

A Cardiovascular Risk Optimization Program in People With Schizophrenia: A Pilot Randomized Controlled Clinical Trial

NÚRIA RIERA-MOLIST, PharmD
MONTSE ASSENS-TAUSTE, RN
PERE ROURA-POCH, MD, MPH
MARTA GUIMERÀ-GALLEN, PsyD
JOSEP MANEL SANTOS-LÓPEZ, PsyD, PhD
MONTERRAT SERRA-MILLAS, MD, PhD
NEUS FRAU-ROSSELLÓ, MD
ESTEFANIA GALLEGO-PEÑA, MD
QUINTÍ FOGUET-BOREU, MD, PhD

Background: Cardiovascular disease is one of the leading causes of premature death in people with schizophrenia. Some modifiable factors that have been implicated include unhealthy lifestyle, medication side effects, and physical comorbidities. The goal of this study was to assess the efficacy of a 6-month, multi-factorial cardiovascular risk intervention to reduce cardiovascular risk (CVR) in people with schizophrenia.

Methods: We conducted a 2-arm, parallel, randomized clinical trial in a regional mental health center. Participants with at least 1 poorly controlled cardiovascular risk factor

(CVRf) (hypertension, diabetes mellitus, hypercholesterolemia, or tobacco smoking) were randomly assigned to the intervention group or to a control group. The subjects in the intervention group received a patient-centered approach that included promoting a healthy lifestyle, pharmacological management of CVRFs, psychotropic drug optimization, and motivational follow-up [Programa d'optimització del RISC Cardiovascular (PRISCA)]. The main outcome was change in CVR as assessed using the Framingham-REGICOR function, after 6 months compared with the baseline in both groups.

RIERA-MOLIST: Department of Pharmacy, Vic University Hospital, Faculty of Medicine, University of Vic–Central University of Catalonia, and Multidisciplinary Inflammation Research Group (MIRG), Institute for Research and Innovation in Life and Health Sciences in Central Catalonia (IRIS-CC), Barcelona, Spain; ASSENS-TAUSTE: Vic University Hospital, Vic, Barcelona, Spain; ROURA-POCH: Department of Clinical Epidemiology and Research, Vic University Hospital, Faculty of Medicine, University of Vic–Central University of Catalonia, and Multidisciplinary Inflammation Research Group (MIRG), Institute for Research and Innovation in Life and Health Sciences in Central Catalonia (IRIS-CC), Vic, Barcelona, Spain; GUIMERÀ-GALLEN: General Health Psychologist and Technician of Occupational Risk Prevention, University of Vic–Central University of Catalonia, Vic, Barcelona, Spain; SANTOS-LÓPEZ: Department of Psychiatry, Vic University Hospital, Faculty of Medicine, University of Vic–Central University of Catalonia, and Innovation in Mental Health and Social Welfare (ISaMBeS), University of Vic–Central University of Catalonia, Vic, Barcelona, Spain; SERRA-MILLAS and FOGUET-BOREU: Department of Psychiatry, Vic University Hospital, Faculty of Medicine, University of Vic–Central University of Catalonia, and Multidisciplinary Inflammation Research Group (MIRG), Institute for Research and Innovation in Life and Health Sciences in Central Catalonia (IRIS-CC), Vic, Barcelona, Spain; FRAU-ROSSELLÓ and GALLEGO-PEÑA: Family and Community Medical Doctors, Primary Care Center of Santa Eugènia de Berga. Catalan Health Institute, Santa Eugènia de Berga, Barcelona, Spain

Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Please send correspondence to: Núria Riera-Molist, PharmD, Hospital Pharmacist, Vic, Consorci Hospitalari de Vic, 1 Francesc Pla “El vigatà”, Vic, Barcelona 08500, Spain (e-mail: nriera@chv.cat).

ACKNOWLEDGMENT: The authors thank all of the health professionals involved in this study. Special thanks to Dr J. Marrugat and Mr. I. Subirana, both from the Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Parc de Recerca Biomèdica, Barcelona, for their kind help in REGICOR function. They also thank Dr R. Elosua for his scientific contribution to the research project. Thanks to Dr P. Marshall for revising the manuscript. Finally, the authors are grateful to the Acadèmia de Ciències Mèdiques i de la Salut de Catalunya i de Balears for promoting research in health sciences and to the Consultori Bayés for the support of doctoral students.

The authors declare no conflicts of interests.

DOI: 10.1097/PRA.0000000000000743

Results: Forty-six participants were randomly assigned to the PRISCA group (n = 23) or the control group (n = 23). The most prevalent CVRFs at baseline were hypercholesterolemia (84.8%) and tobacco smoking (39.1%). The PRISCA group showed a significant reduction in the REGICOR score (−0.96%; 95% CI: −1.60 to −0.32, $P = 0.011$) after 6 months (relative risk reduction of 20.9%), with no significant changes in the control group (0.21%; 95% CI: −0.47 to 0.89, $P = 0.706$). In the PRISCA group, low-density lipoprotein cholesterol also decreased significantly (−27.14 mg/dL; 95% CI: −46.28 to −8.00, $P = 0.008$).

Conclusion: A patient-centered, multifactorial cardiovascular risk intervention improved CVR in people with schizophrenia after 6 months, which was achieved mainly by improving the lipid profile.

(*Journal of Psychiatric Practice* 2023;29:456–468)

KEY WORDS: schizophrenia, severe mental disorder, cardiovascular disease, cardiovascular risk, Framingham-REGICOR, cardiovascular risk factors, physical health, multifactorial intervention, patient-centered intervention

People with schizophrenia have higher premature mortality with a life expectancy of 15 to 20 years less than the general population,^{1,2} and the mortality gap does not seem to be narrowing over time.^{3,4} Although suicides and other unnatural causes are higher in this group, premature mortality is mainly attributed to preventable physical diseases and medical conditions, especially cardiovascular disease (CVD).^{1,2,5} One-third of all natural deaths occurring in people with schizophrenia are attributed to CVD.⁶

Several factors could be implicated in the etiology of CVD in schizophrenia: the disorder itself (which probably has a genetic basis), the side effects of medications, particularly antipsychotics, unhealthy lifestyle and risky behaviors, and poor primary and secondary prevention of CVD.^{7–15} Compared with the general population, people with schizophrenia are more likely to be overweight and to have diabetes mellitus, dyslipidemia, and metabolic syndrome.^{16–20}

