Collection

The CDS website archived a limited data set from the EHR in intervention and control clinics, including demographics, vital signs, diagnoses, medications, allergies, and laboratory values during the study period and for up to 5 years prior to the visit. Data were encrypted and stored in firewall-protected secure servers and linked to each patient using random unique study IDs.

Outcomes

Primary outcomes were change in total modifiable cardiovascular risk and changes in individual modifiable cardiovascular risk factors from index to 12 months. Total modifiable cardiovascular risk was calculated as follows: (*a*) 10-year risk equations estimated cardiovascular risk (modifiable plus non-modifiable) using ACC/AHA[20,21] and Framingham risk equations.[22] For patients less than 40 years old, 10-year risk equations were calculated as if the patient were 40 years old. (*b*) Risk components for each modifiable cardiovascular risk factor were calculated as differences between the calculated risk, using the patient's values, and the goal, using validated risk prediction equations. For BMI, the goal value was a decrease of 3 BMI units (for those with BMI ≥ 28) or a decrease to a BMI of 25 (for those with BMIs 25–27.9). Risk components for modifiable cardiovascular risk factors at goal were calculated as zero. (*c*) Modifiable cardiovascular risk factors were summed to calculate total modifiable cardiovascular risk. The CDS calculated and stored total modifiable risk and each individual cardiovascular risk factor at every encounter in both control and intervention clinics.

Analysis

Data were analyzed from April 2021 to September 2022. Total modifiable cardiovascular risk and individual modifiable cardiovascular risk factors were analyzed using general or generalized linear mixed models. The overall treatment effect on total modifiable cardiovascular risk models was estimated using data from all patients with

SMI. Separate models for patients with each SMI subtype estimated condition-specific treatment effects. For each risk factor, one model estimated the overall and a stratified model estimated the condition-specific treatment effects. The treatment effect was estimated from fixed effects of treatment, time, and treatment by time. The linear time parameter estimated the annual rate of change in outcomes in control clinics, while the sum of the time and treatment by time parameters estimated the annual rate of change in intervention clinics. The time-by-treatment parameter tested the significance of the difference in rates of change in intervention relative to control clinics. All outcomes except smoking potentially had many measurements per person, and the time predictor quantified years elapsed between index date and each measurement. The smoking models were limited to current smokers at index so that the treatment parameter estimated the likelihood of smoking cessation at the last observation, with an offset for time elapsed. The A1c models were limited to patients with diabetes at index. Covariates included sex, age, outcome value at index, health system, and clinic balancing factors. Outcomes were normalized in a manner appropriate to their distributions (eg, log-binomial, log-negative binomial). Random intercepts accounted for non-independence of observations within patients and clinics.

Additional analyses estimated the treatment effect on total modifiable cardiovascular risk and individual modifiable cardiovascular risk factors by patient subtypes (modifiable cardiovascular risk at index, sex, age at index, race/ethnicity). In these analyses, separate models were estimated among all patients with SMI and each SMI condition and then stratified by patient subtype. Otherwise, the patient subtype analyses followed the same approach as the SMI subtype analyses.

RESULTS

A total of 8,922 patients with SMI made an index primary care visit and at least 1 follow-up visit during the intervention period, including 5,901 patients with bipolar disorder, 1,732 patients with schizoaffective disorder, and 1,289 patients with schizophrenia (Table 1). Fifty-five percent of the sample were women, with a mean age of 48 years; patients with bipolar disorder were slightly younger (mean age 47.4 years) and patients with schizophrenia were slightly older (mean age 51.5 years). Relative to patients with bipolar disorder (7.5% Black; 0.9% Asian), there were relatively high percentages of patients self-identifying as Black or Asian among those with diagnoses of schizophrenia (16.4% Black; 3.2% Asian) or schizoaffective disorder (14.3% Black; 2.0% Asian). The percentage of patients identifying as White was higher for those diagnosed with bipolar disorder (87.2%) compared to those diagnosed with schizophrenia (75.4%) or schizoaffective disorder (78.5%). There were no notable differences in the prevalence of patients who self-identified as Native American/Alaska Native, Pacific Islander, Hispanic, or other/unknown across SMI diagnoses.

