



A Review of Cardiovascular Risk Factors in Women with Psychosis

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Abstract: The presence of medical comorbidities in women with psychotic disorders can lead to poor medical and psychiatric outcomes. Of all comorbidities, cardiovascular disease is the most frequent, and the one most likely to cause early death. We set out to review the evidence for cardiovascular risk factors (CRFs) in women with schizophrenia-related disorders and for interventions commonly used to reduce CRFs. Electronic searches were conducted on PubMed and Scopus databases (2017–2022) to identify papers relevant to our aims. A total of 17 studies fulfilled our inclusion criteria. We found that CRFs were prevalent in psychotic disorders, the majority attributable to patient lifestyle behaviors. We found some inconsistencies across studies with regard to gender differences in metabolic disturbances in first episode psychosis, but general agreement that CRFs increase at the time of menopause in women with psychotic disorders. Primary care services emerge as the best settings in which to detect CRFs and plan successive intervention strategies as women age. Negative symptoms (apathy, avolition, social withdrawal) need to be targeted and smoking cessation, a heart-healthy diet, physical activity, and regular sleep routines need to be actively promoted. The goal of healthier hearts for women with psychotic disorders may be difficult, but it is achievable.



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1. Introduction

Medical comorbidities occur frequently in psychotic disorders such as schizophrenia and are associated with poor clinical outcomes and high mortality [1]. Although lifespan in the last few decades has increased in psychotic disorders, recent studies highlight the fact that life expectancy is shorter (by 15–20 years) in these disorders than it is in the general population [2]. Several comorbidities account for the high mortality. The most frequent are hypertension and type 2 diabetes, which can be anticipated by the detection of high levels of cholesterol and triglycerides, sedentary behavior, poor diet, and substance use [3]. Male/female differences are important to note. Metabolic syndrome (MS), which consists of a combination of cardiovascular risk factors (high blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels), is reportedly present in 23.9–34% of women with schizophrenia, but in only 10.8% of their male peers [3]. This suggests that factors beyond schizophrenia disorder itself contribute to risk.

Diet and physical activity are critical elements of risk, as shown by the different rates of MS in the general population in different regions of the world. As an example, in Iranian patients (free of severe mental illness) the overall prevalence of MS is reported as 30.4%, higher in women than in men [4] and reaching a level of 51.6% in postmenopausal women. This illustrates how the advent of menopause can significantly increase women's MS risk [5].

In general, cardiovascular risks in patients with psychosis appear to be on the rise in recent years. A 2022 systematic review found increasing incidence relative to controls, an upward trend that started in the 1990s [6], which coincides with the introduction of second generation antipsychotics for the treatment of schizophrenia, but the synchronous timing may be fortuitous. Mortality has also increased over this period, in association with (as per the meta-analysis of Solmi et al. [7]) low rates of screening and low-quality monitoring and treatment in this population relative to psychosis-free peers.

A 2020 study by Salvi and collaborators shows that the 10-year cardiovascular risk in women with severe mental illness (SMI), a category that essentially overlaps with the presence of psychosis, is higher than that in men and also higher than that in women of similar age in the general population [8]. This is in agreement with other studies that recommend regular monitoring of physical health in primary care services for persons with SMI. A recent retrospective cohort study in Britain investigated disparities in cardiovascular risk, as well as mental and physical health, in non-pregnant women of reproductive age [9]. Women attending mental health services, especially black women, showed a higher prevalence of all cardiovascular risks and, in addition, all physical health diagnoses.

It is paradoxical that, although at higher risk, patients with non-affective psychosis utilize somatic health services less than do their general population peers [10]. Swildens and collaborators conducted a study based on the Psychiatric Case Registry for the Central Netherlands (PCR-MN), which was linked to the Achmea Health Database (AHD). The AHD collects medical insurance data for medical care, drug prescriptions and visits to general physicians (GPs) as well as medical specialists [10]. Psychiatric patients (N = 10,402) were compared with matched controls (N = 61,850) in terms of mean age, duration since earliest registration, and medical specialist attendance. Patients were grouped into four main psychiatric diagnostic categories: non-affective psychosis (e.g., schizophrenia, schizoaffective psychosis, delusional disorder), bipolar disorder, unipolar depressive disorder, and anxiety disorder. Patients with non-affective psychosis showed lower health care utilization compared to matched controls, lower percentages of somatic medication prescriptions and lower GP attendance rates compared to the other groups. The paradox can be explained by patient factors (distrust of the medical system, negative experiences with doctors, apathy and volitional defects, economic barriers, cognitive difficulties), and by poor liaison between mental health practitioners and primary care physicians. The social stigma that is frequently associated with severe mental illness is a further factor negatively influencing attendance rates.