A wealth of information is available on treating the physical comorbidities of people with severe mental disorders and how to deal with medication side effects.^{9,21–24} Likewise, many behavioral and pharmacological interventions to improve cardiovascular risk factors (CVRFs) are available. However, despite favorable results for some variables, such as weight loss, improvement in glucose and lipid levels, and smoking cessation, an impact on overall cardiovascular risk (CVR) has not been reported.^{25–27} Evidence concerning multimodal interventions for CVD management is scarce.²⁸ In a study carried out in England by Osborn et al²⁹ that focused on improving cholesterol levels and CVR through promoting a healthy lifestyle and behavior and adherence to medication, no significant differences were observed between the groups after 12 months. In another multifaceted intervention conducted in Maryland by Daumit et al,³⁰ with an intervention that included behavioral counseling, care coordination, and care management, the CVR score was significantly reduced after 18 months. A third research study carried out in Catalonia by Torralbas-Ortega et al³¹ aimed at promoting healthy habits and improving CVR through a short psychoeducational intervention found no significant improvements in the different variables studied after 1 year.

In this article, we describe a pilot clinical trial of a patient-centered multifactorial intervention aimed at improving CVR in people with schizophrenia.

METHODS

Study Design and Participants

We designed a 2-arm, parallel, randomized clinical trial at the Osona Mental Health Center belonging to the public health system in the province of Barcelona (Catalonia), which has a population of 163,702 inhabitants (according to the 2019 census). We included adults 18 years of age and older who had previously been diagnosed with schizophrenia by a psychiatrist according to the International Classification of Diseases (ICD-10), who had not had any health check-ups by the primary care team in the preceding 6 months, and who had at least 1 of the following poorly

CARDIOVASCULAR RISK PROGRAM FOR SCHIZOPHRENIA

controlled CVRFs: hypertension, diabetes mellitus, hypercholesterolemia, and tobacco smoking. Target goals and pharmacological management were established for each CVRF according to the 2018 Program of Preventive Activities and Health Promotion of the Spanish Society of Family and Community Medicine (Table 1).³² We excluded people who were institutionalized, had suffered a recent psychiatric relapse (within 3 months before the intervention) with or without hospitalization, were diagnosed with intellectual disabilities or cognitive impairment, had an active substance use disorder or were in a methadone maintenance program, had a previous CVD (including heart failure, peripheral arterial disease, coronary artery disease, or stroke), or had a serious comorbid condition that limited life expectancy.

The recruitment period began in January 2020 and ended in October 2020. The study was stopped between March and May 2020 (both inclusive) due to the COVID-19 pandemic. The follow-up period was 6 months for all subjects.

Variables and Instruments

We collected data on sociodemographic, clinical, laboratory, and anthropometric variables (weight was measured in light clothing and without shoes), current tobacco smoking (self-reported), current psychopharmacological treatment and adherence according to the electronic dispensing register. Adherence was calculated by the proportion of days covered, which is the proportion of days a patient has medication available over 6 months from dispensing data records, considering an optimal value of at least 0.8.³³ The prevalence of metabolic syndrome was calculated for each patient at baseline, defined as the presence of at least 3 of the following abnormal components: blood pressure (BP) > 130/85 mm Hg, triglycerides > 150 mg/dL, glycemia > 100 mg/dL, HDL cholesterol <40 mg/dL for men and <50 mg/dL for women, and waist circumference > 94.5 cm for men and > 89.5 cm for women. Subjects who were receiving pharmacological treatment for hypertension, dyslipidemia, or

TABLE 1. Target Goals and Pharmacological Management for CVRFs

<i>CVRF</i>	<i>Target goals</i>	<i>Pharmacological management</i>
Hypertension	SBP <140 mm Hg and DBP <90 mm Hg	ACEi and ARBs constitute the first line of treatment
	High BP was also identified: a device was offered to measure BP at home	Another antihypertensive was added if BP target was not met
Diabetes mellitus	Hb1Ac <7% (7%-8% for people over 60 y of age).	Metformin constitutes the first line of treatment
	Prediabetes was also detected if fasting glucose was 100-125 mg/dL and HbA1c ≥ 6.5%	Another anti-diabetic was added if glycaemic target was not met
Hypercholesterolemia	LDL cholesterol according to CVR:	Statins constitute the first line of treatment
	Very high: LDL <70 mg/dL	Consider fibrates or ezetimibe if statins contraindicated
	High: LDL <100 mg/dL	
	Moderate/low: LDL <115 mg/dL	
Tobacco smoking	Smoking cessation	Nicotine replacement therapy, bupropion, or varenicline

Target goals and pharmacological management proposed by the Spanish Society of Family and Community Medicine.³²

ACEi indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BP, blood pressure; CVR, cardiovascular risk; CVRF, cardiovascular risk factors; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

CARDIOVASCULAR RISK PROGRAM FOR SCHIZOPHRENIA

impaired glucose tolerance/diabetes mellitus were considered to have the respective risk factor.³⁴

The study assessed functionality, quality of life, and CVR with the instruments described below.

Functionality

Functionality was evaluated using the Functioning Assessment Short Test (FAST), which is a brief interview designed to be administered by a trained clinician. It consists of 24 items that are grouped into 6 areas: autonomy, work performance, cognitive functioning, finances, interpersonal relationships, and leisure. Each item is scored on a 4-point scale ranging from 0 (no difficulty) to 3 (high difficulty). Total scores are obtained by adding the scores for each item and range from 0 to 72 points. There are no cut-off points, and the higher the value, the greater the difficulty. In this study, we used the Spanish version of this instrument,³⁵ which has recently been validated for its application in patients with schizophrenia, with good psychometric properties in terms of reliability and validity.³⁶

Quality of Life

Quality of life was measured using the EuroQoL-5D Health Questionnaire (EQ-5D), which is a generic instrument in which subjects assess their state of health in 5 dimensions: mobility, personal care, daily activities, pain/discomfort, and anxiety/depression. The second part consists of a visual analogy scale represented by a vertical line of 20 cm in length graded from 0 (worst health state) to 100 (best health state). We used the Spanish version of this instrument (authorization registration number 39571).³⁷

CVR

CVR was estimated using the following 2 instruments.