Nearly half (46.5%) of patients with SMI were current smokers, and smoking was the largest driver of modifiable cardiovascular risk in each subtype (mean = 1.8%). The mean 10-year ACC/AHA cardiovascular risk for patients with SMI was 9.1%, with the highest risk for those with schizophrenia (11.3%) and the lowest for those with bipolar disorder (8.5%). A similar pattern was observed for total modifiable cardiovascular risk: the mean risk for patients with SMI was 3.6%, with the highest risk for patients with schizophrenia (4.7%) and the lowest risk for patients with bipolar disorder (3.3%). In contrast, 30-year cardiovascular risk was highest for those with schizoaffective disorder, with 44.1% of patients with schizoaffective disorder having 2 or more major cardiovascular risk factors compared to 40.2% of those with schizophrenia and 36.9% of those with bipolar disorder. Individual cardiovascular risk factors were similar across groups at index, except for lipids, with the highest risk for those with schizophrenia, and smoking, with the highest risk for those with schizophrenia or schizoaffective disorder.

At 12 months, intervention patients with SMI had a 4% relative reduction in total modifiable cardiovascular risk at 12 months compared to control (Table 2; relative risk ratio [RR] = 0.96; 95% CI, 0.94 to 0.98). The intervention produced a relative reduction in total modifiable cardiovascular risk for all 3 SMI diagnosis subtypes (Figure 1; bipolar disorder RR = 0.96; 95% CI, 0.94 to 0.99; schizoaffective disorder RR = 0.94; 95% CI, 0.90 to 0.98; schizophrenia RR = 0.92; 95% CI, 0.85 to 0.99). Despite the overall positive effect of the intervention, there were few significant differences in individual modifiable cardiovascular risk factors between intervention and control groups. The only significant differences were in A1c levels, which favored the intervention for patients with bipolar disorder (difference in difference [DD] = −0.14; 95% CI, −0.26 to −0.02) and the control for patients with schizoaffective disorder (DD = 0.18; 95% CI, 0.01 to 0.35).

Differences in rates of change in total modifiable cardiovascular risk from index to 12 months largely favored the intervention (Table 3). When stratified by baseline total modifiable cardiovascular risk, significant differences favoring the intervention were observed for patients with 0% to < 2%, 2 to < 5%, and ≥ 10% risk; for patients with schizophrenia with the lowest total modifiable cardiovascular risk (0% to < 2%); and for patients with bipolar disorder with the highest total modifiable cardiovascular risk (≥ 10%). The intervention improved total modifiable cardiovascular risk for both women and men with SMI, largely driven by results for women with bipolar disorder, women with schizoaffective disorder, and men with schizophrenia. The intervention improved total modifiable cardiovascular risk for patients aged 18–29 years and 50–59 years with SMI, patients ages 18–29 years with bipolar disorder, patients aged 40–49 years with schizoaffective disorder, and patients aged 50–59 years with bipolar disorder. Black intervention patients with SMI or with schizoaffective disorder and White intervention

Table 1. Demographic and Clinical Characteristics at Index Visit by SMI Subtype and Treatment Group

