TECHNICAL COMMENTARY

NeuRA Discover. Conquer. Cure.

SCHIZOPHRENIA LIBRARY

Metabolic abnormalities

Introduction

People with schizophrenia often have increased rates of co-occurring disorders, including metabolic syndrome. Metabolic syndrome is a risk factor for diabetes and cardiovascular diseases and is defined as a clustering of at least three abnormalities such as obesity, high blood pressure, high blood triglycerides, low levels of high-density lipoprotein (HDL) cholesterol and insulin resistance. It is unclear if an increased risk of metabolic syndrome is a consequence of the impact of antipsychotic medications or unhealthy lifestyle choices, or most likely, a combination of both.

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-analysis[1]. Reviews rated as having less than 50% or 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 randomised 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 10 systematic reviews that met our inclusion criteria[3-12].

- Moderate quality evidence suggests that the overall prevalence of metabolic syndrome in people with schizophrenia is around 32%. The most consistent predictors of metabolic syndrome are increased waist size, illness duration over 7.8 years, high blood pressure, high triglycerides, high glucose age over 38 years, and low HDL. Smokers and patients receiving clozapine are also at increased risk.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

TECHNICAL COMMENTARY

NeuRA Discover. Conquer. Cure.

SCHIZOPHRENIA LIBRARY

Metabolic abnormalities

- Compared to age and gender-matched population controls, moderate quality evidence suggests people with chronic schizophrenia have increased rates of abdominal obesity, hypertension, hypertriglyceridemia, and low HDL cholesterol.
- Compared to people in their first episode of psychosis and drug-naive patients, medicated patients have increased rates of metabolic syndrome, diabetes, obesity, high triglycerides, low HDL cholesterol, and hyperglycaemia > 100 mg/dl. There were also increased rates of high blood pressure in first-episode patients compared to un-medicated patients, and increased waist size in un-medicated patients compared to first-episode patients.
- Compared to controls, moderate to high quality evidence finds small effects of reduced total and LDL cholesterol, and increased triglycerides in people with first-episode psychosis, with no changes in HDL cholesterol or leptin levels. There was a large effect of more impaired glucose tolerance and more insulin resistance in people with first-episode psychosis, with no differences in fasting plasma glucose.
- Compared to controls, moderate to high quality evidence finds small decreases in total cholesterol, LDL, and HDL, and a small increase in triglycerides in drug-naive people with first-episode psychosis.
- Compared to people with bipolar disorder or major depression, moderate to low quality evidence found no increased in metabolic syndrome in people with schizophrenia.
- High quality evidence finds small effects of more impaired processing speed and executive functioning in people with schizophrenia and metabolic syndrome compared to patients without metabolic syndrome. Moderate to high quality evidence also finds medium-sized effects of more impaired memory and attention, and a small effect of more impaired global cognition in patients with metabolic syndrome.
- Moderate to high quality evidence suggests benefits of lifestyle interventions for improving cardiometabolic parameters of weight, triglycerides, fasting glucose and insulin.
- Moderate to low quality evidence suggests inadequate monitoring of weight, glucose, lipids, cholesterol and diabetes prior to the implementation of guidelines. Blood pressure and triglycerides were suboptimal pre-guidelines. Following the implementation of guidelines, weight and blood pressure monitoring increased to adequate levels, glucose monitoring increased to suboptimal levels, but lipid monitoring remained inadequate. There was not enough data to assess cholesterol, triglycerides and diabetes post-guidelines.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

TECHNICAL COMMENTARY

Metabolic abnormalities

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 metabolic syndrome vs. people with schizophrenia without metabolic syndrome.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct,) suggests small effects of more impaired processing speed and executive functioning in people with schizophrenia and metabolic syndrome. Moderate to high quality evidence (inconsistent) also finds medium-sized effects of more impaired memory and attention, and a small effect of more impaired global cognition.**

Cognitive functioning

Significant, small to medium-sized effects of more impaired cognition in people with schizophrenia and metabolic syndrome;

Global cognition: 6 studies, N = 2,243, d = 0.28, 95%CI 0.12 to 0.44, $p < 0.001$, $I^2 = 59\%$, $p = 0.03$

