



Diabetes mellitus

Introduction

People with schizophrenia are often reported to have increased rates of co-occurring illnesses, including diabetes mellitus. Diabetes is a state of impaired insulin function, either as a result of reduced insulin production (type I diabetes) or reduced insulin responsiveness (type II diabetes). Insulin regulates blood glucose levels, and reduced insulin function effectively increases blood glucose levels (hyperglycaemia). This is a dangerous state in the long term, and can ultimately damage the retina, kidneys, nerves and blood vessels. Consequently, effective management of diabetes is crucial.

It is unclear if any increased risk in people with schizophrenia is purely a consequence of biological risk, the metabolic impact of antipsychotic administration, or unhealthy lifestyle choices, but it is likely a combination of many factors.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis¹. Reviews rated as

having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomized controlled trials (RCTs) may be downgraded to moderate, or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)². The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found seven systematic reviews that met our inclusion criteria³⁻⁹.

- Moderate quality evidence shows people with multi-episode schizophrenia have



Diabetes mellitus

increased rates of diabetes compared to age and gender-matched population controls, although when type 1 diabetes was assessed separately, there were no increases found.

- People with multi-episode schizophrenia have similar rates of diabetes as people with first-episode psychosis (9.5% vs. 8.7%), while drug naïve patients have slightly lower rates (6.4%).
- High quality evidence finds small effects of more impaired global cognition and memory, and a medium-sized effect of more impaired processing speed in people with schizophrenia and diabetes compared to people with schizophrenia without diabetes.
- Moderate to high quality evidence suggests second generation antipsychotics clozapine, olanzapine, risperidone and quetiapine may be associated with a small increased risk of diabetes mellitus when compared to first generation antipsychotics.
- Moderate to high quality evidence suggests a small effect of greater adherence to diabetes medication in people with schizophrenia than in people without schizophrenia (approximately 17 more days per year).
- Moderate quality evidence suggests access to treatments for diabetes was not significantly different for people with schizophrenia.



Diabetes mellitus

Bora E, Akdede BB, Alptekin K

The relationship between cognitive impairment in schizophrenia and metabolic syndrome: a systematic review and meta-analysis

Psychological Medicine 2017; 47: 1030-40

[View review abstract online](#)

Comparison	Cognitive functioning in people with schizophrenia and diabetes vs. people with schizophrenia without diabetes.
Summary of evidence	High quality evidence (large samples, consistent, precise, direct,) suggests small effects of more impaired global cognition and memory, and a medium-sized effect of more impaired processing speed in people with schizophrenia and diabetes.
Cognitive functioning	
<p><i>Significant, small to medium-sized effects of more impaired cognition in people with schizophrenia and diabetes;</i></p> <p>Global cognition: 6 studies, N = 2,897, $d = 0.28$, 95%CI 0.18 to 0.38, $p < 0.001$, $I^2 = 0\%$, $p = 0.89$ Memory: 5 studies, N = 2,480, $d = 0.22$, 95%CI 0.12 to 0.33, $p < 0.001$, $I^2 = 0\%$, $p = 0.39$ Processing speed: 5 studies, N = 2,480, $d = 0.44$, 95% CI 0.3 to 0.55, $p < 0.001$, $I^2 = 0\%$, $p = 0.49$</p> <p>The effect size for global cognition was similar in the subgroup analyses of studies that were matched for gender ($d = 0.30$), and in studies that included only people with type 2 diabetes ($d = 0.27$).</p> <p>Authors report no evidence of publication bias.</p>	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Cullen AE, Holmes S, Pollak TA, Blackman G, Joyce DW, Kempton MJ, Murray RM, McGuire P, Mondelli V

Associations between non-neurological autoimmune disorders and



Diabetes mellitus

psychosis: a meta-analysis

Biological Psychiatry 2019; 85: 35-48

[View review abstract online](#)

Comparison	Rates of diabetes in people with schizophrenia or other psychotic disorders vs. controls.
Summary of evidence	Moderate quality evidence (large sample, inconsistent, imprecise, direct) finds no increases in rates of type 1 diabetes in people with schizophrenia or other psychotic disorders.
Type 1 diabetes	
<i>No significant differences between groups;</i> 8 population-level studies, OR = 0.79, 95%CI 0.43 to 1.46, $p = 0.46$, $I^2 = 97%$, $p < 0.001$	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Gorczyński P, Firth J, Stubbs B, Rosenbaum S, Vancampfort D

