



Interplay between Schizophrenia, Diabetes, and Cardiovascular Disease

Bhavya Aluri

Abstract

Schizophrenia is a severe, chronic mental illness that affects about 1% of people globally. Due to schizophrenia's psychotic symptoms, patients have a difficult time adhering to medications such as antipsychotics, which can negatively impact both their mental and physical health due to side effects and disorganized thoughts that arise after medication non-adherence. Furthermore, antipsychotics are known to cause weight gain and decrease insulin sensitivity, which can make patients resistant to taking antipsychotics. Nonetheless, along with taking antipsychotics, staying active is important, because antipsychotics can cause weight gain and some antipsychotics, especially second-generation antipsychotics, can reduce insulin sensitivity. Recent studies have shown that schizophrenic patients are more likely to have co-morbid conditions, like type II diabetes and cardiovascular disease.

In this paper, the impact schizophrenia has on both diabetes and cardiovascular disease on diagnosis and symptom management will be explored. Due to the epidemiology, burden of symptoms, and limited methods for effective management of schizophrenia, patients with schizophrenia are more likely to experience more extensive complications from diabetes and cardiovascular disease compared to an otherwise healthy person.

I. Introduction: Overview of Schizophrenia, Diabetes, and Cardiovascular Disease

Overview

Schizophrenia is a complex psychiatric disorder that affects multiple aspects of functioning, from cognition and emotion to social behavior and physical health. While it is often discussed in terms of its psychological and neurological effects, schizophrenia also carries significant implications for physical health, contributing to markedly higher rates of chronic medical conditions in affected individuals. Among the most prevalent and serious of these are diabetes and cardiovascular disease, both of which are leading causes of premature mortality in this population. In this paper, the impact schizophrenia has on both diabetes and cardiovascular disease on diagnosis and symptom management will be explored. Due to the epidemiology, burden of symptoms, and limited methods for effective management of schizophrenia, patients with schizophrenia are more likely to experience more extensive complications from diabetes and cardiovascular disease compared to an otherwise healthy person.

Schizophrenia

Schizophrenia is a severe, chronic mental illness impacting approximately 1% of the general population (1). It is characterized by positive symptoms, which involve the presence of abnormal experiences, hallucinations, delusions, disorganized speech, and abnormal movements, and negative symptoms, which refer to the absence or reduction of normal functions, including the flattened affect, social withdrawal, anhedonia, apathy, and lack of emotions (1). To formally diagnose schizophrenia a person must present with at least one positive symptom, and the symptom must persist for at least six months and significantly impair social or occupational functioning (2).

A definitive cause for schizophrenia has not been elucidated. However, the neurodevelopmental model is the most widely accepted. According to this theory, neurodevelopmental insults (such as viral infections) during the late first or early second trimester of fetal development in utero can lead to the activation of pathologic neural circuits during adolescence or young adulthood that contribute to the emergence of positive or negative symptoms (3). Once diagnosed a combination of cognitive-behavioral therapy and antipsychotic medication is the mainstay of treatment. Hence, schizophrenia is potentially caused by neurodevelopmental insults during fetal development and occurs more frequently in men than women that requires long-term multidisciplinary management and treatment.

Diabetes

Diabetes is a condition in which the pancreas is unable to produce sufficient insulin or the body is insulin resistant. The two types of diabetes are type 1 diabetes and type 2 diabetes. Type 1 diabetes (T1D) is an autoimmune condition in which the pancreas is unable to secrete enough insulin. This type of diabetes can be genetic and often diagnosed in childhood. Type 2 diabetes is caused by insulin resistance and the body is unable to process and react to insulin. Type 2 diabetes (T2D) can be developed during a person's lifetime due to lifestyle choices. Hence, type 2 is more common than type 1 diabetes with approximately 95% of people with diabetes having type 2 diabetes (4).

In the past 20 years, there has been greater than a two-fold increase in the incidence of diabetes worldwide (5). In 2012, one and a half million people passed away primarily due to diabetes (6). Obesity, which is becoming more common in countries like the United States, is one of the factors leading to this increase. Obesity is caused by various factors including processed food, high sugared food, and a sedentary lifestyle, and as countries globally become more industrialized, mass-production of food increases, increasing the risk of developing and the incidence of diabetes worldwide, particularly type 2 diabetes.

Cardiovascular Disease

Cardiovascular disease (CVD) is a term used to characterize a wide range of noncommunicable, cardiovascular diseases. It is becoming more common globally and is the leading cause of death in the United States and worldwide.

A major cause of cardiovascular disease is atherosclerosis. Atherosclerosis is a disease caused by the accumulation of fat and fibrous elements in the large arteries, causing the formation of fatty-fibrous lesions (7). Atherosclerosis is progressive and can get worse if not treated, leading to vessel occlusion. Additional risk factors include family history, poor diet, smoking, and sedentary lifestyle. In a study conducted by Adhikary et al. that collected data from several countries across the globe, it was found that although smoking is common in Pakistan and the United States, there was a higher prevalence of hypertension in the United Kingdom and Tanzania, so different countries have different CVD risk factors (8). Nonetheless, in almost all the countries in the study, both obesity and dyslipidaemia were common (8).