Examining the role of menopause in women's health, we find new occurrences of psychiatric symptoms in 20% of women at this stage of life, as well as increased risk of psychotic exacerbation in women with prior schizophrenia [11]. Medical comorbidities also increase, very likely exacerbated by long term exposure to antipsychotic medications. Examples are tardive dyskinesia and osteoporosis [11] and venous thromboembolism [12]. Cardiovascular risk increases via build-up of coronary atherosclerosis over time and progressive increase in blood pressure [13]. These are preventable factors, but preventive measures are often not implemented in women with psychotic disorders for the reasons outlined above, with consequent poor clinical outcomes and premature deaths.

Aims

In order to determine the feasibility of improved prevention of cardiovascular risks for women with psychosis, we asked the following of the available literature:

- (a) What are the cardiovascular risk factors in this population of women?
- (b) What is the role of menopause?
- (c) How effective are non-pharmacological, life-style targeted interventions in lowering cardiovascular risk in these women?

2. Methods

Electronic searches were conducted in PubMed and Scopus databases by three independent researchers (A.G.-R., M.V.S. and A.G.D.) of relevant papers published over the last five years (2017–October 2022). Reference lists of studies in the field as well as conference proceedings were also searched for additional papers.

The following search terms were used: (schizophrenia OR “delusional disorder”) AND cardiovascular AND women.

More than two hundred titles and abstracts were screened, and data from selected studies were extracted by A.G.-R., M.V.S. and A.G.D. Disagreements were resolved by consensus. For further details on the screening and selection processes, please see Figure 1.

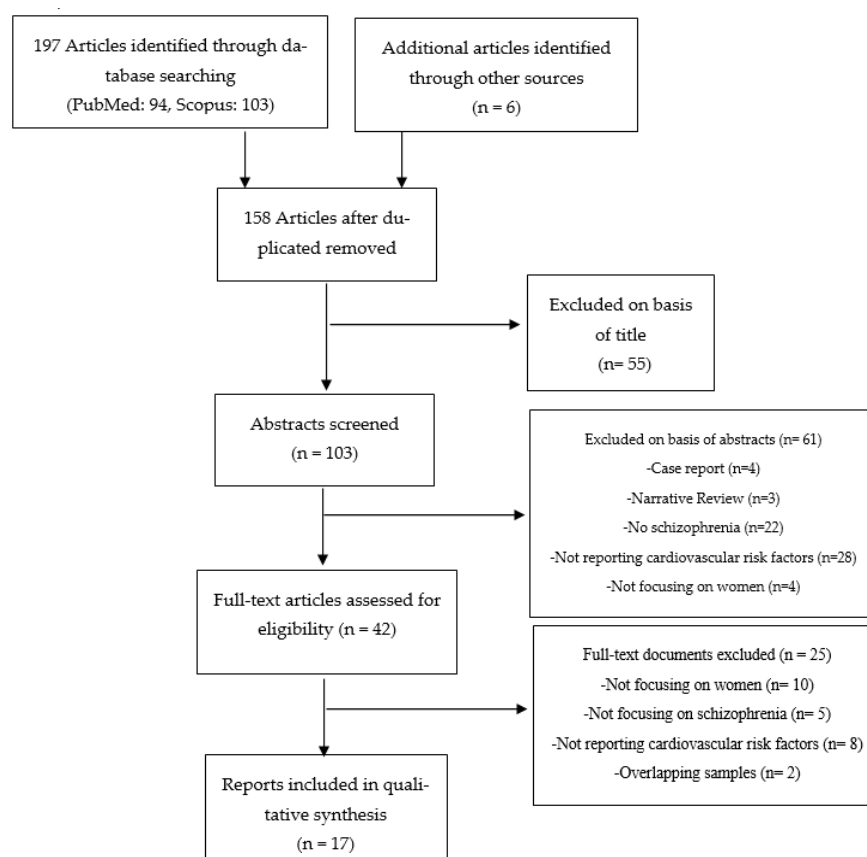


Figure 1. Flow diagram of included studies.

We included studies (1) examining cardiovascular risk factors in the context of schizophrenia and related disorders such as delusional disorder, (2) investigating gender differences and the role of menopause in the emergence of cardiovascular risk factors, (3) exploring treatment strategies capable of modifying cardiovascular risk factors in relevant populations. Case reports were excluded, as were studies that did not explore cardiovascular risk factors in women with schizophrenia spectrum disorders (e.g., irrelevant to our purposes).

3. Results

A total of 203 records were initially identified from titles and abstracts (PubMed: 94; Scopus: 103; other sources: 6). After the screening and selection processes, 17 studies fulfilled our inclusion criteria.