The Framingham algorithm, which was calibrated for the Catalan population (Registre Gironí del Cor, Girona Heart Registry version 3.0, Framingham-REGICOR), estimates the 10-year probability of having a coronary event (eg, angina or myocardial infarction whether fatal or not) in adults 35 to 74 years of age. The risk is considered low if the score is <5%, moderate if the score is 5 to 9.9%, high if the score is 10% to 14.9%, and very high if the score is ≥ 15%.^{38–40}

The QRISK3 algorithm, version 2018.0, estimates the 10-year probability of having a coronary event (heart attack or stroke) in adults 25 to 84 years of age. It includes specific parameters (eg, second-generation atypical antipsychotic use, diagnosis of a severe mental disorder) and the classical factors included in the Framingham tables. The risk is considered low if the score is <10%, moderate if the score is 10% to 20%, and high if the score is > 20%.⁴¹

Procedure and Visits

All subjects attended 3 face-to-face visits, which were carried out by a hospital pharmacist (PhD student) and a mental health nurse. Appointments took place in the outpatient consultation room with access to the institution's medical history, the shared medical history of Catalonia, and electronic medication administration records.

First Visit (Recruitment and Screening)

Written informed consent was obtained from all subjects, and the sociodemographic and physical variables were recorded. A blood test was scheduled, to be carried out at the hospital or at the primary care center (according to the subject's preference).

If at least 1 poorly controlled CVRF was detected (hypertension, diabetes mellitus, hypercholesterolemia, or tobacco smoking, according to the target goals), the subject was randomized and assigned to the intervention group [Programa d'optimització del RISc Cardiovascular (in Catalan) (PRISCA) group] or to the control group (treatment-as-usual), using a computer-generated random sequence. Subjects whose CVRFs were well controlled were informed and excluded from the follow-up.

Second Visit (Baseline)

This visit took place less than a month after the first visit for all subjects.

- PRISCA group: participants from the intervention group received a patient-centered, multifactorial cardiovascular risk program according to the therapeutic plan designed for each subject by a multidisciplinary team of health professionals (2 family and community medical doctors, a mental health nurse, a clinical psychiatrist, a psychologist, and a hospital pharmacist). This group identified the CVRF to be improved

CARDIOVASCULAR RISK PROGRAM FOR SCHIZOPHRENIA

(according to the target goals in Table 1) and proposed a patient-centered approach that might include different types of interventions. The initial management of the CVRFs was non-pharmacological. Pharmacological treatment was added or optimized if the nonpharmacological measures failed (ie, repeatedly obtaining poorly controlled CVRFs according to the cut-off points listed in Table 1, despite the implementation of hygienic-dietary measures) or if pharmacological treatment (eg, statins, antihypertensives or hypoglycemics) needed to be implemented early in the course of treatment in subjects with a high level of CVR. Any medication that was added to the therapeutic plan required an analysis of relevant interactions with current medication and medical and psychiatric comorbidities and monitoring for side effects and tolerance. The potential interventions that could be implemented are described below.

- (a) Lifestyle interventions and behavioral counseling: promoting a healthy diet; promoting individualized regular daily physical activity; encouraging participants to quit smoking and report harmful effects, and offering strategies to beat their nicotine addiction.
- (b) Medication: this was prescribed/optimized for poorly controlled CVRFs (hypertension, diabetes mellitus, hypercholesterolemia, and smoking tobacco) (Table 1), by the family and community physician.
- (c) Optimization of psychotropic drugs: simplification of the pharmacological treatment, dose optimization, or switching to another drug with a better metabolic profile, with medication prescribed by the psychiatrist based on consensus with the patient's referring psychiatrist.
- (d) Monthly motivational intervention: this was carried out by the psychologist to improve adherence, to follow up on any side effects of medication, and to provide positive reinforcement to adhere to the therapeutic plan. The first session took place in a group, while the following sessions were individual (face-to-face or by telephone).
- Control group: participants from the control group were informed about the results of the screening and they were referred to treatment-as-usual by the primary care team.

Final Visit (Closing)

All participants in both the PRISCA and control groups were scheduled to attend a third visit 6 months after the baseline visit during which a number of physical, clinical, and analytical parameters were assessed.

All the information gathered at each visit was recorded in the patient's medical history and shared with specialized and primary care professionals.

Outcomes

The main outcome was an assessment of the efficacy of the multifactorial intervention to improve the CVR score in people with schizophrenia, calculated as the change in CVR score at 6 months compared with the baseline score, using the Framingham-REGICOR function, in each of the study groups. We also calculated change compared with baseline in the secondary variables listed above at 6 months.

Statistical Analysis

A descriptive analysis of the data was carried out with the measures of central tendency (mean) and dispersion (SD) or mean and 95% CI for quantitative variables. Qualitative or categorical variables were described by absolute frequencies and percentages. The analysis was conducted using intention-to-treat principles. Bivariate analyses were performed according to a normal distribution of quantitative variables; the normality of the test was studied using the Kolmogorov-Smirnoff goodness adjustment test, and the quantitative variables were compared using the Student *t* test if the distribution was normal or the Mann-Whitney *U* test if it was not. The χ^2 test was used to compare the qualitative variables. The level of statistical significance used for the hypothesis tests was 5%. The analysis was performed using the IBM SPSS Statistics program for Windows, version 26.

RESULTS

Of the 208 potentially eligible patients who were assessed, 70 were invited to participate in the study. Fifty-nine patients were screened for CVRFs, 46 of whom (22.1% of the potentially eligible patients) had at least 1 poorly controlled CVRF and