Due to the epidemiology, burden of symptoms, and limited methods for effective management of schizophrenia, patients with schizophrenia are more likely to experience more extensive complications from diabetes and cardiovascular disease compared to an otherwise healthy person.

II. Neurobiology of Schizophrenia

Subcortical dopamine dysfunction

The main hypothesis for the cause of a person's psychotic symptoms is subcortical dopamine dysfunction. Studies using PET scans suggest that the striatum, a heterogeneous structure that consists of various neurochemical modulators and types of neurons, is where elevated levels of dopamine are concentrated (8, 9). Schizophrenia patients with psychotic symptoms have changes in the amount of dopamine concentrated in the striatum.

The thalamus is the main part of the brain that relays information to and from the cerebral cortex. The thalamus, cerebral cortex, and associative striatum form the main circuit that causes psychotic symptoms. A change in any of these areas can affect the whole network. This circuit is directly or indirectly connected to several other pathways, such as the hippocampus and amygdala, which regulate emotions and perceptions (8). Symptoms of delusions and hallucinations are primarily caused by cerebral cortex and thalamus dysfunction impacting the striatum and dopamine D2 receptors (10).

Insights from Medications

There are several classes of medications that may increase one's likelihood of experiencing psychotic symptoms. Stimulants like amphetamines increase psychotic symptoms in schizophrenia patients, because they increase the amount of dopamine present in the subcortical pathway (8). There is also a link between marijuana use and increased susceptibility

to schizophrenia in adolescents, because of the main ingredient in marijuana, THC, interfering with brain development and functioning, with there being a higher risk of adolescents developing it when they are more prone to developing schizophrenia due to a family history with schizophrenia (11). Epidemiological and animal studies show that the use of marijuana is associated with schizophrenia outcomes later in life especially during adolescence (12). This carries an increased risk as marijuana is becoming more common amongst adolescents with more adolescents starting marijuana use at a younger age than before (13).

Common comorbidities of schizophrenia are anxiety, depression, substance abuse, post traumatic stress disorder (PTSD), and panic attacks (14). The National Institute of Mental Health's Epidemiologic department conducted two studies including a Catchment Area survey, which is when the geographic region of the area in which the study is conducted is analyzed as well (14). One study found that there was a 28% to 63% prevalence of panic attacks/panic disorder in schizophrenia patients, and the other study found a 45% prevalence, both of which are greater than the 1-3% prevalence of panic attacks in people without schizophrenia (14, 15). Also since trauma can cause schizophrenia and is common in people with schizophrenia, many schizophrenia patients experience PTSD (16).

Although there is currently no cure for schizophrenia, there are treatment options to mitigate the symptoms of schizophrenia. Current treatments for schizophrenia focus on treating symptoms and involve using first-generation antipsychotics (FGAs), typical antipsychotics, or second-generation antipsychotics (SGAs) atypical antipsychotics.

First, first-generation antipsychotics, such as haloperidol, loxapin, and trifluoperazine, were the initial class of medications clinically tested and used for schizophrenia. These antipsychotics could treat positive symptoms, like hallucinations and delusions but did not impact negative symptoms, like social withdrawal and apathy. FGAs also cause side effects including extrapyramidal symptoms, such as movement disorders like acute dystonia, akathisia, and parkinsonism, because of the antagonist activity on the dopamine receptors (8). These extrapyramidal symptoms can affect everyday life as they are debilitating and interfere with social functioning and communication, motor tasks, and activities of daily living, which can lead to an impaired quality of life, treatment nonadherence, increased morbidity, caregiver burden, and increased utilization of healthcare resources (17). The high proportion of patients that had medication non-adherence led to a large amount of illness recurrence despite this class of drug's ability to alleviate symptoms (17).

Since FGAs can only modulate positive symptoms, second generation anti-psychotics (SGAs) were created to regulate both positive and negative symptoms. Since SGAs antagonize both dopamine (D2) receptors and serotonin (5HT) receptors, they cause less extrapyramidal symptoms due to the ability to balance out the symptoms. However, they can still cause side

effects of hypotension and metabolic syndrome, increasing one's likelihood of developing diabetes.

Although SGAs were created to control both positive and negative symptoms, clinical studies show that the effect SGAs have on negative symptoms is not clear, and that these SGAs are not the most reliable treatments for negative symptoms. However, they are more helpful in mitigating the effects of negative symptoms than FGAs. Hence, SGAs are often trialed first with patients due to their milder side effect profile.

III. Schizophrenia and Diabetes

Epidemiological Associations

Risk factors for diabetes include obesity, diets with high sugar and fat content, prior family history of diabetes, and low physical activity. Diabetes is common in schizophrenia patients and 20% of schizophrenia patients have diabetes (18). The onset of diabetes can occur at any age after getting schizophrenia, but it was found that prevalence of diabetes in schizophrenia patients increased with age from 1.6% in the 15–25 age group to 19.2% in the 55–65 age group (18). Hence, diabetes is more common in older schizophrenia patients than younger schizophrenia patients, and this might be because of antipsychotic use or lifestyle (18).