3.1. Cardiovascular Risk Factors in Emerging Psychosis (Objective 1)

First episode of psychosis (FEP) programs are good sources for detecting the presence of early cardiovascular risk. Recent research by Vázquez-Bourgon and colleagues [14]

investigated long-term weight changes and the development of metabolic disorders over a ten-year period in a group of 209 patients with FEP and 57 healthy controls. Anthropometric measures, clinical and demographic data were documented. In the first year of treatment, presumably due to both the effects of antipsychotic treatment and lifestyle, patients with FEP showed a significant increase in body weight, significantly higher than controls. Weight gain was associated with lipid and glycemic disturbances. Women showed a greater increase in body mass index (BMI) than men (6 vs. 4.9, $p = 0.042$), suggesting gender differences in lifestyle and lipid metabolism, and perhaps too, in antipsychotic dose and response.

In the same year, Coentre et al. [15] conducted a one-year longitudinal study of 60 FEP patients. Metabolic variables, clinical, psychopathological and socio-demographic data were assessed at baseline and after one year. Metabolic syndrome increased during the year following the first episode of psychosis, with an increase in triglyceride concentrations, waist circumference, and cholesterol levels. Women constituted 33.3% of the sample but there was no indication of gender differences in metabolic syndrome (MS). No statistically significant gender differences in MS were found either at baseline (0% women vs. 6.7% men, $p = 0.291$) or at follow-up (3.3% women vs. 8.3% men; $p = 0.057$).

A longitudinal study of drug-naïve schizophrenia patients with no medical comorbidity [16] also investigated the metabolic profile of FEP patients. By contrast with the previous study, women were in the majority in this sample (women: 56.7%, men: 43.3%). Women showed a higher prevalence of subclinical metabolic abnormalities than men, irrespective of specific antipsychotic treatment. For instance, there was a tendency toward higher total cholesterol levels (mg/dl) in women compared to men [45.64 (20.61) vs. 34.03 (28.87), $p = 0.071$].

In summary, in currently available research, there are inconsistencies with regard to gender differences in the development of metabolic disturbances in longitudinal studies of FEP patients. In general, however, women show higher BMI than men, and by extension, higher cardiovascular risk. The potential effect of menopause was impossible to determine from these studies because FEP patients are almost exclusively below menopausal age. Table 1 presents the main characteristics and results from cited studies investigating cardiovascular risk factors in women with emerging psychoses.

3.2. Cardiovascular Risk Factors and Gender Differences in Persistent Schizophrenia (Objective 1)

The literature suggests that menopause (perhaps confounded by age) increases cardiovascular risk factors in women. Rossom et al. investigated the cardiovascular risk of primary care patients with and without severe mental illness (SMI) at 10 years and at 30 years following first assessment [17]. Total cardiovascular risk was calculated using two different algorithms. For patients aged 40–75 without prior cardiovascular disease, the 10-year cardiovascular risk was calculated using the atherosclerotic cardiovascular disease risk score, which ranges from 0 to 100 and calculates the risk for myocardial infarction over the next 10 years. For patients aged 18–59 without prior cardiovascular disease, a 30-year risk was estimated using the Framingham risk score. From a total sample of 11,333 patients with SMI and 579,924 patients without SMI, SMI patients showed significantly higher cardiovascular risk. No gender differences were reported.

In a sample of 305 elderly Chinese patients with schizophrenia and 130 healthy controls matched for sex and age, Li and collaborators examined gender difference in the association between cardiovascular risk factors and cognitive dysfunction [18]. For the assessment of cognitive function, the Montreal Cognitive Assessment (MoCA) was used, and the Positive and Negative Syndrome Scale (PANSS) assessed psychopathology. A positive correlation was found between MoCA scores and body mass index in men. Women were more often obese (21.3%) than men (11.7%), but there was no correlation with MoCA scores in women. The conclusion was that gender differences in obesity exist but do not predict cognitive differences in elderly patients with schizophrenia ($p > 0.05$). A recent systematic review and meta-analysis investigating the association between cognitive dysfunction and

cardiovascular risk in patients with schizophrenia found that, in both men and women, MS (hypertension, diabetes, excess visceral fat, and abnormal cholesterol or triglyceride levels) was positively associated with impairment in cognitive domains [19].

Table 1. Characteristics of cardiovascular risk factor studies in women with emerging psychosis.