		Bipolar Disorder			Schizoaffective Disorder			Schizophrenia		
Variable	Overall	Total	CTRL	INT	Total	CTRL	INT	Total	CTRL	INT
Total n	8,922	5,901	2,866	3,035	1,732	855	877	1,289	657	632
Site A	3,919	2,636	1,473	1,163	787	409	378	496	234	262
Site B	3,299	2,171	893	1,278	586	292	294	542	297	245
Site C	1,704	1,094	500	594	359	154	205	251	126	125
Demographic Characteristics										
Male, n	4,006	2,274	1,097	1,177	862	445	417	870	448	422
Male, %	44.9	38.5	38.3	38.8	49.8	52.0	47.5	67.5	68.2	66.8
Age										
Mean	48.4	47.4	47.1	47.6	49.5	49.2	49.8	51.5	51.3	51.6
SD	13.4	13.5	13.4	13.6	12.8	13.2	12.4	13.0	13.3	12.6
Median	50	48	48	48	51	51	52	54	54	54
P25, P75	38, 59	36, 58	36, 57	36, 58	40, 59	39, 60	40, 59	43, 61	42, 61	44, 61
Race/ethnicity										
Asian, n	129	53	30	23	35	9	26	41	15	26
%	1.4	0.9	1.0	0.8	2.0	1.1	3.0	3.2	2.3	4.1
Black, n	902	442	189	253	248	108	140	212	92	120
%	10.1	7.5	6.6	8.3	14.3	12.6	16.0	16.4	14.0	19.0
Native American, n	182	112	44	68	41	13	28	29	12	17
%	2.0	1.9	1.5	2.2	2.4	1.5	3.2	2.2	1.8	2.7
Other and Unknown, n	223	143	82	61	46	26	20	34	21	13
%	2.5	2.4	2.9	2.0	2.7	3.0	2.3	2.6	3.2	2.1
Pacific Islander, n	12	8	2	6	3	1	2	1	1	0
%	0.1	0.1	0.1	0.2	0.2	0.1	0.2	0.1	0.2	0.0
White, n	7,474	5,143	2,519	2,624	1,359	698	661	972	516	456
%	83.8	87.2	87.9	86.5	78.5	81.6	75.4	75.4	78.5	72.2
Hispanic, n	124	78	46	32	35	21	14	11	5	6
%	1.4	1.3	1.6	1.1	2.0	2.5	1.6	0.9	0.8	0.9
Total Cardiovascular Risk										
10-year ASCVD risk[a]										
n	5,081	3,140	1,538	1,602	1,094	519	575	847	427	420
Mean	9.1	8.5	8.2	8.8	9.4	9.3	9.4	11.3	11.3	11.4
SD	8.8	8.9	8.7	9.1	8.1	7.6	8.4	9.2	9.0	9.4
Median	6.3	5.6	5.5	5.7	7.1	7.1	7.1	8.7	8.9	8.5
P25, P75	3.0, 12.4	2.6, 11.3	2.5, 10.9	2.7, 11.7	3.5, 12.8	3.4, 13.5	3.6, 12.4	4.6, 15.2	4.7, 14.9	4.4, 15.9
30-year lifetime risk[b]										
n	5,098	3,266	1,635	1,631	1,098	533	565	734	363	371
CV risk factors										
All optimal, %	2.5	2.2	2.1	2.2	2.6	2.4	2.7	4.0	4.4	3.5
≥ 1 not optimal, %	7.7	7.9	8.0	7.8	7.5	7.1	7.8	7.6	8.0	7.3
≥ 1 elevated, %	4.1	4.0	4.0	4.1	3.9	3.8	4.1	4.4	5.0	3.8
1 major, %	46.8	49.0	48.9	49.1	42.0	45.2	38.9	43.9	42.4	45.3
≥ 2 major, %	38.9	36.9	37.0	36.8	44.1	41.5	46.5	40.2	40.2	40.2
Total modifiable CV risk										
Mean	3.6	3.3	3.2	3.3	4.2	4.1	4.2	4.7	4.5	4.8
SD	5.6	5.3	5.2	5.4	5.9	5.9	5.8	6.3	6.1	6.5
Median	1.6	1.4	1.4	1.4	2.1	2.1	2.1	2.4	2.3	2.5
P25, P75	0.3, 4.3	0.3, 3.7	0.3, 3.6	0.3, 3.7	0.4, 5.3	0.4, 5.3	0.3, 5.3	0.5, 6.0	0.5, 6.0	0.6, 6.1
Cardiovascular Risk Factor: Smoking										
Current smoking %	46.5	45.6	45.0	46.1	48.6	49.9	47.3	48.0	46.4	49.7
Modifiable risk										
Mean	1.8	1.6	1.6	1.6	2.2	2.2	2.3	2.4	2.2	2.5
SD	3.1	2.8	2.7	2.9	3.6	3.7	3.5	3.5	3.3	3.7
Median	0	0	0	0	0	0	0	0	0	0
P25, P75	0, 2.7	0, 2.3	0, 2.3	0, 2.3	0, 3.6	0, 3.5	0, 3.7	0, 3.8	0, 3.6	0, 4.0
Cardiovascular Risk Factor: BMI										
BMI (kg/m^2)										
Mean	32.7	32.5	32.6	32.5	33.5	33.6	33.5	32.1	32.5	31.6
SD	7.9	7.9	7.8	7.9	8.3	8.7	7.8	7.3	7.5	7.0
Median	31.5	31.4	31.3	31.4	32.5	32.5	32.3	31.2	31.6	30.7
P25, P75	27.2, 36.9	27.1, 36.7	27.3, 36.7	27.0, 36.7	27.8, 37.8	27.8, 37.8	27.8, 38.0	27.4, 36.1	27.3, 36.7	27.0, 35.5
Modifiable risk										
Mean	0.4	0.3	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.5
SD	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5
Median	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.3
P25, P75	0.1, 0.5	0.1, 0.4	0.1, 0.4	0.1, 0.5	0.1, 0.6	0.1, 0.6	0.1, 0.7	0.1, 0.8	0.1, 0.8	0.1, 0.8

(continued)

Table 1 (continued).