CARDIOVASCULAR RISK PROGRAM FOR SCHIZOPHRENIA

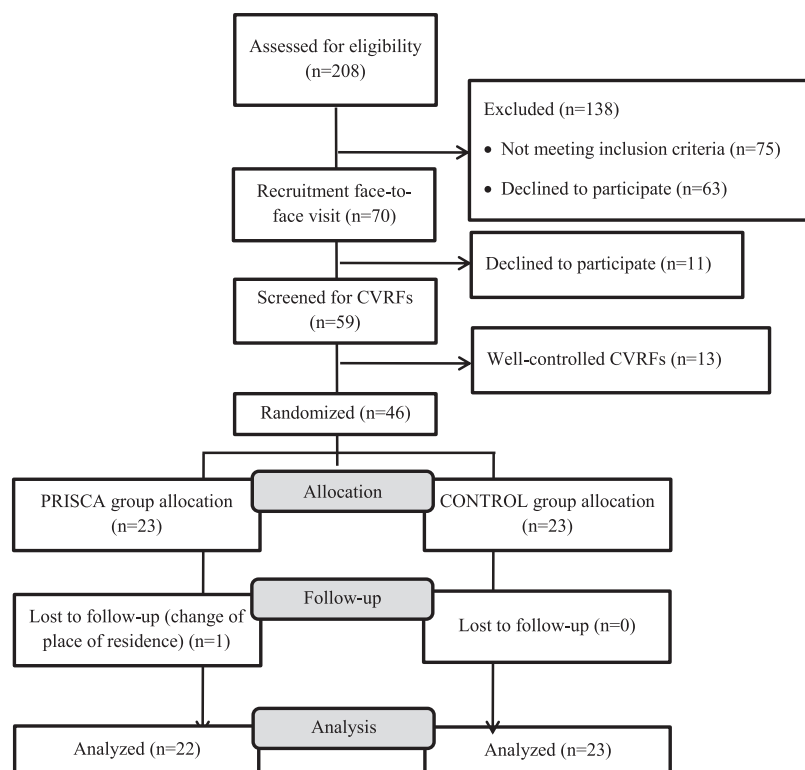
were included in the study and randomly assigned to the PRISCA group ($n = 23$) or the control group ($n = 23$). Figure 1 shows the CONSORT flow chart⁴² of participants. The mean age of the participants was 52.6 years (SD 11.1 y), 56.5% were men, with a mean body mass index of 30.8 kg/m² (SD 5.0) and a mean REGICOR score of 4.5% (SD 3.2%). Hypercholesterolemia followed by tobacco smoking were the most prevalent poorly controlled CVRFs in the sample, and 93.5% of the participants were being treated with atypical antipsychotics, with over half receiving clozapine or olanzapine. The baseline characteristics of the participants are shown in Table 2.

All of the subjects included in the PRISCA group ($n = 22$) received information about promoting healthy lifestyles and behaviors. Specific medication for CVRFs (eg, antihypertensives, antidiabetic medications, or statins) was initiated or optimized in 72.7% ($n = 16$) of the subjects, and psychotropic

treatment was optimized in 13.6% ($n = 3$) of the patients. Of the 22 subjects included in the PRISCA group, 72.7% ($n = 16$) of the participants completed the motivational intervention, with a mean of 4.7 (0.9) sessions attended during the follow-up period. During the follow-up period, 56.5% of the participants in the control group and 47.8% in the intervention group ($P = 0.555$), had visits with their primary care team, with a mean of 1.17 (1.47) and 0.52 (0.59) visits, respectively ($P = 0.058$). None of the participants suffered any cardiovascular event during the study.

At the 6-month assessment, a statistically significant reduction in Framingham-REGICOR score (-0.96% ; 95% CI: -1.60 to -0.32 , $P = 0.011$), which was equivalent to a relative risk reduction of 20.9%, was observed in the PRISCA group. Significant reductions in total cholesterol (-30.27 mg/dL; 95% CI: -51.78 to -8.77 , $P = 0.008$) and low-density lipoprotein (LDL) cholesterol (-27.14 mg/dL; 95%

FIGURE 1. Flow chart of participants.



CVRFs indicates cardiovascular risk factors; PRISCA, Programa d'optimització del RISc Cardiovascular.

CARDIOVASCULAR RISK PROGRAM FOR SCHIZOPHRENIA

TABLE 2. Baseline Characteristics of the Participants

	<i>Total (N = 46)</i>	<i>PRISCA group (n = 23)</i>	<i>Control group (n = 23)</i>	<i>P</i>
Age, mean (SD), y	52.6 (11.1)	50.2 (11.3)	55.0 (10.7)	0.182
Male, %	56.5	52.2	60.9	0.337
Cohabitation, %				
Own family	28.3	30.4	26.1	0.780
Parents	50.0	43.5	56.5	
Alone	17.4	21.7	13.0	
In a group	4.3	4.3	4.4	
Level of education, %				
None or primary	54.4	43.4	65.2	0.319
Secondary	15.2	17.4	13.0	
After 16 y of age	30.4	39.1	21.8	
Duration of schizophrenia, mean (SD), y	20.4 (11.1)	18.2 (10.9)	22.6 (11.0)	0.199
No. previous hospitalizations, mean (SD)	1.7 (1.7)	1.6 (1.0)	1.8 (2.2)	0.594
Physical measures, mean (SD)				
SBP, mm Hg	122.5 (15.5)	120.5 (14.6)	124.5 (16.4)	0.330
DBP, mm Hg	81.5 (9.7)	81.6 (8.8)	81.4 (10.7)	0.144
BMI, kg/m ²	30.8 (5.0)	29.6 (3.9)	32.0 (5.7)	0.096
Waist circumference, cm	107.8 (11.2)	106.1 (10.4)	109.6 (12.0)	0.656
Laboratory measures, mean (SD)				
Glycemia, mg/dL	104.9 (32.7)	98.3 (14.6)	113.4 (45.0)	0.391
HbA1c, %	5.9 (1.6)	5.7 (0.7)	6.2 (2.2)	0.055
Total cholesterol, mg/dL	222.2 (32.5)	222.9 (32.4)	221.6 (33.2)	0.941
LDL cholesterol, mg/dL	137.9 (30.1)	135.6 (31.4)	140.1 (29.3)	0.586
HDL cholesterol, mg/dL	51.4 (13.9)	51.6 (13.3)	51.2 (17.8)	0.476
Triglycerides, mg/dL	177.4 (103.3)	178.7 (73.9)	176.0 (127.9)	0.344
GF, mL/min	81.2 (13.7)	83.0 (12.6)	79.4 (14.8)	0.567
CVR, mean (SD), %				
REGICOR*	4.5 (3.2)	4.5 (3.6)	4.5 (2.8)	0.457
QRISK3	10.8 (8.8)	8.7 (8.5)	12.9 (8.7)	0.921
Patients with MetS, %	44.4	39.1	50.0	0.333
Criteria for enrollment in the study, %				
Hypertension/High BP	21.7	17.4	26.1	0.361
DM/prediabetes	10.9	8.7	13.0	0.500
Hypercholesterolemia	84.8	82.6	87.0	0.500
Tobacco smoking	39.1	39.1	39.1	0.618
Psychotropic medication,† %				
Any atypical antipsychotic (oral or LAI)	93.5	95.7	91.3	0.600
Clozapine or olanzapine	58.7	65.2	52.2	0.275
Mood stabilizers	8.7	17.4	0.0	0.054
Antidepressants	32.6	39.1	26.1	0.265
Functionality, FAST, mean (SD)	16.3 (10.8)	13.2 (10.5)	19.4 (10.5)	0.051
Quality of life, VAS, mean (SD)	68.1 (15.1)	71.4 (15.2)	64.7 (14.5)	0.168

*People between 35 and 74 years of age in PRISCA (n = 19) and control (n = 20) groups).