Authors and Publication Year	Study Design	Sample	Assessment Instrument	Results
Vázquez-Bourgon et al., 2022 [14]	Prospective longitudinal study (10-year follow-up)	FEP, $n = 209$ (women, $n = 95$) Healthy controls, $n = 57$ (women, $n = 24$)	- Diagnosis (SCID-I) - Clin assessment: SANS, SAPS, BPRS - Demograph. data - Lab: glucose, cholest, HDL, triglyc	Weight gain associated with lipid & glycemic change. Women had higher BMI than men ($p = 0.042$).
Coentre et al., 2022 [15]	Prospective longitudinal study (1 year follow-up)	FEP: $n = 60$ (women, $n = 20$)	- Clin assessment: GAF, PANSS, BDI - Metabolic assessment: waist circumference, BP - Lab: triglyc. HDL, cholest. glucose.	No sign. difference at baseline ($p = 0.291$).
Zhang et al., 2021 [16]	Prospective longitudinal study (8-month follow-up)	FEP, $n = 67$ (women, $n = 38$)	- Clin assessment: PANSS, HAMA, HAMD-24, Cognitive assess. - Physical exam: wt, ht, BP, pulse - Lab: triglyc, cholest, prl, uric acid, homocyst	FEP present metabolic abnormalities irrespective of AP, esp. tendency in women ($p = 0.071$)

Abbreviations: BDI, Beck Depression Inventory; bp, blood pressure; BPRS, Brief Psychiatric Rating Scale; cholest, cholesterol; FEP, First Episode of Psychosis; GAF, Global Assessment of Functioning; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; HDL, High Density Cholesterol; ht, height; PANSS, Positive and Negative Syndrome Scale; prl, prolactin; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SCID-I, Structured Clinical Interview for Diagnosis- I; triglyc, triglycerides; wt, weight.

To test for the effects of physical inactivity, a recent study investigated peak oxygen uptake (VO₂ peak) and its association with other cardiovascular risk factors in 48 outpatients with schizophrenia, schizotypal or delusional disorders (28 men, 20 women) [20]. The VO₂ peak was not correlated with physical activity in male patients. In women, a weak association was found (steps per day: $r^2 = 0.26$; counts per minute: $r^2 = 0.25$; $p < 0.05$) BMI (26.0 ± 6.1 kg/m²). The authors concluded that the use of the VO₂ peak for the cardiovascular disease risk profile was not a useful marker for targeted risk reduction.

Mucheru et al. conducted a cross-sectional analysis of data from Australian adults living with psychosis who participated in the Survey of High Impact Psychosis (SHIP) [21]. A two-phase sampling technique was used. The sample was a census of individuals who were in contact with the mental health system and/or community-managed organizations. The objective was to identify patterns of lifestyle risk factors associated with selected demographic variables by performing logistic regressions on the following factors: nutrition, smoking, and physical activity, all three potential predictors of dyslipidemia, hypertension and hyperglycemia. The total sample consisted of 1825 patients (men: 1087; women: 738); schizophrenia was the most common diagnosis (47%). Clozapine use, sex, and age were noted as potential confounding factors. Smoking status turned out to be the only factor associated with dyslipidemia. Sex and age had no significant impact in the relationship between lifestyle risk factors and dyslipidaemia, hypertension, or hyperglycaemia.

Healthcare utilization and medical expenditure have been evaluated in patients with schizophrenia suffering from type 2 diabetes mellitus [22]. Huang et al. compared outpatient visits and hospitalization rates, and outpatient and inpatient expenditure in this group against those of healthy controls [22]. Old age, low incomes, and high rates of diabetic complications were positively associated with the total number of outpatient visits and hospitalizations. Women had higher rates of outpatient visits compared to men (11.04 more visits, 95% CI [9.00–13.08], but less frequent hospitalizations (0.80, 95% CI [0.76–0.85]) and lower medical expenditures (NT\$45,482.60 less (95% CI [–55,820.60 TO 35,144.70])). Tylec et al. [23] investigated the occurrence of cardiovascular risk factors in patients with schizophrenia as well as the association with length of stay at long-term care facilities and with treatment factors. Data were obtained from 71 patients diagnosed with paranoid schizophrenia (41 men, 30 women) who were hospitalized for at least seven months in a residential care facility at two departments of psychiatry. Sociodemographic and clinical data were collected from medical records. Body mass index, blood pressure, heart rate and capillary blood glucose were noted, as were illness duration, the care facility, the type of treatment, and the mean antipsychotic dose in chlorpromazine equivalents. Most (74.6%) of the sample had at least one cardiovascular risk factor. Men's cardiovascular-related factors were judged to carry more risk than those of women, but women showed higher rates of risks rated as moderate (26.7% vs. 9.8%).