Mechanisms

Patients with schizophrenia are more likely to get Type 2 diabetes than the general public for various reasons including the antipsychotics affecting insulin sensitivity and resulting in weight gain indirectly. Schizophrenic patients also have a higher risk of depression and a sedentary lifestyle with poor lifestyle decisions leading to weight gain and decreased insulin sensitivity (19). The risk of a sedentary lifestyle and poor diet choices can be due to depression, a low socioeconomic status-due to schizophrenia symptoms causing inability to work and unemployment-, or low income as many schizophrenics have depression and a low income and socioeconomic status (19). Type 2 diabetes is especially common in schizophrenics who do not take any antipsychotics.

The Link Between Antipsychotic Non-Adherence and Increased Diabetes Risk

Not taking antipsychotics can increase the risk of developing diabetes in people with schizophrenia. A study conducted by Ryan et al., comparing the incidence of diabetes before and after antipsychotics (such as olanzapine, clozapine, quetiapine, risperidone, aripiprazole, paliperidone, ziprasidone, and lurasidone) were given by measuring fasting glucose levels (20). The results showed prior to any antipsychotic treatment more than 15% ($n = 4$) of the patients exhibited impaired fasting glucose tolerance compared with 0% of the age-matched healthy control individuals (20). The study also showed that the prevalence of Type 2 diabetes is also about 2-4 times higher in patients with schizophrenia than in the general population, potentially

due to not adhering to antipsychotic medications, poor diet and lifestyle choices, and side effects from antipsychotics (21, 22, 23, 24, 25, 26).

This link between diabetes and schizophrenia has been found more commonly in older antipsychotic naïve patients than younger antipsychotic naïve patients, and an age-associated confounding effect has been observed, meaning that as the patient's age increases regardless of schizophrenia diagnosis, they have a higher chance of getting diabetes (27). A cross-sectional study conducted by Subramaniam et al. with 194 treatment-naïve patients with schizophrenia of different age groups with 155 males and 39 females in Singapore explored how age affects incidence of diabetes in schizophrenia patients in Singapore (28). The results of the study showed that when the antipsychotic naïve patients were arranged based on age, their rates of diabetes were approximately two-fold higher than the general population of Singapore (17.3% versus 9.6% at 40–49 years and 50.0% versus 21.8% at 50–59 years, respectively in each case), showing that it is more common for older individuals with schizophrenia to have diabetes than younger individuals, and people without schizophrenia (27). The mechanisms underlying the increased risk of insulin resistance, prediabetes, or type 2 diabetes among patients with schizophrenia appear to be multifactorial and complex, with genetic risk factors, lifestyle risk factors, and certain medicines, including some antipsychotics, also playing a role (27).

Antipsychotic-induced weight gain and insulin resistance

Most antipsychotics cause weight gain called antipsychotic-induced weight gain (AIWG) (29). However, weight gain is a side effect that is more common for SGAs than FGAs (30). In a study conducted by Sudar et al., 150 schizophrenia patients who were on an antipsychotic drug were studied and their BMIs were recorded (31). The results of the study show that certain antipsychotics cause more weight gain than others. Clozapine and olanzapine are more likely to cause weight gain compared to other antipsychotics, while haloperidol, lurasidone, ziprasidone, aripiprazole and amisulpiride are less likely to cause weight gain (29). The risk of gaining weight is highest during the first year of treatment and is higher for children than adults (29). Weight gain can lead to obesity, which is a reason for the increased risk of diabetes and higher mortality rates. It was also found that second-generation antipsychotics like olanzapine, especially, lower insulin sensitivity and causes an increase in postprandial insulin, insulin levels after eating a meal (32).

Clinical Implications

Underdiagnosis and undertreatment

People with schizophrenia have a higher risk of developing diabetes than people without schizophrenia. However, diabetes is more difficult to diagnose in schizophrenics due to patients

with schizophrenia being unable to properly express their symptoms, so doctors usually do not think to test schizophrenic patients for diabetes (33). Hence, it can remain undiagnosed for a long time. About 40% of people diagnosed with schizophrenia do not receive a follow-up from a primary care physician within 30 days of diagnosis and 60% do not receive a follow-up from a psychiatrist, but the reasons behind this are unknown (34).

Treatment options for diabetes can vary based on type. Type 1 diabetes is treated differently than type 2 diabetes. For example, some types of diabetes may use insulin treatment, while others do not. People with schizophrenia usually have Type 2 diabetes and are two to five times more likely to get Type 2 diabetes than the general public for several reasons. These reasons include not taking antipsychotics, antipsychotics affecting insulin sensitivity and indirectly causing weight gain, and depression leading to sedentary lifestyle with unhealthy lifestyle decisions (19). This causes weight gain and reduced insulin sensitivity. To treat diabetes in schizophrenic patients weight management, encouraging physical activity, monitoring antipsychotic use and encouraging the intake of diabetes medications (18).

Worsened glycemic control and complications

It has been found that approximately 44% of schizophrenics are not adherent to their diabetes medications (35). This can make it harder to control glucose levels and lead to complications. Additionally, antipsychotic-induced weight gain can cause insulin resistance, causing type 2 diabetes. This can also make it harder to control glucose levels. To reduce the risk of complications, it is important to encourage a more active lifestyle, encourage taking diabetes medications, and monitor the amount of medication given.

IV. Schizophrenia and Cardiovascular Disease (CVD)

Increased risk of Myocardial Infarction, Stroke, and Cardiovascular Mortality in Schizophrenic Patients

The types of cardiovascular disease that have caused the most number of deaths globally are stroke and ischaemic heart disease (IHD) (36). Diabetes increases the risk for developing CVD and can cause more severe and fatal CVD. Since there is a strong link between CVD and diabetes, people with schizophrenia have a high risk for developing CVD (36).