†Only medication with a proportion of days covered (PDC) of at least 0.8 were considered.

BMI indicates body mass index; BP, blood pressure; CVR, cardiovascular risk; DBP, diastolic blood pressure; DM, diabetes mellitus; FAST, functioning assessment short test (functionality); GF, glomerular filtrate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LAI, long-acting injectable; LDL, low-density lipoprotein; MetS, metabolic syndrome; QRISK3,⁴¹ QRISK3 cardiovascular risk algorithm; REGICOR,³⁸ REgistre Gironí del COR Framingham algorithm; SBP, systolic blood pressure; VAS, visual analogy scale (quality of life); SD, standard deviation.

CARDIOVASCULAR RISK PROGRAM FOR SCHIZOPHRENIA

CI -46.28 to -8.00 , $P = 0.008$) were also observed in the PRISCA group (Table 3). In the control group, no statistically significant changes were observed in Framingham-REGICOR scores or cholesterol levels.

After 6 months, 54.5% of participants in the PRISCA group showed a reduction in their number of poorly controlled CVRFs from baseline, 36.4% had no change, and 9.1% had an increase in the number of poorly controlled CVRFs. The distribution in the control group was 17.4%, 73.9%, and 8.7%, respectively. Statistically significant differences were observed between the PRISCA and control groups ($\chi^2 = 7.565$, $P < 0.05$) (Fig. 2).

DISCUSSION

Overview of Key Findings

To the best of our knowledge, the PRISCA study described here involved one of the few multimodal interventions conducted in people with schizophrenia in which CVR was used as an outcome. We found that a patient-centered, multifactorial, and multidisciplinary intervention reduced CVR in subjects with schizophrenia after 6 months, with the improvement equivalent to a relative risk reduction of 20.9%. This improvement in CVR was mainly due to the reduction in total and LDL cholesterol levels, achieved through improved dietary habits and the prescription, where appropriate, of statins. This was a significant reduction in LDL cholesterol which, according to the evidence, leads to a reduction in the risk of major cardiovascular events, even in young and low-risk people.⁴³ This result was also relevant given that the participants included in the study had not had any health check-ups by the primary care team in the previous 6 months. This implies a proactive detection of CVRFs in a population that does not usually consult primary care services. Cholesterol reduction secondary to statin use may explain part of the results. However, the study design does not allow us to isolate the contribution of other factors such as diet, physical activity, and optimization of psychotropic drugs. Consequently, it is questionable whether the introduction of a lipid-lowering treatment could have a similar effect on the proposed intervention *per se*.

Given the lack of consensus on CVR prediction models in schizophrenia, testing of QRISK3

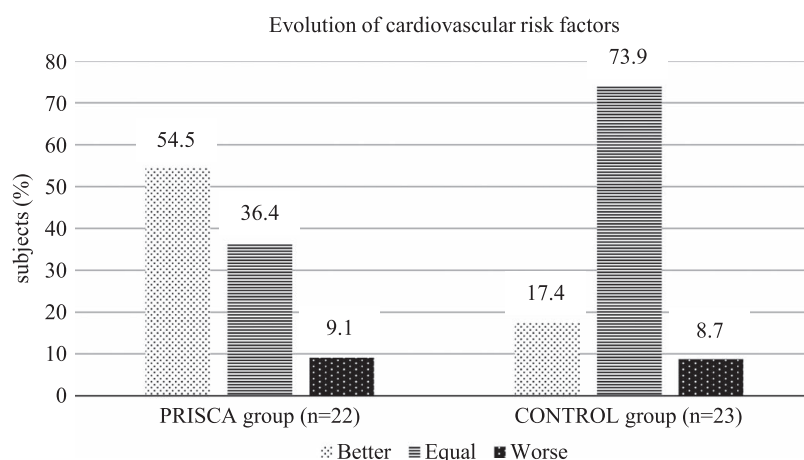
function appeared to be a more realistic option as it incorporated parameters specific to this population group, such as the presence of schizophrenia as a severe mental disorder or the use of second-generation antipsychotics.^{7,41,44} Using this estimation function, no significant differences were observed at 6 months compared with baseline in either of the study groups. The small sample size and the short follow-up period probably conditioned this result. Some authors suggest conventional estimators, like REGICOR, are not suitable for estimating the true risk in this population,^{44,45} which could lead to inadequate screening and treatment. Thus, it would be interesting to have a validated, consensual, and systematized estimation function in clinical practice that would facilitate risk stratification, decision-making, and early management^{21,45} in people with severe mental disorders.

The magnitude of CVR observed in our study using the Framingham-REGICOR function was comparable to that observed in the study of a multifaceted intervention by Daumit et al.³⁰ Those researchers found a reduction of relative risk of 12.7% using the Framingham function after 18 months in people with serious mental illness (59.1% of whom were diagnosed with schizophrenia) using behavioral counseling and coordination with mental health staff to encourage the achievement of health goals. In the PRISCA intervention, having a multidisciplinary group that included both primary care physicians and mental health professionals was probably key in optimizing CVR through screening and management of CVRF in people with schizophrenia. On the other hand, in the PRISCA study, statins were prescribed when appropriate, in addition to promoting improved dietary habits, which is different from what occurred in the Osborn et al.²⁹ intervention in England, in which the researchers suggested that suboptimal use of statins was one of the reasons why significant improvements in cholesterol and CVR were not observed after 12 months.