Variable	Overall	Bipolar Disorder			Schizoaffective Disorder			Schizophrenia		
		Total	CTRL	INT	Total	CTRL	INT	Total	CTRL	INT
Cardiovascular Risk Factor: Lipids										
Total cholesterol (mg/dL)										
Mean	183.9	188.3	187.8	188.8	177.9	178.3	177.6	174.3	175.8	172.9
SD	45.8	46.3	47.6	45.0	46.4	51.7	40.6	40.5	41.1	39.9
Median	180	185	185	185	174	174	174	170	172	169
P25, P75	154, 208	159, 213	158, 212	160, 213	148, 202	147, 203	149, 202	145, 198	145, 199	145, 197
LDL (mg/dL)										
Mean	104.8	107.9	107.4	108.3	100.1	99.6	100.6	98.8	100.1	97.6
SD	35.5	35.3	35.2	35.4	35.4	36.1	34.7	35.0	35.4	34.5
Median	102	105	105	106	98	96	99	96	97	95
P25, P75	80, 126	84, 130	83, 129	84, 130	76, 120	75, 118	76, 121	75, 119	75, 121	74, 115
HDL (mg/dL)										
Mean	46.6	48.0	47.8	48.2	44.6	44.5	44.7	43.6	43.6	43.5
SD	15.0	15.6	15.6	15.7	13.8	14.0	13.6	13.5	13.8	13.1
Median	44	45	45	46	42	43	42	41	41	41
P25, P75	36, 54	37, 56	37, 55	38, 56	35, 52	35, 52	36, 51	35, 50	35, 50	34, 51
Triglycerides (mg/dL)										
Mean	171.3	170.2	170.6	169.8	180.7	192.2	169.6	162.6	163.9	161.4
SD	201.1	171.5	175.5	167.7	307.5	420.9	123.6	105.5	103.3	107.7
Median	136	134	135	133	142	142	143	138	139	134
P25, P75	93, 202	92, 200	91, 199	93, 201	96, 208	92, 210	102, 207	92, 204	94, 206	90, 203
Modifiable risk										
Mean	0.6	0.6	0.6	0.6	0.7	0.6	0.7	0.9	0.8	0.9
SD	1.7	1.6	1.6	1.6	1.6	1.5	1.7	2.0	1.8	2.1
Median	0	0	0	0	0	0	0	0	0	0
P25, P75	0, 0	0, 0	0, 0	0, 0	0, 0.4	0, 0.2	0, 0.5	0, 0.9	0, 0.9	0, 0.9
Cardiovascular Risk Factor: Blood Pressure										
SBP (mm Hg)										
Mean	124.3	124.8	124.7	125.0	123.2	122.8	123.5	123.5	123.8	123.1
SD	16.6	16.7	16.7	16.6	16.4	15.8	16.9	16.3	16.4	16.2
Median	123	124	123	124	122	122	123	122	122	122
P25, P75	113, 134	114, 134	113, 134	114, 135	112, 132	111, 132	112, 133	112, 133	112, 134	112, 33
DBP (mm Hg)										
Mean	78.3	78.8	78.9	78.8	77.6	77.4	77.8	77.1	77.2	77.0
SD	11.3	11.4	11.3	11.4	11.2	11.0	11.5	11.0	11.1	11.0
Median	78	79	78	79	78	77	78	78	78	78
P25, P75	70, 85	71, 86	71, 86	71, 86	70, 84	70, 84	70, 85	70, 84	70, 84	69, 84
Modifiable risk										
Mean	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.3
SD	1.3	1.3	1.2	1.3	1.5	1.4	1.6	1.3	1.3	1.3
Median	0	0	0	0	0	0	0	0	0	0
P25, P75	0, 0	0, 0	0, 0	0, 0	0, 0	0, 0	0, 0	0, 0	0, 0	0, 0
Cardiovascular Risk Factor: A1c										
Diagnosed diabetes, n	1,858	1,045	523	522	474	212	262	339	160	179
A1c[c] (%)										
Mean	7.2	7.4	7.2	7.3	7.1	7.3	7.0	6.9	6.9	6.9
SD	1.7	1.8	1.9	1.7	1.7	1.8	1.6	1.5	1.6	1.6
Median	6.8	6.9	7.0	6.9	6.6	6.8	6.6	6.5	6.6	6.5
P25, P75	6.1, 7.8	6.1, 8.1	6.2, 8.1	6.1, 8.0	6.0, 7.6	6.0, 8.1	6.0, 7.5	6.0, 7.3	6.1, 7.4	6.0, 7.3
Modifiable risk										
Mean	1.0	1.1	1.2	1.1	0.9	1.2	0.6	0.8	0.7	0.9
SD	2.9	3.1	3.4	2.7	2.5	2.9	2.2	3.0	2.6	3.2
Median	0	0	0	0	0	0	0	0	0	0
P25, P75	0, 0.5	0, 0.7	0, 0.7	0, 0.7	0, 0.4	0, 0.6	0, 0.2	0, 0	0, 0.2	0, 0