A study conducted using the Comparative Risk Assessment technique of the Global Burden of Disease (GBD), a method used to measure the disability and death caused by diseases, injuries and risk factors, to calculate attributable burden (36). Meta-regression was used to pool relative risks (RRs) for stroke, IHD, and diabetes (37, 38). This was then put together with the estimates of the frequency of GBD schizophrenia to calculate the number of years of life lost (YLLs) and deaths (36). Additionally, the ratio of explained fatal burden to unexplained fatal burden was calculated (36).

The relative risks for diabetes, stroke, and IHD- calculated in the study- were 4.08, 1.86, and 2.36 respectively. Approximately 1.5 million years of life lost and 50,000 deaths worldwide from these diseases were caused by schizophrenia. About 11% of years of life lost and 13% of deaths attributed to schizophrenia were explained by IHD, diabetes, and stroke collectively (36). Additionally, schizophrenia patients are three times more likely to get myocardial infarction than the general public most likely due to unhealthy diet, smoking, neglecting health, and reduced access to healthcare (39).

Metabolic syndrome

Metabolic syndrome (MetS) is a group of conditions that increase the risk of CVD, type 2 diabetes, and strokes. Schizophrenia increases the risk for developing metabolic syndrome. There are many potential causes for MetS in schizophrenia patients. Cardio-metabolic risk factors are attributable to unhealthy lifestyle, including poor diet and sedentary behaviour (40).

Lifestyle

Schizophrenics have higher smoking, hypertension, and sedentary lifestyle rates than people without schizophrenia. Roughly two out of three schizophrenics smoke (41). 2/3rds of schizophrenia patients are also overweight due to various factors, such as sedentary lifestyles, diet, antipsychotic medications. This can lead to an increased risk of developing CVD.

Healthcare Disparities & Behavioral contributors: poor diet, low physical activity, substance use

Schizophrenic patients are more likely to get CVD than a person without schizophrenia, but those with schizophrenia have a lower chance of having any medical record of CVD (42). Also, a meta-analysis showed that people with schizophrenia get fewer screenings for CVD and poorer quality treatment compared to those without schizophrenia. This is possibly because people with schizophrenia experience high rates of unemployment due to their symptoms hindering their ability to work, leading to lower income and socioeconomic status (43, 44, 45, 46, 47). Being unemployed or having a low income prevents access to high quality screenings and treatments, such as somatic treatment, treatment focused on improving physical health treatment (48).

Schizophrenia patients tend to not adhere to taking medications, especially pill-based antipsychotic medication due cognitive impairment and constant need for assistance to make sure the pills are taken (2). Non adherence usually increases the risk of cardiovascular disease. In a study conducted by Chang et al. conducted on 80,581 schizophrenia patients in Korea aged between 20 and 40 years, the patients were separated into quartiles by adherence determined by their two-year medication possession ratio (49). It was found that the individuals in the quartile who adhered to taking their antipsychotics had fewer incidences of cardiovascular disease than those in the quartile with individuals who did not take antipsychotics (49).

Hence, long-action injection (LAI) medications are used as they assist with non-adherence to antipsychotics due to their ability to release medication slowly into the bloodstream, allowing for them to be used less frequently than pills. Some LAI medications include risperidone, olanzapine, aripiprazole, and paliperidone (50). However, these LAIs can sometimes lead to an increased risk of cardiovascular disease. In a two-center-based cross-sectional study conducted with 130 patients with either schizophrenia or schizoaffective disorders, it was found that the risk for developing cardiovascular disease depends on the type of medication given and how long the patient was on the antipsychotic (50).

Current diagnosis for cardiovascular disease includes using CT scans, MRIs, and PET scans. Cardiovascular disease is most treatable when detected in its early stages (51). People with schizophrenia have a lower ability to express pain, making diagnosing CVD more difficult (33).

Treatments

Various treatment options are present for cardiovascular diseases. Transcatheter intervention in heart valve disease, minimally invasive cardiac surgery, or a hybrid approach in coronary artery disease and structural heart disease (aortic, mitral and tricuspid valves) are the current primary treatment methods used in interventional cardiology and cardiac surgery (51). As new treatments are being developed, patients who are at high or prohibitive risk for surgery can be treated with modern transcatheter techniques, and patients for which surgery is highly risky or prohibitively risky can qualify for transcatheter aortic valve implantation (TAVI) or transcatheter mitral valve implantation (TMVI) as treatment (50). Additionally, statins can be used to control cholesterol levels, which can reduce LDL levels, reducing the risk of developing CVD (52).

Also, a randomized clinical study conducted by Riera-Molist et al. on participants who are 18 years and older, using a primary care team for health check-ups, found that a multidisciplinary intervention strategy that is multifactorial and patient-centered is effective in lessening cardiovascular risk (CVR). Within 6 months, by improving LDL levels through improving diet and using statins as needed, the CVR for schizophrenia patients lowered by 20.9% (52). This also worked for people who are young and/or have a low CVR (53).