Our study found no improvement in tobacco cessation, despite the high prevalence of tobacco use in the study's population, and despite being one of the strongest predictors of mortality in people with serious mental illness.¹¹ The high prevalence of smoking and the high rates of nicotine addiction in individuals with schizophrenia

TABLE 3. Outcomes at 6 Months						
	PRISCA group			Control group		
	Baseline	Change at 6 mo from baseline	P	Baseline	Change at 6 mo from baseline	P
REGICOR (%)*	4.60 (3.57)	−0.96 (−1.60 to −0.32)	0.011	4.46 (2.83)	0.21 (−0.47 to 0.89)	0.706
QRISK3 (%)	8.84 (8.68)	−0.58 (−1.41 to 0.25)	0.159	12.90 (8.65)	−0.22 (−1.00 to 0.56)	0.569
SBP (mm Hg)	121.41 (14.31)	1.36 (−4.07 to 6.80)	0.607	124.52 (16.36)	1.00 (−3.35 to 5.35)	0.638
DBP (mm Hg)	82.00 (8.80)	−0.96 (−4.45 to 2.54)	0.576	81.35 (10.65)	1.44 (−1.47 to 4.34)	0.318
BMI (kg/m ²)	29.61 (3.89)	−0.08 (−0.79 to 0.62)	0.808	32.02 (5.65)	−0.38 (−1.03 to 0.26)	0.233
Waist circumference (cm)	105.81 (9.99)	−2.17 (−4.14 to −0.20)	0.033	109.86 (12.24)	−0.14 (−1.62 to 1.33)	0.842
Glycemia (mg/dL)	97.81 (15.14)	7.43 (−0.02 to 14.87)	0.050	113.38 (45.00)	−3.19 (−23.13 to 16.75)	0.742
HbA1c (%)	5.70 (0.70)	−0.05 (−0.32 to 0.22)	0.689	6.19 (2.16)	−0.45 (−1.18 to 0.29)	0.222
Total cholesterol (mg/dL)	220.64 (31.24)	−30.27 (−51.78 to −8.77)	0.008	221.57 (33.20)	0.83 (−12.33 to 13.98)	0.898
LDL cholesterol (mg/dL)	134.55 (31.73)	−27.14 (−46.28 to −8.00)	0.008	140.13 (29.29)	−4.74 (−15.47 to 5.99)	0.369
HDL cholesterol (mg/dL)	49.59 (9.34)	2.77 (−0.79 to 6.33)	0.120	51.22 (14.78)	2.83 (−0.24 to 5.89)	0.069
Triglycerides (mg/dL)	182.95 (72.74)	−29.55 (−60.87 to 1.78)	0.063	175.96 (127.91)	52.96 (8.88 to 97.03)	0.021
GF (mL/min)	81.86 (12.49)	3.52 (−2.31 to 9.36)	0.222	79.39 (14.75)	4.70 (−0.054 to 9.48)	0.054
FAST (functionality)	13.23 (10.51)	−2.05 (−4.31 to 0.21)	0.073	19.03 (10.52)	−0.91 (−4.16 to 2.34)	0.567
VAS (quality of life)	71.57 (15.58)	4.14 (−1.68 to 9.96)	0.153	64.69 (14.48)	−4.48 (−12.43 to 3.47)	0.255
Values are presented as mean and SD. The change is expressed as the difference in means at 6 months from baseline and presented as a 95% CI.						
*People between 35 and 75 years of age in the PRISCA (n = 19) and CONTROL (n = 20) groups.						
BMI indicates body mass index; DBP, diastolic blood pressure; FAST, functioning assessment short test (functionality); GF, glomerular filtrate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; REGICOR, ³⁸ REgistre GIroní del COR Framingham algorithm; SBP, systolic blood pressure; VAS, visual analogy scale (quality of life).						

FIGURE 2. Change in the number of poorly controlled cardiovascular risk factors after the intervention, by groups.



The figure represents the change in the number of poorly controlled CVRFs in the PRISCA and control groups, at 6 months compared with baseline. “Better” means a reduction in the number of poorly controlled CVRFs; “equal” means the same number of poorly controlled CVRFs as at baseline; and “worse” means an increase in the number of poorly controlled CVRFs compared with baseline. Statistically significant differences were observed between the PRISCA and control groups ($\chi^2 = 7.565$, $P < 0.05$). CVRFs indicates cardiovascular risk factors; PRISCA, Programa d’optimització del RISc CArdiovascular.

are well known and are much higher than in those with other mental disorders and in the general population.^{7,19} It is also well known that the rate of smoking cessation in those with schizophrenia is lower than in healthy smoking controls, suggesting that the measures adopted to promote smoking cessation have been insufficient or inadequate. Therefore, such programs should be much more specific, highly specialized, and persistent,⁴⁶ and they should be adapted to the individual’s cognitive situation.⁴⁷

The development of our study coincided with the COVID-19 pandemic, which was declared as soon as the study had started. This posed an additional hardship, affecting the people who participated in this study physically, socioeconomically, and emotionally. Some authors have suggested that the existing inequalities between people with schizophrenia and the general population have increased even further as a result of the pandemic.⁴⁸ COVID-19 has increased the prevalence of physical health problems and the risk of premature death in people with severe mental disorders, resulting in increased physical health disparities in people living with mental illness.⁴⁹

Strengths and Limitations of the Study

Our study had several strengths. First, through initial screening, poorly controlled CVRFs were detected that would otherwise probably not have been diagnosed and controlled in the short term. Second, it was a patient-centered, multidisciplinary intervention involving professionals from different disciplines. Third, it enabled the transfer of information about physical health and co-responsibility.

Our study also had several limitations. First, the sample size was small, which could compromise the results of the study and its external validity. Thus, only 22.2% of the potential subjects were included, which represents a notable reduction of the sample, a common aspect in studies involving people with schizophrenia.^{50,51} These results should be confirmed in studies with a larger sample size and under more favorable conditions. Second, the impact of the intervention on reduction in CVR obtained at 6 months could have lost its efficacy with a longer follow-up. However, this pilot study will allow the authors to carry out an intervention similar to PRISCA, with a larger sample and longer follow-up. Third, we did not find any effect on the

CARDIOVASCULAR RISK PROGRAM FOR SCHIZOPHRENIA

management of tobacco dependence, which requires an intensive and integrated approach. A fourth limitation was the lack of blinding due to study design.