Castillejos and colleagues carried out an observational cross-sectional study of patients from the Malaga Schizophrenia Case Registry (RESMA), which is a registry of attendees at community mental health units [24]. A total of 528 patients fulfilled the inclusion criteria; 494 were included in the study. The authors recorded the number of cardiovascular risk factors, e.g., type 2 diabetes, hypertension, hypercholesterolemia, obesity, and smoking, as documented by the referring GPs. Gender, age, marital status and other clinical and sociodemographic variables were also recorded. Data on attendance at GP and nursing appointments were noted by using a digitized primary care records program. The proportion of men among the patients was 70%. Of the total sample, cardiovascular risk factors were only recorded in 59.7% of patients. Almost half of such patients had one factor; 16.1% had two or more. Older age, more primary care visits, and urban residence were associated with higher rates of cardiovascular risk factors. This study highlights the relevance of recording these variables in primary care, so that appropriate intervention can be planned. The authors found that being male was positively associated with fewer cardiovascular risk factors (W-Wilcoxon: 30,202.5, $p = 0.028$).

The same research group conducted a cross-sectional study of patients with schizophrenia and related disorders attending primary care centers. The study's aim was to identify factors pertaining to patient, diagnosis, and primary care center that correlated with adherence to follow-up appointments [25]. An increased number of visits to GPs was positively associated with female gender, married status, receipt of antipsychotic medication, and attendance at mental health sessions. Older age correlated, surprisingly, with less GP contact. In summary, women showed a higher number of contacts with GPs compared to men (W-Wilcoxon, 10,172; $p \leq 0.001$).

Recent studies have tried to correlate clinical and psychosocial factors with cardiovascular risk factors in persons with schizophrenia. Jakobsen et al. [26] investigated the association between psychopathological symptoms (e.g., positive, negative, cognitive), global functioning, employment status, and friendships, with waist circumference, high density lipoprotein (HDL), systolic blood pressure and HbA1C in 428 individuals diagnosed with schizophrenia and related disorders. Negative symptoms were negatively associated with cardiorespiratory fitness, dietary quality, body mass index, and HDL levels. Cardiovascular fitness and HDL were positively correlated with global functioning and cognitive symptoms. Duration of illness and psychotic symptoms other than negative and cognitive were not associated with cardiovascular indicators. Although the workload in the exercise tasks was different between women and men, no gender differences were reported.

To sum up, cardiovascular risk factors are frequent in patients with chronic psychotic disorders and are potentially associated with the presence of cognitive decline. Negative symptoms of schizophrenia are more closely associated with cardiovascular risk factors than positive symptoms. Lifestyle behaviors such as smoking emerge as potential targets of intervention. Women show higher attendance rates at primary care compared to men and primary care appears to be an ideal setting for assessing and documenting cardiovascular risk factors to facilitate the planning of future service needs.

3.3. Cardiovascular Factors Pre and Post Menopause in Women with Schizophrenia (Objective 2)

With respect to menopause, it has been shown that, at this time of life, women develop increased abdominal fat, with an accompanying rise in plasma levels of cholesterol and triglycerides [27,28]. The literature shows that cardiovascular risk increases with advanced age in both men and women, but the remodeling of blood vessels and heart takes place earlier, in middle age, and differs between the sexes [29]. Recent evidence suggests that the effect of menopause on cardiovascular risk factors spikes when menopause occurs early [30].

A systematic review and meta-analysis investigated the association between age at onset of menopause, as well as time since onset of menopause, on cardiovascular outcomes and mortality [13,30]. Coronary heart disease was highest in women experiencing either pre-menopause or early-onset menopause (RR:1.50, 95% CI [1.28–1.76], as well as overall cardiovascular mortality (RR:1.19, CI 95% [1.08–1.31].

In women with schizophrenia, cardiovascular risk factors increase at pre-menopause, likely due to a double effect: aging and the decline in estrogen levels.

Table 2 summarizes the main results with regard to gender differences in cardiovascular risk in patients with schizophrenia-related disorders.

Table 2. Cardiovascular Risk in Women and Men with Schizophrenia-related Disorders.

Cardiovascular Risk Factors (CVRF) in Women with Emerging Psychoses		
Anthropometric measures	BMI Body weight Waist circumference	In FEP, general increase in BMI. More in women Higher weight in women
Lipid levels	Triglycerides Cholesterol	More subclinical metabolic abnormalities in women
Cardiovascular risk factors (CVRF) in women with persistent schizophrenia		
General CVRF	Effect of: Menopause Aging	Increased risk with age, esp. women with early onset menopause
		Men: more high-risk factors Women: more moderate risk factors
Primary care prevention/identification of CVRF	Visits to GP	Women show higher attendance at health services

Abbreviations: BMI, Body Mass Index; CVRF, Cardiovascular Risk Factors; FEP, First Episode of Psychosis; GP, General Practitioner.