V. Discussion: Integration of Literature Review

Interplay between Diabetes and CVD in Schizophrenic Patients

Schizophrenia increases the risk for both diabetes and CVD. The symptoms of schizophrenia can cause depression. Co-morbid conditions of depression include obesity, risk factors for poor diet in CVD and diabetes.

Being antipsychotic naive can also increase diabetes and CVD as shown by the study, which found that fasting glucose levels were higher for schizophrenia patients before taking

antipsychotics than after (20). The link between not taking antipsychotics and a higher risk of developing diabetes, as shown by the study conducted by Subramaniam et al., has been found to increase with age (28). For cardiovascular disease, a study conducted on people with schizophrenia aged 20-40 years and separated by adherence to antipsychotics, found that CVD was less prevalent in those who adhered to taking antipsychotics than in those who did not (49).

However, antipsychotics must be taken cautiously as all antipsychotics cause weight gain as shown by the study conducted by Sudar et al. (31). Antipsychotics have also been shown to lower insulin sensitivity (19). This can lead to type 2 diabetes, and/or CVD. Hence, it is important to stay active, and have a healthy diet, and have routine primary healthcare even when on antipsychotics.

Medication Management

Diabetes

To treat diabetes in patients with schizophrenia, screening for diabetes should be done every three months once the patient starts taking antipsychotics and can gradually be reduced to every six to twelve months, HbA1c would be better than a fasting blood sugar test; screening for co-morbid illnesses, like obstructive sleep apnea, tobacco dependence, and hypertension; weight management is important. Taking an antipsychotic with a lower risk of weight gain, developing diabetes, and psychotropic effects, such as sexual dysfunction and gastroparesis that can make symptoms and/or complications of diabetes worse, and getting bariatric surgery if eligible and needed (18). Insulin and other medication should be titrated as per the need of the individual patient. There would also need to be more frequent checks for insulin and wounds.

Cardiovascular Disease

Weight management, being active, eating healthy, reducing smoking, and taking medications are important to treating CVD in schizophrenics. Also as the study conducted by Riera-Molist found, a multidisciplinary intervention that is patient-centered and multifactorial is effective at reducing the risk of developing cardiovascular disease through reducing LDL levels by rectifying diet and using statins when necessary (52).

Importance of taking antipsychotics

It is important to take antipsychotics even though they can cause weight gain or insulin resistance, because they will control schizophrenia symptoms. By not taking antipsychotics, schizophrenia symptoms can worsen. This can lead to further cognitive impairment., unhealthy lifestyle choices and habits such as smoking and drinking. Hence, increasing the risk of developing diabetes or CVD. In addition, based on the study conducted by Ryan et al., the risk of developing diabetes increases with age, especially if antipsychotics are not taken (20).

Barriers to integrated care and prevention

It can be difficult to prevent and care for diabetes and CVD in schizophrenia patients, because schizophrenics are not good with taking their medications because of their schizophrenia causing cognitive impairment, leading to a constant need for assistance to take medications, especially pills. Additionally, they struggle with properly communicating their symptoms, so diagnosis itself can be a challenge. However, it can be effectively managed if someone, such as family or a caretaker is educated about the illness and can take care of weight management, diet, blood pressure, and medications for the schizophrenic patient (18). Nevertheless, many patients do not have support from a caretaker given their symptoms. Hence, it is difficult for schizophrenia patients to effectively manage their symptoms.

Role of lifestyle interventions and integrated behavioral-physical healthcare

This has helped schizophrenics with their symptoms, and has caused them to be more active, reducing the chance of weight gain and insulin resistance that can cause diabetes and cardiovascular disease.

Public Health and Policy Considerations

It should be considered that antipsychotics, especially SGAs, can induce weight gain and insulin resistance. Hence, physicians should consider giving antipsychotics that have a lower chance of causing weight gain and/or insulin resistance. Additionally, schizophrenia patients tend to have a hard time with adhering to their medications, so it should be part of policy for physicians to educate caretakers to properly monitor the medications. Moreover, increasing access to somatic healthcare should be a priority. This can be done by identifying local health care barriers (which can persist both in the organization of the services as well as in the minds of politicians, directors, professionals, and patients) and reducing them (48).

VII. Conclusion

This paper discussed the relationship between schizophrenia, diabetes, and cardiovascular disease. It has been found that people with schizophrenia are more prone to developing diabetes and cardiovascular disease and that people with schizophrenia experience more complications from diabetes and cardiovascular disease. It is important to take antipsychotics to prevent the development of diabetes or CVD from not taking antipsychotics. However, antipsychotics must be taken cautiously because of their ability to cause weight gain and insulin resistance. Physical activity, having a healthy diet, and not smoking or drinking can reduce the risk of developing diabetes or CVD.

It is important to educate caretakers of schizophrenia and its effects on physical health. This will allow caretakers to know how to take better care of their schizophrenia patient, which can reduce the risk of the schizophrenia patient developing diabetes and/or CVD. It is important to



advocate for systemic reform for the care of people with schizophrenia, so that they can get better treatment.