Are people with schizophrenia adherent to diabetes medication? A comparative meta-analysis

Psychiatry Research 2017; 250: 17-24

[View review abstract online](#)

Comparison	Rates of adherence to diabetes medication in people with schizophrenia compared to people without schizophrenia.
Summary of evidence	Moderate to high quality evidence (large sample size, inconsistent, precise, direct) suggests a small effect of more adherence to diabetes medication in people with schizophrenia than people without schizophrenia.
Adherence to diabetes medication	
<i>More people with schizophrenia adhered to diabetes medication than those without schizophrenia;</i>	



Diabetes mellitus

10 studies, N = 33,680, OR = 1.34, 95%CI 1.18 to 1.52, $p < 0.01$

People with schizophrenia adhered to medication on 77.3% of days prescribed;

7 studies, N = 32,080, 95%CI 73.6% to 81%, $I^2 = 99%$

People with schizophrenia adhered to medication on 4.6% more days per year than those without schizophrenia;

4 studies, N = 190,220, 95%CI 2.4% to 6.7%, $p < 0.01$, $I^2 = 92%$

Equating to approximately 17 more days per year adherent to medication.

Factors associated with diabetes medication adherence were older age, number of outpatient visits, along with multiple medication administration variables.

Consistency in results	Inconsistent where reported.
Precision in results	Precise for OR.
Directness of results	Direct

Mitchell AJ, Malone D, Doebbeling CC

Quality of medical care for people with and without comorbid mental illness and substance misuse: systematic review of comparative studies

The British Journal of Psychiatry 2009; 194: 491-499

[View review abstract online](#)

Comparison	<p>Quality of medical care for comorbid diabetes in people with schizophrenia.</p> <p>Note: results are reported only for defined schizophrenia spectrum disorder samples presented separately to other psychiatric illnesses.</p>
Summary of evidence	<p>Moderate quality evidence (medium to large samples, unable to assess consistency or precision, direct) suggests access to treatments for diabetes was not significantly different for people with schizophrenia.</p>
Quality of medical care for diabetes	
<p><i>Quality of care reported for various comorbid conditions in people with schizophrenia;</i></p> <p>One study (N = 200) reported on the quality of general medical care (assessed as self-reported service use and perceived barriers, compared to healthy controls from national survey data) and</p>	

found that compared to controls, people with schizophrenia were more likely to have visited a doctor (OR = 2.00); had a full physical exam (OR = 2.69); but less likely to visit a dentist (OR = 0.46).

Patients were more likely to report perceived barriers to medical care (OR > 3).

One study (N = 199) reported on the quality of medical care for diabetes in schizophrenia spectrum compared to non-psychiatric control with diabetes, and found that patients with schizophrenia were less likely to receive diabetes education ($p = 0.002$). People with schizophrenia had significantly better levels of a diabetes health marker (HbA_{1c}) than controls ($p < 0.01$). There was no difference in the number of outpatient visits, emergency visits or hospitalisations.

One study (N = 3,808), including 214 with a schizophrenia spectrum disorder, reported on the quality of medical care for diabetes in schizophrenia spectrum compared to non-psychiatric control, and found that people with schizophrenia were slightly more likely than control to be on insulin therapy (OR = 1.44, $p = 0.08$, not significant). Those with schizophrenia were significantly more likely to receive an older treatment prescription for hyperlipidaemia (OR = 1.85, $p < 0.05$) and be referred for nutritional counselling. People with schizophrenia were significantly more likely to miss at least one outpatient appointment ($p < 0.001$).

One study (N = 11,043) included 705 schizophrenia patients compared to bipolar disorder and non-psychiatric controls with diabetes, and found that those with mental illness were more likely to have better levels of a diabetes health marker (HbA_{1c}) than controls (no statistics reported).