3.4. Interventions in Cardiovascular Health in Patients with Psychosis (Objective 3)

A good starting point from which to examine the feasibility and effectiveness of interventions in cardiovascular health in this population is a recent review on primary care prevention of cardiovascular health in patients with severe mental illness (SMI) [31]. This review addressed interventions for obesity, smoking, hyperglycemia, physical activity and cardiorespiratory fitness. Results showed that trials of pharmacological interventions for weight gain and smoking have positive effects. The conclusion was that a combination of pharmacological plus lifestyle interventions is promising, but that the evidence for positive effects on cardiovascular health is, thus far, sparse. It was suggested that system, individual, and professional barriers to effective intervention in the schizophrenia population need to

be specifically targeted. Blood pressure, lipid profile, excess body weight, smoking and other risk factors did not differ, according to this review, between men and women, and there was no mention of the role of menopause nor of the need for sex-specific interventions.

Heald et al. [32], in a cross-sectional study, assessed lifestyle factors, (e.g., diet, physical activity) in a group of 37 outpatients suffering from schizophrenia; most were men. There was a high prevalence of poor diet, smoking and inadequate physical activity. The implementation of a dietary intake of fruit and vegetables was recommended. Many patients appeared to have insight into their unhealthy lifestyle, increasing the likelihood of potential interventions being successful. Central adiposity affected 92% of men compared to 91.7% of women. Here again, gender differences were not found.

In a Norwegian mental health service, Ringen et al. [33] investigated levels of assessment of cardiovascular risk factors and risk intervention in patients diagnosed with SMI. In a sample of 264 patients, smoking cessation advice was offered to 45% of the sample who were daily smokers, and 4% were referred to specific intervention programs. Sixty-two per cent presented with obesity for which lifestyle interventions were offered. The authors concluded that 10% of their sample showed high cardiovascular risk, and that only half had been adequately screened. Women had received adequate intervention less often than men (Body weight: 75% vs. 86.5%; waist circumference: 52.8% vs. 58.1%). Similarly, a study by Tylec et al. [23] investigated cardiovascular risk factors (e.g., sex, age, cholesterol levels, body mass index and blood pressure) in long-term residential facilities in patients with schizophrenia aged 40–86. The conclusion was that interventions focused on healthy lifestyles do positively impact body weight; dietary regimens were the most common form of intervention. The study also found that physical activity prescription was able to reduce abdominal obesity and improve blood pressure. This is in agreement with Bueno-Antequera et al. [34] who conducted a study of 142 patients with SMI and evaluated four main health indices: smoking status, body mass index, level of physical activity, and dietary quality. High levels of sedentary behavior were associated with high cardiovascular risk. They reported prevalence of ideal cardiovascular health: body mass index (16.9%), physical activity (83.1%), healthy diet (10.4%), blood pressure (40.4%), cholesterol (62.9%), non-smoking (40.4%). Women presented with blood pressure and glucose parameters closer to the ideal more frequently than men (% blood pressure ideal: men, 35.5%; women, 55.9%), (% glucose ideal: men, 61%; women, 87.5%). The recommendation was for all care providers to actively promote cardiovascular fitness.

A recent cross-sectional study described the nutritional habits of 31 outpatients with schizophrenia and investigated the association of diet with illness severity [35]. The study evaluated demographic and clinical characteristics, duration of illness, BMI, abdominal perimeter, and responses to questionnaires about eating, nutrition, and physical activity. The results showed that 74.2% of patients ate meat weekly and 77.4% had fewer than three fruit dishes per day. The vast majority did not follow the World Health Organization (WHO) recommendations on physical activity. Clinical severity, marital status and cohabitation were associated with poor eating behaviors and nutritional habits. Overall, the recommendation was for clinicians to emphasize good dietary habits.

Hjorth et al. [36] carried out a 30-month follow-up study of 54 outpatients with schizophrenia. It consisted of individual visits, group sessions and clinical care in a mental health clinic. Whereas women who participated showed a significant reduction in waist circumference, men paradoxically increased waist circumference after participating in the program (women: −11.4 cm; men, 3.3 cm). Consumption of fast food and soft drinks, however, was significantly reduced, as well as cigarette smoking. Light physical activity was increased in women. The findings suggested that, in the context of schizophrenia, it was easier to reduce cardiovascular risk factors in women than in men.

Other targets to improve cardiovascular health are sleep and negative symptoms. Jakobsen et al. [26] investigated the association between clinical and psychosocial factors and cardiovascular risk factors in 418 people with schizophrenia. They found that negative symptoms were negatively associated with cardiovascular fitness, dietary quality,

HDL, and with increasing BMI, waist circumference and increased HbA1C. This suggests addressing negative symptoms via cognitive behavioral therapy, cognitive remediation, social cognition training, family intervention, social skills [37] in order to reduce morbidity and mortality in persons with schizophrenia.