References

1. Luvsannyam, E., Jain, M. S., Pormento, M. K. L., Siddiqui, H., Balagtas, A. R. A., Emuze, B. O., & Poprawski, T. (2022). Neurobiology of Schizophrenia: A Comprehensive Review. *Cureus*, 14(4), e23959. <https://doi.org/10.7759/cureus.23959>
2. Rahman, T., & Lauriello, J. (2016). Schizophrenia: An Overview. *Focus (American Psychiatric Publishing)*, 14(3), 300–307. <https://doi.org/10.1176/appi.focus.20160006>
3. Fatemi, S. H., & Folsom, T. D. (2009). The neurodevelopmental hypothesis of schizophrenia, revisited. *Schizophrenia bulletin*, 35(3), 528–548. <https://doi.org/10.1093/schbul/sbn187>
4. Campbell, R. K. (2009). Type 2 diabetes: where we are today: an overview of disease burden, current treatments, and treatment strategies. *Journal of the American Pharmacists Association*, 49(5), S3-S9.
5. Zimmet, P. Z., Magliano, D. J., Herman, W. H., & Shaw, J. E. (2014). Diabetes: a 21st century challenge. *The lancet. Diabetes & endocrinology*, 2(1), 56–64. [https://doi.org/10.1016/S2213-8587\(13\)70112-8](https://doi.org/10.1016/S2213-8587(13)70112-8)
6. Roglic, Gojka. WHO Global report on diabetes: A summary. *International Journal of Noncommunicable Diseases* 1(1):p 3-8, Apr–Jun 2016. | DOI: 10.4103/2468-8827.184853
7. Lusis A. J. (2000). Atherosclerosis. *Nature*, 407(6801), 233–241. <https://doi.org/10.1038/35025203>
8. Adhikary, D., Barman, S., Ranjan, R., & Stone, H. (2022). A Systematic Review of Major Cardiovascular Risk Factors: A Growing Global Health Concern. *Cureus*, 14(10), e30119. <https://doi.org/10.7759/cureus.30119>
9. Betensky, J. D., Robinson, D. G., Gunduz-Bruce, H., Sevy, S., Lencz, T., Kane, J. M., Malhotra, A. K., Miller, R., McCormack, J., Bilder, R. M., & Szeszko, P. R. (2008). Patterns of stress in schizophrenia. *Psychiatry research*, 160(1), 38–46. <https://doi.org/10.1016/j.psychres.2007.06.001>
10. Kesby, J. P., Eyles, D. W., McGrath, J. J., & Scott, J. G. (2018). Dopamine, psychosis and schizophrenia: the widening gap between basic and clinical neuroscience. *Translational psychiatry*, 8(1), 30. <https://doi.org/10.1038/s41398-017-0071-9>
11. Degenhardt, L., Hall, W., & Lynskey, M. (2003). Testing hypotheses about the relationship between cannabis use and psychosis. *Drug and alcohol dependence*, 71(1), 37–48. [https://doi.org/10.1016/s0376-8716\(03\)00064-4](https://doi.org/10.1016/s0376-8716(03)00064-4)
12. Casadio, P., Fernandes, C., Murray, R. M., & Di Forti, M. (2011). Cannabis use in young people: the risk for schizophrenia. *Neuroscience and biobehavioral reviews*, 35(8), 1779–1787. <https://doi.org/10.1016/j.neubiorev.2011.04.007>
13. Hickman, M., Vickerman, P., Macleod, J., Kirkbride, J., & Jones, P. B. (2007). Cannabis and schizophrenia: Hickman, M., Vickerman, P., Macleod, J., Kirkbride, J., & Jones, P. B.

- (2007). Cannabis and schizophrenia: model projections of the impact of the rise in cannabis use on historical and future trends in schizophrenia in England and Wales. *Addiction* (Abingdon, England), 102(4), 597–606.
<https://doi.org/10.1111/j.1360-0443.2006.01710.x>
14. Buckley, P. F., Miller, B. J., Lehrer, D. S., & Castle, D. J. (2009). Psychiatric comorbidities and schizophrenia. *Schizophrenia bulletin*, 35(2), 383–402.
<https://doi.org/10.1093/schbul/sbn135>
15. Bystritsky, A., Kerwin, L., Niv, N., Natoli, J. L., Abrahami, N., Klap, R., Wells, K., & Young, A. S. (2010). Clinical and subthreshold panic disorder. *Depression and anxiety*, 27(4), 381–389. <https://doi.org/10.1002/da.20622>
16. Morgan, C., & Fisher, H. (2007). Environment and schizophrenia: environmental factors in schizophrenia: childhood trauma--a critical review. *Schizophrenia bulletin*, 33(1), 3–10.
<https://doi.org/10.1093/schbul/sbl053>
17. D'Souza RS, Aslam SP, Hooten WM. Extrapyramidal Side Effects. [Updated 2025 Jan 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK534115/>
18. Annamalai, A., & Tek, C. (2015). An overview of diabetes management in schizophrenia patients: office based strategies for primary care practitioners and endocrinologists. *International journal of endocrinology*, 2015, 969182. <https://doi.org/10.1155/2015/969182>
19. Suvisaari, J., Keinänen, J., Eskelinen, S., & Mantere, O. (2016). Diabetes and Schizophrenia. *Current diabetes reports*, 16(2), 16.
<https://doi.org/10.1007/s11892-015-0704-4>
20. Ryan, M. C., Collins, P., & Thakore, J. H. (2003). Impaired fasting glucose tolerance in first-episode, drug-naïve patients with schizophrenia. *The American journal of psychiatry*, 160(2), 284–289. <https://doi.org/10.1176/appi.ajp.160.2.284>
21. Holt, R. I., Bushe, C., & Citrome, L. (2005). Diabetes and schizophrenia 2005: are we any closer to understanding the link?. *Journal of psychopharmacology* (Oxford, England), 19(6 Suppl), 56–65. <https://doi.org/10.1177/0269881105058379>
22. Chien, I. C., Hsu, J. H., Lin, C. H., Bih, S. H., Chou, Y. J., & Chou, P. (2009). Prevalence of diabetes in patients with schizophrenia in Taiwan: a population-based National Health Insurance study. *Schizophrenia research*, 111(1-3), 17–22.
<https://doi.org/10.1016/j.schres.2009.04.003>
23. Bresee, L. C., Majumdar, S. R., Patten, S. B., & Johnson, J. A. (2010). Prevalence of cardiovascular risk factors and disease in people with schizophrenia: a population-based study. *Schizophrenia research*, 117(1), 75–82.
<https://doi.org/10.1016/j.schres.2009.12.016>
24. Ratliff, J. C., Palmese, L. B., Reutenauer, E. L., Liskov, E., Grilo, C. M., & Tek, C. (2012). The effect of dietary and physical activity pattern on metabolic profile in individuals with schizophrenia: a cross-sectional study. *Comprehensive psychiatry*, 53(7), 1028–1033.
<https://doi.org/10.1016/j.comppsy.2012.02.003>