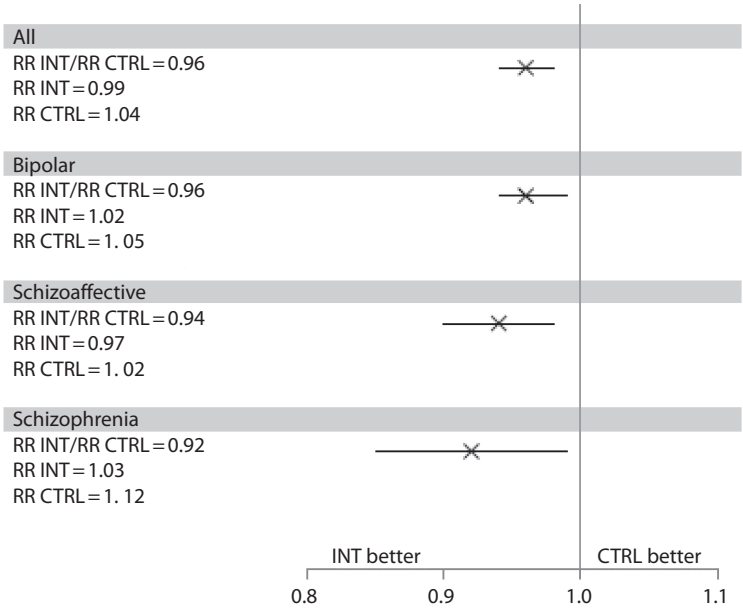
[a]10-year ASCVD risk is calculated only for patients aged 40–75 years without known CVD (n = 5,081).
[b]30-year lifetime risk of CVD is calculated only for patients aged 18–59 years without known CVD (n = 5,098). CV risk factor categories are defined as follows[22]:
Optimal: total cholesterol < 180 mg/dL, BP < 120/80 mm Hg, nonsmoker and nondiabetic.
Not optimal: total cholesterol 180–199 dL, SBP 120–139 mg Hg, DBP 80–89 mm/Hg, nonsmoker and nondiabetic
Elevated: total cholesterol 200–239 mg/dL, SBP 140–159 mm Hg, DBP 90–99 mm Hg, nonsmoker and nondiabetic.
Major: total cholesterol ≥ 240 mg/dL, SBP ≥ 160 mm Hg, DBP ≥ 100 mm Hg, smoker or diabetic.
[c]A1c calculated for patients with diabetes who had available A1c tests within the past 5 years (n = 1,858).
Abbreviations: A1c = glycosylated hemoglobin, ASCVD = atherosclerotic cardiovascular disease, BMI = body mass index, BP = blood pressure, CTRL = control, CV = cardiovascular, CVD = cardiovascular disease, DBP = diastolic blood pressure, HDL = high-density lipoprotein, INT = intervention, LDL = low-density lipoprotein, P25 = 25th percentile, P75 = 75th percentile, SMI = serious mental illness, SBP = systolic blood pressure.

Table 2. Relative Risk Ratios Comparing Rate of Change in Outcomes From Index to 12 Months Among Patients in Intervention Relative to Control Clinics

	Overall			Bipolar Disorder			Schizoaffective Disorder			Schizophrenia		
		95% CL			95% CL			95% CL			95% CL	
Variable	Value	LL	UL	Value	LL	UL	Value	LL	UL	Value	LL	UL
Total modifiable CV risk[a,c]	0.96	0.94	0.98	0.96	0.94	0.99	0.94	0.90	0.98	0.92	0.85	0.99
Quit smoking[a,d]	1.11	0.92	1.33	1.10	0.89	1.37	1.06	0.71	1.57	1.19	0.73	1.95
BMI[b,c,+]	0.07	0.01	0.13	0.06	0.00	0.13	0.02	−0.10	0.14	0.24	0.09	0.39
LDL[b,c]	−0.92	−4.65	2.80	−0.02	−4.93	4.88	−2.70	−10.15	4.74	−0.54	−9.35	8.27
SBP[b,c]	1.03	−1.04	3.09	1.39	−1.09	3.87	2.18	−2.73	7.10	−2.17	−7.63	3.29
A1c[b,c,*]	−0.04	−0.13	0.05	−0.14	−0.26	−0.02	0.18	0.01	0.35	−0.10	−0.33	0.12

[a]Relative risk ratio and 95% CL.
[b]Difference in difference and 95% CL.
[c]Adjusted for system, clinic balancing factors, outcome at index, sex, age at index.
[d]Adjusted for system, clinic balancing factors, sex, age at index; offset by ln(time to last visit).
*$P < .05$ for treatment-by-time-by-condition interaction.
+$P = .05$ for treatment-by-time-by-condition interaction.
Abbreviations: A1c = glycosylated hemoglobin, BMI = body mass index, CL = confidence limit, CV = cardiovascular, LDL = low-density lipoprotein, LL = lower limit, SBP = systolic blood pressure, UL = upper limit.