Implications for Future Research

The vulnerability and idiosyncrasy of people living with schizophrenia require rethinking so that preventive programs are close to them, accessible, proactive, and efficient. As health professionals, we aim to design, implement, and promote approaches that ensure the cardiovascular health of this population group.

CONCLUSIONS

A patient-centered, multifactorial cardiovascular risk intervention reduced CVR in people with schizophrenia after 6 months, which was achieved mainly by improving the lipid profile.

FUNDING INFORMATION

The clinical trial was conducted according to the published protocol (ClinicalTrials.gov ID: NCT04276012). Both the study protocol and the informed consent form were approved by the Ethics Committee of the Vic University Hospital, Vic Hospital Consortium (Code of Ethics Committee 2019053, Internal code AC274) October 15, 2019. The Ethics Committee also approved an information sheet with understandable language and informed consent. Written informed consent for study participation was obtained from all the participants who enrolled in the study.

The researchers guarantee that data treatment follows regulations in accordance with the current legislation regarding the protection of personal data: Organic Law 3/2018, of December 5 on the Protection of Personal Data. The researchers guarantee the anonymity of the data according to national and international norms, the Declaration of Helsinki and Tokyo on ethical aspects, and the norms of Good Practice in Research.

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

This trial project was awarded the XX Osona Research Grant by the Acadèmia de Ciències Mèdiques i de la Salut de Catalunya i de Balears,

September 2019. N.R.M. was awarded the XXII Beca Consultori Bayés en Ciències de la Salut for her Doctoral Thesis project, of the Medicine and Biomedical Sciences Program, University of Vic–Central University of Catalonia, 08500 Vic, Barcelona, Spain, November 2021.

N.R.M. and Q.F.B. conducted the review of the available scientific literature and the study design. N.R.M., M.A.T., M.G.G., N.F.R., and E.G.P. integrated the multidisciplinary group and derived activities. N.R.M. coordinated the study. M.A.T. and N.R.M. conducted the face-to-face visits. P.R.P., Q. F.B., and N.R.M. performed the statistical analysis of the data and its interpretation. Q.F.B., M.S.M., and J.M.S.L. acted as principal consultants and provided supervision. N.R.M. and Q.F.B. drafted the manuscript. All authors reviewed and provided modifications of the draft. All authors reviewed the final draft of the manuscript.

REFERENCES

1. Correll CU, Solmi M, Veronese N, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry*. 2017;16: 163–180.
2. Hjorthøj C, Stürup AE, McGrath JJ, et al. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. *Lancet Psychiatry*. 2017;4:295–301.
3. Hayes JF, Marston L, Walters K, et al. Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000–2014. *Br J Psychiatry*. 2017;211: 175–181.
4. Lee EE, Liu J, Tu X, et al. A widening longevity gap between people with schizophrenia and general population: a literature review and call for action. *Schizophr Res*. 2018;196:9–13.
5. Nordentoft M, Wahlbeck K, Hällgren J, et al. Excess mortality, causes of death and life expectancy in 270,770 patients with recent onset of mental disorders in Denmark, Finland and Sweden. *PLoS One*. 2013;8: e55176.
6. Olfson M, Gerhard T, Huang C, et al. Premature mortality among adults with schizophrenia in the United States. *JAMA Psychiatry*. 2015;72:1172–1181.
7. Castillo Sánchez M, Fàbregas Escurriola M, Fernández Sanmartín MI, et al. Cardiovascular disease and mortality in people with schizophrenia or antipsychotic treatment: a cohort study in primary care. *Psychiatry Res*. 2021;306:114233.
8. Correll CU, Detraux J, de Lepeleire J, et al. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia,