Memory: 6 studies, N = 2,243, d = 0.39, 95%CI 0.09 to 0.69, $p = 0.01$, $I^2 = 87\%$, $p < 0.01$

Attention: 5 studies, 1,855, d = 0.40, 95%CI 0.12 to 0.68, $I^2 = 80\%$, $p < 0.01$

Processing speed: 6 studies, N = 2,243, d = 0.21, 95% CI 0.13 to 0.30, $p < 0.001$, $I^2 = 0\%$, $p = 0.42$

Executive functioning: 3 studies, 1,558, d = 0.17, 95% CI 0.06 to 0.27, $p = 0.002$, $I^2 = 0\%$, $p = 0.81$

The effect size for global cognition was larger in the subgroup analyses of studies that were matched for gender (d = 0.36) or age and gender (d = 0.35).

Authors report possible publication bias for attention, memory and global cognition, although there were only slight reductions in the effect sizes for global cognition and memory in trim-and-fill analyses.

Consistency in results	Consistent for processing speed and executive functioning only.
Precision in results	Precise
Directness of results	Direct

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Bruins J, Jorg F, Bruggeman R, Slooff C, Corpeleijn E, Pijnenborg M

The effects of lifestyle interventions on (long-term) weight management, cardiometabolic risk and depressive symptoms in people with psychotic disorders: a meta-analysis

PLoS ONE 2014; 9(12): e112276

View review abstract online

Comparison	**Lifestyle interventions (diet, exercise, education) vs. treatment as usual.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests benefits of lifestyle interventions for improving cardiometabolic parameters of weight, triglycerides, fasting glucose and insulin.**

Cardiometabolic parameters

A significant, small effect favouring lifestyle interventions over treatment as usual for improved;

Triglycerides: 8 RCTs, N = 659, SMD = -0.27, 95%CI -0.49 to -0.04, $p = 0.02$, $I^2 = 51\%$

Fasting glucose: 8 RCTs, N = 688, SMD = -0.24, 95%CI -0.32 to -0.10, $p = 0.001$, $I^2 = 0\%$

Insulin: 6 RCTs, N = 481, SMD = -0.28, 95%CI -0.56 to -0.01, $p = 0.04$, $I^2 = 52\%$

Subgroup analysis including only high-quality studies (k = 3) resulted in a non-significant effect size for insulin.

No differences were reported for;

Total cholesterol: 7 RCTs, N = 590, SMD = -0.27, 95%CI -0.59 to 0.05, $p = 0.10$, $I^2 = 72\%$

HDL-cholesterol: 8 RCTs, N = 627, SMD = 0.28, 95%CI -0.16 to 0.73, $p = 0.21$, $I^2 = 91\%$

LDL-cholesterol: 5 RCTs, N = 517, SMD = -0.27, 95%CI -0.75 to 0.22, $p = 0.28$, $I^2 = 87\%$

Systolic blood pressure: 7 RCTs, N = 615, SMD = -0.22, 95%CI -0.49 to 0.05, $p = 0.10$, $I^2 = 60\%$

Diastolic blood pressure: 3 RCTs, N = 171, SMD = -0.08, 95%CI -0.57 to 0.41, $p = 0.74$, $I^2 = 64\%$

Weight loss or prevention of weight gain

A significant, medium-sized effect favouring lifestyle interventions over treatment as usual for;

Weight loss or weight gain prevention: 24 RCTs, N = 1,464, SMD = -0.63, 95%CI -0.84 to -0.42, $p < 0.00001$, $I^2 = 70\%$, $p < 0.00001$