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Smith M, Hopkins D, Peveler RC, Holt RIG, Woodward M, Ismail K

First- v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis

The British Journal of Psychiatry, 2008; 192: 406-411

[View review abstract online](#)

Comparison	First generation vs. second generation antipsychotics.
Summary of evidence	Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests second generation antipsychotics clozapine, olanzapine, risperidone and quetiapine may be associated with a small increased risk of diabetes mellitus when compared to any first generation antipsychotic.
Diabetes	



Diabetes mellitus

11 observational studies (N ~87,000) with median duration of follow-up of 12 months, showed a small increased risk of diabetes mellitus in patients prescribed second generation antipsychotics clozapine, olanzapine, risperidone or quetiapine vs. any first generation antipsychotic;

All antipsychotics: 11 studies, RR = 1.32, 95%CI 1.15 to 1.51, $p < 0.05$, $I^2 = 80%$, $p < 0.001$

Risperidone: 6 studies, RR = 1.16, 95%CI 0.99 to 1.35, $p = 0.05$, I^2 not reported

Quetiapine: 3 studies, RR = 1.28, 95%CI 1.14 to 1.45, $p < 0.05$, I^2 not reported

Olanzapine: 8 studies, RR = 1.28, 95%CI 1.12 to 1.45, $p < 0.05$, I^2 not reported

Clozapine: 7 studies, RR = 1.39, 95%CI 1.24 to 1.55, $p < 0.05$, I^2 not reported

Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Vancampfort D, Wampers M, Mitchell AJ, Correll CU, De Hert A, Probst M, De Hert A

A meta-analysis of cardio-metabolic abnormalities in drug naive, first-episode and multi-episode patients with schizophrenia versus general population controls

World Psychiatry 2013; 12: 240-250

[View review abstract online](#)

Comparison	Rates of diabetes in people with chronic schizophrenia vs. age and gender-matched population controls, and vs. patients with first-episode schizophrenia or those who are drug-naïve.
Summary of evidence	Moderate quality evidence (large samples, inconsistent, mostly imprecise, direct) suggests people with chronic schizophrenia have increased rates of diabetes compared to age and gender-matched population controls, with similar rates in first-episode patients (9.5% vs. 8.7%). Drug naïve patients had lower rates of diabetes (6.4%).

Diabetes

Patients with multi-episode schizophrenia were at increased risk for diabetes compared to matched population controls;



Diabetes mellitus

15 studies, N = 3,998,469, OR = 1.99, 95%CI 1.55 to 2.54, $p < 0.001$, $Q = 3718.8$, $p < 0.001$

Multi-episode patients (N = 116,751; 9.5%) had similar rates of diabetes as first-episode (N = 1,033; 8.7%) and drug-naïve patients (N = 346; 6.4%), $p = 0.56$.

Consistency in results	Inconsistent
Precision in results	Precise for hypertension only
Directness of results	Direct

Vancampfort D, Correll CU, Galling B, Probst M, De Hert M, Ward PB, Rosenbaum S, Gaughran F, Lally J, Stubbs B

Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis

World Psychiatry 2016; 15(2): 166-174

[View review abstract online](#)

Comparison	Risk of type 2 diabetes in people with schizophrenia vs. controls and vs. schizophrenia spectrum disorders (schizoaffective disorder, schizophreniform disorder, related psychoses), bipolar disorder, and major depressive disorder.
Summary of evidence	Moderate quality evidence (large samples, some inconsistency, imprecise, direct) suggests a medium-sized effect of increased risk of type 2 diabetes in people with multi-episode, but not first-episode, schizophrenia compared to controls, with no differences compared to people with bipolar disorder or major depressive disorder.

Type 2 diabetes

A medium-sized, significant effect suggests patients with schizophrenia are at increased risk of type 2 diabetes compared to controls;

29 studies, N = 115,538, RR = 2.04, 95%CI 1.69 to 2.49, $p < 0.001$, $I^2 = 97.8\%$, $p < 0.001$

A small, significant effect suggests patients with bipolar disorder are at increased risk of type 2 diabetes compared to controls;

6 studies, N = 54,688, RR = 1.89, 95%CI 1.29 to 2.77, $p < 0.001$, $I^2 = 7.3\%$, $p = 0.34$