CARDIOVASCULAR RISK PROGRAM FOR SCHIZOPHRENIA

- depression and bipolar disorder. *World Psychiatry*. 2015; 14:119–136.
9. Abosi O, Lopes S, Schmitz S, et al. Cardiometabolic effects of psychotropic medications. *Horm Mol Biol Clin Investig*. 2018;36:1–15.
10. Pillinger T, McCutcheon RA, Vano L, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2020;7:64–77.
11. Dickerson F, Origoni A, Rowe K, et al. Risk factors for natural cause mortality in a cohort of 1494 persons with serious mental illness. *Psychiatry Res*. 2021;298:113755.
12. Firth J, Stubbs B, Teasdale SB, et al. Diet as a hot topic in psychiatry: a population-scale study of nutritional intake and inflammatory potential in severe mental illness. *World Psychiatry*. 2018;17:365–367.
13. Collins C, Finegan P, O'Shea M, et al. Promoting physical health among people with enduring mental illness: a qualitative study of healthcare providers' perspectives. *BMJ Open*. 2021;11:44855.
14. Ayerbe L, Forgnone I, Foguet-Boreu Q, et al. Disparities in the management of cardiovascular risk factors in patients with psychiatric disorders: a systematic review and meta-analysis. *Psychol Med*. 2018;48:2693–2701.
15. Nielsen RE, Banner J, Jensen SE. Cardiovascular disease in patients with severe mental illness. *Nat Rev Cardiol*. 2021;18:136–145.
16. Castillo-Sánchez M, Fàbregas-Escurriola M, Bergè-Baquero D, et al. Schizophrenia, antipsychotic drugs and cardiovascular risk: descriptive study in primary care. *Eur Psychiatry*. 2015;30:535–541.
17. Vancampfort D, Stubbs B, Mitchell AJ, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry*. 2015;14: 339–347.
18. Gardner-Sood P, Lally J, Smith S, et al. Cardiovascular risk factors and metabolic syndrome in people with established psychotic illnesses: baseline data from the IMPaCT randomized controlled trial. *Psychol Med*. 2015; 45:2619–2629.
19. Lemogne C, Blacher J, Airagnes G, et al. Management of cardiovascular health in people with severe mental disorders. *Curr Cardiol Rep*. 2021;23:7.
20. Afzal M, Siddiqi N, Ahmad B, et al. Prevalence of overweight and obesity in people with severe mental illness: systematic review and meta-analysis. *Front Endocrinol (Lausanne)*. 2021;12:769309.
21. Liu NH, Daumit GL, Dua T, et al. Excess mortality in persons with severe mental disorders: a multilevel intervention framework and priorities for clinical practice, policy and research agendas. *World Psychiatry*. 2017;16:30–40.
22. World Health Organization (WHO). WHO Guidelines: Management of Physical Health Conditions in Adults with Severe Mental Disorders. World Health Organization; 2018. Accessed May 20, 2021. <https://www.who.int/publications/i/item/978-92-4-155038-3>
23. Cooper SJ, Reynolds GP, Barnes TRE, et al. BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. *J Psychopharmacol*. 2016; 30:717–748.
24. Howell S, Yarovova E, Khwanda A, et al. Cardiovascular effects of psychotic illnesses and antipsychotic therapy. *Heart*. 2019;105:1852–1859.
25. Vancampfort D, Firth J, Correll CU, et al. The impact of pharmacological and non-pharmacological interventions to improve physical health outcomes in people with schizophrenia: a meta-review of meta-analyses of randomized controlled trials. *World Psychiatry*. 2019;18:53–66.
26. McGinty EE, Baller J, Azrin ST, et al. Interventions to address medical conditions and health-risk behaviors among persons with serious mental illness: a comprehensive review. *Schizophr Bull*. 2016;42:96–124.
27. Gierisch JM, Nieuwsma JA, Bradford DW, et al. Pharmacologic and behavioral interventions to improve cardiovascular risk factors in adults with serious mental illness: a systematic review and meta-analysis. *J Clin Psychiatry*. 2014;75:e424–440.
28. Canejo C. Managing cardiovascular disease risk in patients with severe mental illness. *Lancet Psychiatry*. 2018;5:97–98.
29. Osborn D, Burton A, Hunter R, et al. Clinical and cost-effectiveness of an intervention for reducing cholesterol and cardiovascular risk for people with severe mental illness in English primary care: a cluster randomised controlled trial. *Lancet Psychiatry*. 2018;5:145–154.
30. Daumit GL, Dalcin AT, Dickerson FB, et al. Effect of a comprehensive cardiovascular risk reduction intervention in persons with serious mental illness: a randomized clinical trial. *JAMA Netw Open*. 2020;3:e207247.
31. Torralbas-Ortega J, Paños-Martínez M, Patró-Moncunill E, et al. Efficacy of a short psychoeducational group intervention for the prevention of cardiovascular risk in patients with severe mental disorder: a randomized trial. *J Nerv Ment Dis*. 2020;208:222–229.
32. Brotons Cuixart C, Alemán Sánchez JJ, Banegas Banegas JR, et al. Recomendaciones preventivas cardiovasculares. Actualización PAPPS 2018. *Aten Primaria*. 2018;50 (suppl 1):4–28.
33. Arnet I, Abraham I, Messerli M, et al. A method for calculating adherence to polypharmacy from dispensing data records. *Int J Clin Pharm*. 2014;36:192–201.
34. Cuesta M, Fuentes M, Rubio M, et al. Incidence and regression of metabolic syndrome in a representative sample of the Spanish population: results of the cohort di@bet.es study. *BMJ Open Diabetes Res Care*. 2020;8: e001715.
35. Ribeiro RA, Sánchez-Moreno J, Martínez-Aran DA, et al. Prueba breve de evaluación del funcionamiento (FAST). Cibersam. Published online 2008:25. https://bi.cibersam.es/media/1018/fast_prueba-breve-de-evaluacion-del-funcionamiento.pdf.
36. Luján-Lujan EM, García-León MÁ, Rodríguez-Cano E, et al. Validity of the Functioning Assessment Short Tests (FAST), in patients with schizophrenia. *Rev Psiquiatr Salud Ment (Engl Ed)*. 2022;15:157–166.
37. Badia X, Roset M, Montserrat S, et al. La versión española del EuroQol: descripción y aplicaciones [The Spanish version of EuroQol: a description and its applications. European Quality of Life scale]. *Med Clin (Barc)*. 1999;112(suppl 10):79–85.
38. Marrugat J, D'Agostino R, Sullivan L, et al. An adaptation of the Framingham coronary heart disease risk function to European Mediterranean areas. *J Epidemiol Community Health*. 2003;57:634–638.
39. Marrugat J, Subirana I, Ramos R, et al. Derivation and validation of a set of 10-year cardiovascular risk

CARDIOVASCULAR RISK PROGRAM FOR SCHIZOPHRENIA

- predictive functions in Spain: the FRESCO Study. *Prev Med.* 2014;61:66–74.
40. Marrugat J, Subirana I, Comín E, et al. Validity of an adaptation of the Framingham cardiovascular risk function: the VERIFICA study. *J Epidemiol Community Health.* 2007;61:40–47.
 41. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ.* 2017;357:j2099.
 42. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ.* 2010;340:c332.
 43. Wang N, Fulcher J, Abeysuriya N, et al. Intensive LDL cholesterol-lowering treatment beyond current recommendations for the prevention of major vascular events: a systematic review and meta-analysis of randomised trials including 327 037 participants. *Lancet Diabetes Endocrinol.* 2020;8:36–49.
 44. Cunningham R, Poppe K, Peterson D, et al. Prediction of cardiovascular disease risk among people with severe mental illness: a cohort study. *PLoS One.* 2019;14:e0221521.
 45. Goldfarb M, de Hert M, Detraux J, et al. Severe mental illness and cardiovascular disease: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2022;80:918–933.
 46. Zeng LN, Zong QQ, Zhang L, et al. Worldwide prevalence of smoking cessation in schizophrenia patients: A meta-analysis of comparative and observational studies. *Asian J Psychiatr.* 2020;54:102190.
 47. Foguet-Boreu Q, Guàrdia Sancho A, Santos Lopez JM, et al. Association between cognitive impairment and cardiovascular burden in patients with severe mental disorder. *Cogn Neuropsychiatry.* 2020;25:1–13.
 48. Melamed OC, Hahn MK, Agarwal SM, et al. Physical health among people with serious mental illness in the face of COVID-19: concerns and mitigation strategies. *Gen Hosp Psychiatry.* 2020;66:30–33.
 49. Roberts R, Johnson C, Hopwood M, et al. The potential impact of a public health approach to improving the physical health of people living with mental illness. *Int J Environ Res Public Health.* 2022;19:11746.
 50. Walters SJ, Dos Anjos Henriques-Cadby IB, Bortolami O, et al. Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. *BMJ Open.* 2017;7:e015276.
 51. Liu Y, Pencheon E, Hunter RM, et al. Recruitment and retention strategies in mental health trials—a systematic review. *PLoS One.* 2018;13:e0203127.