Waist circumference: 10 RCTs, N = 705, SMD = -0.37, 95%CI -0.60 to -0.13, p = 0.002, I^2 = 56% Subgroup analyses including only high quality studies (k = 4), or studies with long-term follow up (k = 7, 2-6 months follow-up) found similar results for weight loss and weight gain prevention, but a non-significant effect size for waist circumference. *Larger effects were reported for weight gain prevention than weight loss;* Weight gain prevention: 8 RCTs, N = 411, SMD -0.84, 95%CI -1.28 to -0.40, p = 0.0002, I^2 = 76%, p = 0.0001 Weight loss: 16 RCTs, N = 1,053, SMD = -0.52, 95%CI -0.72 to -0.31, p < 0.00001, I^2 = 55%, p = 0.004 *Larger effects were reported for individual therapies than group therapies;* Individual intervention: 5 RCTs, N = 201, SMD = -0.67, 95%CI -1.04 to -0.30, p = 0.0004, I^2 = 35%, p = 0.19 Group intervention: 10 RCTs, N = 560, SMD = -0.36, 95%CI -0.60 to -0.13, p = 0.002, I^2 = 42%, p = 0.08

Consistency in results	Inconsistent, apart from individual interventions and fasting glucose.
Precision in results	Precise
Directness of results	Direct

Misiak B, Stanczykiewicz B, Laczmanski L, Frydecka D

Lipid profile disturbances in antipsychotic-naive patients with first-episode non-affective psychosis: A systematic review and meta-analysis

Schizophrenia Research 2017; 190: 18-27

View review abstract online

Comparison	**Metabolic disturbances in antipsychotic-naïve patients with first-episode psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly consistent, precise, direct) finds small decreases in total cholesterol, LDL and HDL levels, and a small increase in triglycerides in patients.**
Lipid profile	

Significant, small decreases in patients in; Total cholesterol: 17 studies, N = 1,604, *g* = -0.16, 95%CI -0.27 to -0.06, *p* = 0.003, I^2 = 17% LDL: 15 studies, N = 1,601, *g* = -0.13, 95%CI -0.24 to -0.01, *p* = 0.034, I^2 = 0% HDL: 17 studies, N = 1,655, *g* = -0.27, 95%CI -0.49 to -0.05, *p* = 0.018, I^2 = 75% *Significant, small increases in patients in;* Triglycerides: 18 studies, N = 1,743, *g* = 0.22, 95%CI 0.11 to 0.32, *p* < 0.001, I^2 = 0% After removing single studies in sensitivity analysis, the estimate for LDL levels was insignificant. There were no moderating effects of age, BMI or cigarette smoking.

Consistency in results	Consistent, apart from HDL.
Precision in results	Precise
Directness of results	Direct

Mitchell AJ, Vancampfort D, De Hert M

Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders – A systematic review and meta-analysis

Schizophrenia Bulletin 2011; doi:10.1093/schbul/sbr148

View review abstract online

Comparison	**Prevalence rates of metabolic syndrome in people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) suggests that the overall prevalence of metabolic syndrome in people with schizophrenia is around 32%.** **The best predictors of high rates of metabolic syndrome in people with schizophrenia include increased waist size, illness duration over 7.8 years, high blood pressure, high triglycerides, high glucose age over 38 years, and low HDL. Smokers and patients receiving clozapine are also at increased risk.**
Metabolic syndrome	

Metabolic abnormalities

Worldwide prevalence of metabolic syndrome in people with schizophrenia

Overall: 126 studies, N = 25,692, 32.5%, 95%CI 30.1% to 35.0%

Subgroup analysis of different measures (ordered highest to lowest)

IDF: 15 studies, N = 1,266, 35.3%, 95%CI 23.1% to 48.6%

ATP III: 80 studies, N = 17,005, 32.8%, 95%CI 30.0% to 35.7%

Adapted ATP: 12 studies, N = 2,716, 28.6%, 95%CI 19.8% to 38.3%

Subgroup analysis of different countries (ordered highest to lowest)

Finland: 5 studies, N = 158, 34.5%, 95%CI 25.4% to 44.2%

United States: 26 studies, N = 7,037, 32.5%, 95%CI 26.6% to 38.7%

Spain: 6 studies, N = 2,187, 30.2%, 95%CI 23.6% to 37.2%

Turkey: 9 studies, N = 702, 30.1%, 95%CI 24.7% to 35.8%

Subgroup analysis of different samples (ordered highest to lowest)

Older participants (≥ 50 years): 14 studies, N = 6,396, 39.2%, 95%CI 32.6% to 46.1%