Zhu et al. [38] explored primary care sleep records from the UK Biobank. Patients were divided into five main groups according to their sleep duration: less than 5 h, 5–6 h, 6–7 h, 7–8 h and >8 h. A significant “U-shaped” association was found between sleep duration and illness status. Six-to-eight hours of sleep was found to correlate with better long-term health, whereas both too short and too long sleep duration correlated with an increased frequency of metabolic and mental disease, suggesting that interventions focused on sleep could improve metabolic outcomes, and, by implication, aid cardiovascular health.

In summary, comprehensive clinical care for patients with psychosis is potentially effective in reducing cardiovascular risk factors.

Table 3 summarizes potential targets of intervention to reduce cardiovascular risk factors in women with schizophrenia spectrum disorders. Table 4 presents the main characteristics of the studies investigating the effectiveness of interventions in women.

Table 3. Targets of Intervention in Women with Schizophrenia Spectrum Disorders and Cardiovascular Risk Factors.

Target	Intervention	Potential Effects
Smoking and metabolic profiles	Smoking cessation, weight loss, physical activity	Reduction of unhealthy lifestyle behaviors
Dietary habits and physical activity	Budgeting, food guidance, exercise	Reduction of cardiovascular risk
Negative symptoms	Cognition, stimulation, interaction, socialization	Reduction of cardiovascular risk
Sleep	Sleep studies, Sleep hygiene, CBT	Improvement of metabolic indices

Table 4. Main characteristics of recent studies investigating interventions that aim to reduce cardiovascular risk in women with schizophrenia-related disorders.

Authors and Year of Publication	Study Design	Participants	Assessment	Main Results
Ringen et al. [33]	Register study (mental health care centres), observational design.	SZ, $n = 207$ (women, $n = 85$)	<ul style="list-style-type: none"> - Cardiometabolic risk assessment with Healthy Heart Tool - Do pts. with risk factors receive recommended Rx? 	<ul style="list-style-type: none"> - Sedentary lifestyle, obesity and hypercholesterolemia associated with less dietary advice. - Advice on physical activity needed in 70% of pts. - Women less likely to receive dietary advice.
Bueno-Antequera et al. [34]	Observational study	SMI $n = 142$ (women, $n = 34$)	<ul style="list-style-type: none"> - Assessment of sedentary behaviour, - Cardiovascular fitness and muscular strength via activity monitor, 6 min walk test, handgrip test 	Cardiovascular fitness associated with better diet and BMI in pts with SMI.

Table 4. Cont.

Authors and Year of Publication	Study Design	Participants	Assessment	Main Results
Zurrón-Madera et al. 2019 [35]	Cross-sectional descriptive study	SZ, <i>n</i> = 31	<ul style="list-style-type: none"> - Clinical characteristics: CGI, CGI-S, LOI, BMI, abdom. perimeter - Survey: diet and physical activity. 	<ul style="list-style-type: none"> - Pts with schizophrenia do not readily follow recommendations. - Clinical severity and cohabitation associated with poor diet.
Hjorth et al. [36]	Naturalistic and intervention follow-up study (30-month program)	SZ, <i>n</i> = 54 (women, <i>n</i> = 32)	<ul style="list-style-type: none"> - Assessment: weight, height, WC, fat%, BP, pulse - Lab: total cholesterol, LDL, HDL, triglycerides, and HbA1c. 	It is possible to reduce CRF.

Abbreviations: BMI, Body Mass Index; CGI, Clinical Global Impression; CGI-S, Clinical Global Impression-Schizophrenia; CRF, Cardiovascular Risk Factors; HbA1c, Haemoglobin A1c; HDL, High Density Cholesterol; Lab, Laboratory; LDL, Low Density Cholesterol; LOI, Length of Illness; SZ, Schizophrenia; SMI, Severe Mental Illness; WC, waist circumference.

4. Discussion

In order to determine the feasibility and effectiveness of interventions that help to reduce cardiovascular risks in women with psychotic disorders, we explored the literature on cardiovascular risk factors in this population both in emergent and in persistent psychosis. We also examined the role of menopause in exacerbating cardiovascular risk, as well as the effectiveness of attempts to reduce the risk.

There is agreement in the literature that cardiovascular risk factors are frequently already present in young patients with FEP [12–14]. Most studies do not report on gender differences and do not take age or antipsychotic type or dose into account. The evidence that exists shows that women present with higher body mass index (BMI), but men show more dangerous-to-health cardiovascular-related risk factors [21]. FEP patients have a higher prevalence of cardiovascular risk factors than same age peers and the risk increases with age. This means that an opportunity exists for implementing and evaluating early intervention to reduce cardiovascular morbidity and early mortality.