25. Brown, S., Birtwistle, J., Roe, L., & Thompson, C. (1999). The unhealthy lifestyle of people with schizophrenia. *Psychological medicine*, 29(3), 697–701.
<https://doi.org/10.1017/s0033291798008186>
26. Strassnig, M., Brar, J. S., & Ganguli, R. (2003). Nutritional assessment of patients with schizophrenia: a preliminary study. *Schizophrenia bulletin*, 29(2), 393–397.
<https://doi.org/10.1093/oxfordjournals.schbul.a007013>
27. Zhuo, C., Zhang, Q., Wang, L., Ma, X., Li, R., Ping, J., Zhu, J., Tian, H., & Jiang, D. (2024). Insulin Resistance/Diabetes and Schizophrenia: Potential Shared Genetic Factors and Implications for Better Management of Patients with Schizophrenia. *CNS drugs*, 38(1), 33–44. <https://doi.org/10.1007/s40263-023-01057-w>
28. Subramaniam M, Chong SA, Pek E. Diabetes mellitus and impaired glucose tolerance in patients with schizophrenia. *Can J Psychiatry*. 2003;48:345–347. doi: 10.1177/070674370304800512.
29. Dayabandara, M., Hanwella, R., Ratnatunga, S., Seneviratne, S., Suraweera, C., & de Silva, V. A. (2017). Antipsychotic-associated weight gain: management strategies and impact on treatment adherence. *Neuropsychiatric disease and treatment*, 13, 2231–2241.
<https://doi.org/10.2147/NDT.S113099>
30. Simpson, M. M., Goetz, R. R., Devlin, M. J., Goetz, S. A., & Walsh, B. T. (2001). Weight gain and antipsychotic medication: differences between antipsychotic-free and treatment periods. *The Journal of clinical psychiatry*, 62(9), 694–700.
<https://doi.org/10.4088/jcp.v62n0906>
31. Sudar, F. P., Zekerallah, S. S., Paulzen, M., Mathiak, K., & Gaebler, A. J. (2025). Unraveling antipsychotic induced weight gain in schizophrenia—A proof-of-concept study exploring the impact of the cumulative historical occupancy of different receptors by antipsychotics. *Psychiatry Research*, 348, 116452.
32. Teff, K. L., Rickels, M. R., Grudziak, J., Fuller, C., Nguyen, H. L., & Rickels, K. (2013). Antipsychotic-induced insulin resistance and postprandial hormonal dysregulation independent of weight gain or psychiatric disease. *Diabetes*, 62(9), 3232–3240.
<https://doi.org/10.2337/db13-0430>
33. Kallur, A., Yoo, E., Bien-Aime, F., & Ammar, H. (2022). Diagnostic Overshadowing and Pain Insensitivity in a Schizophrenic Patient With Perforated Duodenal Ulcer. *Cureus*, 14(2), e21800. <https://doi.org/10.7759/cureus.21800>
34. Anderson, K. K., & Kurdyak, P. (2017). Factors Associated with Timely Physician Follow-up after a First Diagnosis of Psychotic Disorder. *Canadian journal of psychiatry. Revue canadienne de psychiatrie*, 62(4), 268–277.
<https://doi.org/10.1177/0706743716673322>
35. Gorczynski, P., Firth, J., Stubbs, B., Rosenbaum, S., & Vancampfort, D. (2017). Are people with schizophrenia adherent to diabetes medication? A comparative meta-analysis. *Psychiatry research*, 250, 17–24.
<https://doi.org/10.1016/j.psychres.2017.01.049>