Figure 1. Relative Risk Ratios for Change in Total Modifiable Cardiovascular Risk From Index to 12 Months by SMI Diagnosis, Intervention vs Control



Abbreviations: CTRL = control, INT = intervention, RR = relative risk, SMI = serious mental illness.

patients with SMI or bipolar disorder had lower total modifiable cardiovascular risk at 12 months compared to control, while Asian intervention patients with bipolar disorder or schizophrenia had higher total modifiable cardiovascular risk at 12 months compared to control.

DISCUSSION

This randomized clinical trial of a cardiovascular intervention is one of the first to successfully address cardiovascular risk in those with SMI and to present baseline cardiovascular risk and outcomes by SMI subtype. Examining intervention impact by SMI subtype is important given the observed differences in baseline levels of cardiovascular risk and cardiovascular risk factor control across SMI subtypes in population studies. Additionally, the medications used to treat schizophrenia, schizoaffective disorder, and bipolar disorder may differ in their impact on cardiovascular risk and likelihood of cardiovascular risk factor control. Results show that despite the expected variation in baseline cardiovascular risk and cardiovascular risk factor control, the beneficial impact of the intervention on total modifiable cardiovascular risk and most individual cardiovascular risk factors was similar across subtypes of SMI. Results were mixed when examined by sex (the intervention improved cardiovascular risk for women with bipolar or schizoaffective disorder and for men with schizophrenia), age (the intervention improved cardiovascular risk for patients with bipolar disorder aged

Table 3. Relative Risk Ratios Comparing Rate of Change in Total Modifiable Cardiovascular Risk From Index to 12 Months Among Patients in Intervention Relative to Control Clinics by Patient Subgroups

	Overall			Bipolar Disorder			Schizoaffective Disorder			Schizophrenia		
		95% CL			95% CL			95% CL			95% CL	
Variable	Δ	LL	UL	Δ	LL	UL	Δ	LL	UL	Δ	LL	UL
All patients[a]	0.96	0.94	0.98	0.96	0.94	0.99	0.94	0.90	0.98	0.92	0.85	0.99
Total modifiable CV risk[b]												
0 to < 2%	0.96	0.92	0.99	0.97	0.93	1.03	0.95	0.87	1.05	0.81	0.72	0.92
2 to < 5%	0.96	0.93	0.99	0.98	0.93	1.03	0.93	0.85	1.00	0.95	0.86	1.06
5 to < 10%	0.97	0.93	1.01	0.97	0.91	1.03	0.93	0.85	1.01	1.03	0.93	1.13
≥ 10%	0.96	0.92	0.99	0.91	0.86	0.96	0.98	0.90	1.07	1.05	0.96	1.14
Sex[c]												
Female	0.95	0.92	0.97	0.94	0.92	0.98	0.92	0.87	0.98	1.03	0.94	1.14
Male	0.96	0.94	0.99	0.98	0.94	1.02	0.94	0.88	1.00	0.94	0.88	0.99
Age at index, y[d]												
18–29	0.89	0.81	0.98	0.81	0.72	0.90	1.17	0.92	1.47	0.99	0.74	1.30
30–39	0.97	0.92	1.03	0.99	0.92	1.05	0.97	0.84	1.12	0.84	0.69	1.00
40–49	0.98	0.94	1.03	1.06	1.00	1.12	0.75	0.67	0.82	1.12	0.98	1.28
50–59	0.93	0.90	0.96	0.93	0.88	0.97	0.96	0.89	1.03	0.92	0.85	1.00
60–75	0.97	0.94	1.01	0.95	0.90	1.00	1.03	0.95	1.11	0.98	0.90	1.06
Race/ethnicity[a]												
Asian	1.11	0.93	1.33	1.56	1.16	2.07	0.82	0.51	1.32	1.52	1.04	2.21
Black	0.93	0.88	0.98	0.96	0.88	1.04	0.83	0.75	0.92	1.01	0.90	1.12
Native American/ Alaska Native	0.98	0.85	1.13	1.03	0.85	1.24	1.20	0.88	1.62	...	...	...
White	0.96	0.94	0.98	0.96	0.92	0.98	0.97	0.92	1.02	0.99	0.93	1.04
Hispanic	0.87	0.75	1.01	0.98	0.78	1.23	0.92	0.70	1.18	...	...	...