Increased cardiovascular risk factors in individuals suffering from persistent schizophrenia is sometimes linked to the presence of cognitive defect [17–26]. Cognitive problems may lie at the root of lack of screening and low GP attendance, though motivational factors are also important, as is general mistrust of people and institutions. Lifestyle factors (smoking, substance use, low physical activity, unhealthy diet) are pertinent and antipsychotic treatment is probably a major contributor. Care providers need to recognize the many determinants of poor cardiovascular health in this population and be diligent in the provision of preventive and early interventional measures. We looked but could not find indications of gender differences in cardiovascular variables in recent primary care study reports [24].

We did find that, at pre-menopause, cardiovascular risk factors increase in women, attributable to both aging and fluctuating estrogen levels [11–13]. Although women with schizophrenia show higher attendance rates at both primary and mental health services compared to men, GP contact surprisingly wanes with increasing age [24,25]. In women with schizophrenia, psychotic symptoms increase in severity at menopause, which often leads to increased doses of antipsychotic medication, with the attendant risks to heart health [39]. Because of the association between cardiovascular risk and ovarian aging [27], several studies have emphasized the importance of extra monitoring of women's health at the time of menopause and implementing early intervention strategies that reduce cardiovascular risk. This is especially recommended in the context of schizophrenia because of the use of antipsychotic medications [28].

Existing evidence points to primary care as the best setting for assessing and documenting cardiovascular risk factors and for planning future preventive services for women. Mental health services, however, must also be on the alert. For instance, negative psychotic symptoms are positively associated with cardiovascular risk, which points to the need for increased attempts to address difficult-to-treat negative symptoms [26].

Smoking cessation programs, exercise programs (focusing on physical activity to reduce sedentary behaviour), nutrition education (healthy diet), and sleep hygiene programming need to start as early as possible and to intensify during pre-menopause in women.

Effective intervention is, in theory, feasible but barriers to success may be symptoms such as apathy and avolition, cognitive defects, hallucinations and delusions, addiction, as well as lack of resources and family and friend support, and perceived stigma. Other barriers are diagnostic overshadowing on the part of healthcare providers [40], and medical silos that prevent medical and psychiatric practitioners from communicating effectively [41].

We found evidence suggesting that community programs that include individual assessment, family and group work, and interest in the specific needs of women with serious mental illness can be effective in reducing cardiovascular risk in women [36]. A recent review focusing on male and female care needs in schizophrenia describes a new unit for the assessment and intervention for women with schizophrenia [42]. This unit offers programs based on individual/group patient/family therapy, medication adherence programs with therapeutic drug monitoring when necessary, and close collaboration with primary care, as well as home-based services.

A major limitation of this review is the lack of specific evidence of cardiovascular risk in women with psychotic disorders at various stages of the life cycle. Another limitation is the paucity of studies that examine the effectiveness of interventions aimed to reduce cardiovascular risk factors in women. Very few studies have investigated gender differences in cardiovascular health in this population and even fewer have explored cardiovascular risk factors in midlife women with schizophrenia spectrum disorders. Although antipsychotic medications appear clinically to increase risk, we could not find many studies in women with schizophrenia who were not exposed to antipsychotics. More drug-naïve studies in incident patients are needed. Moreover, although menopause has been strongly implicated as a turning point in women's rate of emergence of cardiovascular diseases, the evidence remains poor for the population with psychotic disorders. Altogether, few studies have specifically explored the cardiovascular risk of women with schizophrenia and related disorders.

5. Conclusions

Cardiovascular risk factors (CRFs) are prevalent in psychotic disorders, and are mainly attributed to patient lifestyle behaviors, though several other societal and system factors contribute. Gender differences in CRFs have been found in first-episode-psychosis patients and in patients with more chronic forms of psychosis, but the results are inconsistent. CRFs probably increase in women with psychosis at the time of menopause, as they do in women in the general population, but this has not yet been effectively shown.

Primary care services are recognized as appropriate settings in which to identify CRFs early so that timely intervention strategies can be implemented. In psychiatric settings, negative symptoms (apathy, avolition, social withdrawal) need to be targeted and smoking cessation, a heart-healthy diet, physical activity, and regular sleep routines need to be actively promoted.

Future research is needed to investigate the efficacy of preventive interventions aimed to reduce CRFs in women suffering from psychotic disorders, particularly as they reach menopausal age. It is recommended that community mental health interventions consider gender-specific approaches to this population of women. Inflammation, immunity, and lipid metabolism all differ substantially between men and women, as do lifestyle habits that contribute to cardiovascular disease and early death. The effectiveness of pre-

cision medicine is furthered by differentiating the prevention, early detection, and early intervention requirements of women and men.

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