36. Ali, S., Santomauro, D., Ferrari, A. J., & Charlson, F. (2023). Schizophrenia as a risk factor for cardiovascular and metabolic health outcomes: a comparative risk assessment. *Epidemiology and psychiatric sciences*, 32, e8.
<https://doi.org/10.1017/S2045796023000045>
37. Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., Charlson, F. J., Norman, R. E., Flaxman, A. D., Johns, N., Burstein, R., Murray, C. J., & Vos, T. (2013). Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet* (London, England), 382(9904), 1575–1586. [https://doi.org/10.1016/S0140-6736\(13\)61611-6](https://doi.org/10.1016/S0140-6736(13)61611-6)
38. Vigo, D., Thornicroft, G., & Atun, R. (2016). Estimating the true global burden of mental illness. *The lancet. Psychiatry*, 3(2), 171–178.
[https://doi.org/10.1016/S2215-0366\(15\)00505-2](https://doi.org/10.1016/S2215-0366(15)00505-2)
39. Jindal, R., MacKenzie, E. M., Baker, G. B., & Yeragani, V. K. (2005). Cardiac risk and schizophrenia. *Journal of psychiatry & neuroscience : JPN*, 30(6), 393–395.
40. DE Hert, M., Schreurs, V., Vancampfort, D., & VAN Winkel, R. (2009). Metabolic syndrome in people with schizophrenia: a review. *World psychiatry : official journal of the World Psychiatric Association (WPA)*, 8(1), 15–22.
<https://doi.org/10.1002/j.2051-5545.2009.tb00199.x>
41. Castle, D., & Li, A. (2023). Physical health monitoring for people with schizophrenia. *Australian prescriber*, 46(4), 75–79. <https://doi.org/10.18773/austprescr.2023.024>
42. Smith, D. J., Langan, J., McLean, G., Guthrie, B., & Mercer, S. W. (2013). Schizophrenia is associated with excess multiple physical-health comorbidities but low levels of recorded cardiovascular disease in primary care: cross-sectional study. *BMJ open*, 3(4), e002808. <https://doi.org/10.1136/bmjopen-2013-002808>
43. Mueser, K. T., & McGurk, S. R. (2004). Schizophrenia. *Lancet* (London, England), 363(9426), 2063–2072. [https://doi.org/10.1016/S0140-6736\(04\)16458-1](https://doi.org/10.1016/S0140-6736(04)16458-1)
44. Jarvis G. E. (2007). The social causes of psychosis in North American psychiatry: a review of a disappearing literature. *Canadian journal of psychiatry. Revue canadienne de psychiatrie*, 52(5), 287–294. <https://doi.org/10.1177/070674370705200503>
45. Agerbo, E., Byrne, M., Eaton, W. W., & Mortensen, P. B. (2004). Marital and labor market status in the long run in schizophrenia. *Archives of general psychiatry*, 61(1), 28–33.
<https://doi.org/10.1001/archpsyc.61.1.28>
46. First, M. B., & Tasman, A. (2004). DSM-IV-TR mental disorders: Diagnosis, etiology, and treatment. (No Title).
47. Green M. F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia?. *The American journal of psychiatry*, 153(3), 321–330.
<https://doi.org/10.1176/ajp.153.3.321>
48. Ringen, P. A., Engh, J. A., Birkenaes, A. B., Dieset, I., & Andreassen, O. A. (2014). Increased mortality in schizophrenia due to cardiovascular disease - a non-systematic

- review of epidemiology, possible causes, and interventions. *Frontiers in psychiatry*, 5, 137. <https://doi.org/10.3389/fpsyt.2014.00137>
49. Chang, J., Kim, J. A., Kim, K., Choi, S., Kim, S. M., Nam, Y. Y., Park, S., Goo, A. J., & Park, S. M. (2020). Association of antipsychotics adherence and cardiovascular disease among newly diagnosed schizophrenia patients: A national cohort among Koreans. *Asian journal of psychiatry*, 52, 102161. <https://doi.org/10.1016/j.ajp.2020.102161>
50. Andor, M., Dehelean, L., Arnăutu, D. A., Neagu, M. N., Nistor, D., Manea, M. M., Romosan, A. M., & Kundnani, N. R. (2024). Schizophrenia and Heart Health: Are Antipsychotics a Friend or Foe?. *Journal of personalized medicine*, 14(8), 814. <https://doi.org/10.3390/jpm14080814>
51. Samanidis, G. (2024). Current Challenges in Diagnosis and Treatment of Cardiovascular Disease. *Journal of Personalized Medicine*, 14(8), 786. <https://doi.org/10.3390/jpm14080786>
52. Riera-Molist, N., Assens-Tauste, M., Roura-Poch, P., Guimerà-Gallent, M., Santos-López, J. M., Serra-Millas, M., Frau-Rosselló, N., Gallego-Peña, E., & Foguet-Boreu, Q. (2023). A Cardiovascular Risk Optimization Program in People With Schizophrenia: A Pilot Randomized Controlled Clinical Trial. *Journal of psychiatric practice*, 29(6), 456–468. <https://doi.org/10.1097/PRA.0000000000000743>
53. Wang, N., Fulcher, J., Abeysuriya, N., Park, L., Kumar, S., Di Tanna, G. L., Wilcox, I., Keech, A., Rodgers, A., & Lal, S. (2020). 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. *The lancet. Diabetes & endocrinology*, 8(1), 36–49. [https://doi.org/10.1016/S2213-8587\(19\)30388-2](https://doi.org/10.1016/S2213-8587(19)30388-2)