[a]Adjusted for system, clinic balancing factors, modifiable CV risk at index, sex, and age at index.
[b]Adjusted for system, clinic balancing factors, sex, and age at index.
[c]Adjusted for system, clinic balancing factors, modifiable CV risk at index, and age at index.
[d]Adjusted for system, clinic balancing factors, modifiable CV risk at index, and sex.
Abbreviations: CL = confidence limit, CV = cardiovascular, LL = lower limit, UL = upper limit.

18–29 years or 50–59 years and patients with schizoaffective disorder aged 40–49 years), or race (the intervention significantly improved cardiovascular risk for Black patients with schizoaffective disorder and White patients with bipolar disorder).

One strength of this study is the ability to present baseline cardiovascular risk stratified by SMI diagnosis. Observed differences in baseline cardiovascular risk between SMI subtypes may have been due at least in part to differences in demographics. While patients with schizophrenia had the highest 10-year cardiovascular risk at index, they also had an older mean age, and age is a strong contributor to cardiovascular risk.[25] Although analyses were adjusted for age, these adjustments are often imperfect. Additionally, patients with schizophrenia were more likely to be Black, and previous studies have found significantly higher risk for CVD for Black patients (1.6–2.4 times) compared to White patients.[26] However, it is important to note that these documented differences were not due to race itself, which is a social concept, but due to differences in clinical and social factors, including social determinants of health and systemic racism. There are few existing studies examining cardiovascular risk for people of color with SMI, but there is some evidence that Black and possibly Hispanic patients with SMI have higher rates of obesity and diabetes than do White patients with SMI.[27] Further, our results indicate that Black patients with SMI were more likely to be diagnosed with schizophrenia or schizoaffective disorder than White patients with SMI, potentially pointing to a disparity in SMI diagnosis. Similarly, a 2018 meta-analysis[28] of 14 studies found that Black individuals were diagnosed with schizophrenia at much higher rates than White individuals (odds ratio = 2.43; 95% CI, 1.59 to 3.72), a finding that held true regardless of whether or not the studies used structured instrument diagnostic assessments. Ultimately, interventions like this one may prove helpful in narrowing the gap in disparities in cardiovascular care for patients with SMI, and particularly for patients of color with SMI.

While smoking and BMI were the largest contributors to total modifiable cardiovascular risk in this population of people with SMI, our intervention did not have an impact on these individual cardiovascular risk factors. The CDS recommended smoking cessation medications, nicotine replacement therapy, smoking quit lines, and referrals for diet and exercise counseling when indicated, but more intensive interventions are clearly needed to impact smoking and obesity rates. There have been several small-scale trials of behavioral interventions that were effective in reducing smoking rates for people with SMI, enrolling tens to several hundred people, with effect sizes often comparable to those seen for similar interventions in general populations.[29–31] Similarly, intensive interventions have been effective in reducing BMI for small samples of people with SMI.[32,33] While our study did not significantly reduce BMI and smoking, it did reduce overall modifiable cardiovascular risk to a small but clinically meaningful degree and was able to do so for a much larger population of people with SMI with a much smaller cost per participant than more intensive interventions. Additionally, because the CDS is automated, the intervention is largely sustainable, requiring only minimal maintenance when clinical guidelines or EHR software are updated. In fact, shortly after this study ended,

Table 4. Comparison of Current Study Results With Others Reporting Individual CV Risk Factors for People With and Without SMI

Characteristic	Current Study (Intervention and Control Groups With SMI; Index)	Correll et al 2010[34] (Observational Study of Patients With SMI)		Daumit et al 2020[35] (Intervention Group With SMI; Baseline)	Peters et al 2019[36] (NHANES Observational Study of General Population; 2013–2016 Data)	
N	8,922	10,084		132	35,416	
Mean age, y	48.4	44.7		48.5	47.3	
Women, %	55	57		53	51	
White, %	83.8	55		51	36.6	
Black, %	10	19		46	20.7	
Unknown/other race, %	3	20		2	15.1	
Mean Values	All	Women	Men	All	Women	Men
SBP, mm Hg	124.3	128	130	118.1	119.8	124.1
DBP, mm Hg	78.3	80	80	75.3	NR	NR
Total cholesterol, mg/dL	183.9	188	184	178.9	193.9	188.3
LDL, mg/dL	104.8	NR	NR	101.9	NR	NR
HDL, mg/dL	46.6	44	39	49.2	59.8	48.2
Triglycerides, mg/dL	171.3	166	173	140.2	NR	NR
Fasting glucose, mg/dL	NR	101	102	106.5	NR	NR
A1c, %[a]	7.2*	NR	NR	6.0	5.6	5.7
BMI, kg/m^2	32.7	31.8	30.4	34.4	29.6	29.0
Current smoker, %	46.5	NR	NR	49.2	18.4	21.7
Estimated 10-year ASCVD risk, %	9.1	NR	NR	11.5	NR	NR