A small, significant effect suggests patients with major depressive disorder are at increased risk of type 2 diabetes compared to controls;



Diabetes mellitus

3 studies, N = 10,895, RR = 1.43, 95%CI 0.88 to 2.25, $p = 0.029$, (I^2 not reported), Q-value for $I^2 = 2.15$, $p = 0.34$

A small, significant effect suggests patients with multi-episode schizophrenia are at increased risk of type 2 diabetes compared to controls;

38 studies, N = 5,756,134, RR = 1.85, 95%CI 1.45 to 2.37, $p < 0.001$, (I^2 not reported), Q-value for $I^2 = 1302.0$, $p < 0.001$

There were no significant differences in risk of type 2 diabetes between patients with first-episode schizophrenia and controls;

3 studies, N not reported, RR = 4.64, 95%CI 0.73 to 29.3, $p = 0.10$, (I^2 and Q-value not reported), p for $I^2 = 0.23$

There were no significant differences in risk of type 2 diabetes between patients with schizophrenia and patients with schizophrenia spectrum disorders;

3 studies, N = 60,657, OR = 0.80, 95%CI 0.52 to 1.25, $p = 0.33$, $I^2 = 24.9\%$, $p = 0.26$

There were no significant differences in risk of type 2 diabetes between patients with schizophrenia and patients with bipolar disorder;

6 studies, N = 109,143, OR = 1.22, 95%CI 0.84 to 1.77, $p = 0.28$, $I^2 = 70.8\%$, $p = 0.004$

There were no significant differences in risk of type 2 diabetes between patients with schizophrenia and patients with depressive disorder;

2 studies, N = 11,804, OR = 1.27, 95%CI 0.96 to 1.68, $p = 0.10$, $I^2 = 0\%$, $p = 0.80$

Consistency in results	Consistent apart from schizophrenia vs. controls, multi-episode schizophrenia vs. controls, and schizophrenia vs. bipolar disorder.
Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

CI = Confidence Interval, d = Cohen's d standardised mean effect, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RR = relative risk

Diabetes mellitus

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small¹⁰.

† Different effect measures are reported by different reviews.

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if $RR > 2$ or < 0.5 and a large effect if $RR > 5$ or < 0.2 ¹¹. InOR stands for

logarithmic OR where a InOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomized trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardized mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small

Diabetes mellitus

effect, 0.5 a moderate effect, and 0.8 and over represents a large effect¹⁰.

Correlation coefficients (eg, *r*) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforeseen confounding variables. An *r* of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardized (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardized regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from *Q* (chi-square) for the test of heterogeneity with the following formula¹⁰;

$$I^2 = \left(\frac{Q - df}{Q} \right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed¹².

|| Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.



Diabetes mellitus

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADE Working Group (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Mitchell AJ, Malone D, Doebbeling CC (2009): Quality of medical care for people with and without comorbid mental illness and substance misuse: Systematic review of comparative studies. *British Journal of Psychiatry* 194: 491-9.
4. Smith M, Hopkins D, Peveler RC, Holt RI, Woodward M, Ismail K, *et al.* (2008): First- v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. *British Journal of Psychiatry* 192: 406-11.
5. Vancampfort D, Correll C, Galling B, M P, De Hert M, Ward P, *et al.* (2016): Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. *World Psychiatry* 15: 166-74.
6. Vancampfort D, Wampers M, Mitchell A, Correll CU, De Herdt A, Probst M, *et al.* (2013): A meta-analysis of cardio-metabolic abnormalities in drug naive, first-episode and multi-episode patients with schizophrenia versus general population controls. *World Psychiatry* 12: 240-50.
7. 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.
8. Bora E, Akdede BB, Alptekin K (2017): The relationship between cognitive impairment in schizophrenia and metabolic syndrome: a systematic review and meta-analysis. *Psychological Medicine* 47: 1030-40.
9. Cullen AE, Holmes S, Pollak TA, Blackman G, Joyce DW, Kempton MJ, *et al.* (2019): Associations Between Non-neurological Autoimmune Disorders and Psychosis: A Meta-analysis. *Biological Psychiatry* 85: 35-48.
10. Cochrane Collaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
11. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
12. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. Version 3.2 for Windows.