[a]A1c calculated for patients with diabetes who have available A1c tests within the past 5 years (n = 1,858).
Abbreviations: A1c = glycosylated hemoglobin, ASCVD = atherosclerotic cardiovascular disease, BMI = body mass index, DBP = diastolic blood pressure, HDL = high-density lipoprotein, LDL = low-density lipoprotein, NHANES = National Health and Nutrition Examination Surveys, NR = not reported, SMI = serious mental illness, SBP = systolic blood pressure.

the CDS was activated for all primary care clinics in 2 of the 3 health systems in this study and has been continuously in use since this time. The ideal approach to addressing smoking and BMI may combine a low-intensity far-reaching intervention, such as this one, with more targeted intensive interventions tailored to individual risk factors.

In the interest of contextualizing our findings, we sought other studies comparing cardiovascular risk factors across SMI subtypes but did not find such studies in the literature. However, there are 2 studies that reported baseline/cross-sectional cardiovascular risk factors for patients with SMI (combined, not presented by SMI subtype), and these are summarized along with our index study values in Table 4. The first was a 2010 study of 10,084 patients with SMI, including depression, who participated in a national 1-day metabolic health fair.[34] The mean age was younger than in our sample (44.7 vs 48.4 years), with similar sex distribution and a higher percentage of Black patients (19% vs 10%). Results for individual cardiovascular risk factors were generally similar to ours, with slightly higher blood pressures and total cholesterol levels and slightly lower BMI, HDL and triglyceride levels. The second was a 2020 study that reported baseline values for patients with SMI, including depression, by treatment group.[35] This sample was similar to ours in terms of age and sex, but Black patients constituted a higher percentage of the sample (46% vs 10%). Compared to our study, BP, total cholesterol, and LDL values were somewhat lower; triglyceride levels were markedly lower (a mean of 140.2 vs 171.3 mg/dL); and BMI and smoking rates were somewhat higher. Notably, estimated 10-year cardiovascular risk was higher at 11.5% compared to 8.3% in our sample. Ultimately, it is likely that selection effects contributed to some of the observed differences across these studies.

For additional context, we compared data from our study and the two just described to a general population sample of 35,416 Americans completing the 2013–2016 National Health and Nutrition Examination Surveys (NHANES).[36] Mean age, sex distribution, and mean systolic BP were similar to those in the SMI studies, while total cholesterol and HDL were slightly higher and A1c and BMI were slightly lower. Most strikingly, smoking rates were considerably lower in the NHANES cohort, averaging 20% compared to 48% in the SMI studies. Given that smoking is a large driver of cardiovascular risk, this difference in smoking rates is particularly important. It is also disappointing, given that effective treatments are available for smoking cessation for patients with SMI.[37] While the finding that 48% of individuals with SMI smoke compares favorably to the 83% of people with bipolar disorder and 90% of people with schizophrenia who reported smoking in the National Epidemiologic Survey on Alcohol and Related Conditions in 2001–2005,[38] there is still considerable room for improvement.

Several factors may limit the interpretation of our data. This study was conducted in 3 integrated health care systems in the Midwest, and results may not be generalizable to other care settings or patient populations. Data relied on diagnostic codes documented in the EHR by frontline clinicians and may reflect misclassification of SMI and SMI subtypes. This trial was a pragmatic clinical trial that utilized usual primary care visits, with frequency of visits and variable measurement determined by patients and their care teams. As such, 12-month outcome measures were derived from EHR data. We were not able to collect data on clinician behavior in response to the CDS intervention, and this is an important area for future study. Despite these

potential limitations, this study provides an opportunity to examine baseline cardiovascular risk and risk factors by SMI subtypes as well as the intervention's impact across SMI subtypes. Such data have rarely been reported in prior studies.

In conclusion, this CDS intervention produced a 4% relative reduction in total modifiable cardiovascular risk at 12 months for intervention patients with SMI versus control, an effect consistently observed across all 3 subtypes of SMI. Nearly half of patients with SMI were current smokers, and smoking was the leading driver of modifiable cardiovascular risk. Additionally, the mean BMI for patients with SMI fell within the obesity range, with a mean of 32.7. More robust interventions to address smoking and obesity rates for people with SMI are needed to significantly impact cardiovascular risk in this at-risk population.

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