Neither drug naive nor first-episode schizophrenia: 112 studies, N = 24,892, 35.3%, 95%CI 32.8% to 37.8%

Males: 31 studies, N = 5,789, 34.8%, 95%CI 29.2% to 40.6%

Females: 30 studies, N = 3,794, 34.8%, 95%CI 29.5% to 40.3%

Outpatients: 49 studies, N = 10,680, 31.8%, 95%CI 27.5% to 36.2%

Inpatients: 46 studies, N = 6,770, 30.4%, 95%CI 26.7% to 34.2%

First-episode schizophrenia only: 7 studies, N = 490, 13.0%, 95%CI 7.2% to 20.1%

Drug naive and first-episode schizophrenia: 14 studies, N = 800, 11.3%, 95%CI 7.3% to 16.1%

Subgroup analysis of different comorbid conditions (ordered highest to lowest)

Smokers: 41 studies, N = 8,789, 54.2%, 95%CI 50.9% to 57.5%

Overweight (ATP): 53 studies, N = 14,305, 49.4%, 95%CI 44.8% to 53.3%

Overweight (IDF): 8 studies, N = 263, 44.4%, 95%CI 32.3% to 56.8%

Low high-density lipoprotein cholesterol: 76 studies, N = 19,280, 42.6%, 95%CI 39.3% to 46.0%

Hypertriglyceridemia: 77 studies, N = 19,831, 39.3%, 95%CI 35.0% to 43.6%

High blood pressure: 72 studies, N = 18,657, 38.7%, 95%CI 35.6% to 41.9%

Hyperglycaemia (>110 mg/dl; ATP): 47 studies, N = 13,784, 19.5%, 95%CI 16.9% to 22.2%

Hyperglycaemia (> 100mg/ dl): 28 studies, N = 6,499, 18.8%, 95%CI 15.5% to 22.4%

Diabetes: 14 studies, N = 2,186, 10.9%, 95%CI 7.0% to 15.5%

Subgroup analysis of different antipsychotics using ATP III criteria (ordered highest to lowest)

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Clozapine: 13 studies, N = 673, 51.9%, 95%CI 45.8% to 57.9% Olanzapine: 12 studies, N = 1,056, 28.2%, 95%CI 19.1% to 38.4% Risperidone: 9 studies, N = 659, 27.9%, 95%CI 12.6% to 46.5% Unmedicated: 7 studies, N = 297, 20.2%, 95%CI 15.9% to 24.9% Authors report that the best predictors of metabolic syndrome (rates > 32.8%) in people with schizophrenia include waist size (AUC = 0.828), illness duration (> 7.8 years), high blood pressure, high triglycerides, high glucose and low HDL and age (> 38 years).	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; not a standardised measure.
Directness in results	Direct

Mitchell AJ, Delaffon V, Vancampfort D, Correll CU, De Hert M

Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: systematic review and meta-analysis of screening practices

Psychological Medicine 2012; 42: 125-147

View review abstract online

Comparison	**Rates of routine clinical monitoring/screening for metabolic risk factors in people taking antipsychotic medication, and testing the benefits of introducing screening guidelines on rates.** **< 50% of patients routinely screened = inadequate** **50% to < 70% of patients routinely screened = suboptimal** **70% to < 80% of patients routinely screened = adequate** **80% to < 90% of patients routinely screened = good** **> 90% of patients routinely screened = optimal**
Summary of evidence	**Moderate to low quality evidence (unclear sample sizes, inconsistent, unable to assess precision, direct) suggests inadequate monitoring of weight, glucose, lipids, cholesterol and diabetes prior to the implementation of guidelines. Blood pressure and triglycerides were suboptimal pre-guidelines.** **Following the implementation of guidelines, weight and blood pressure monitoring increased to adequate levels, glucose**

	monitoring increased to suboptimal levels, but lipid monitoring remained inadequate. There was not enough data to assess cholesterol, triglycerides and diabetes post-guidelines.
Weight monitoring	
Inadequate monitoring of weight pre-guidelines; 19 studies, (N = not reported), 47.9%, 95%CI 32.4% to 63.67%, I^2 = 99.6% *Adequate monitoring of weight post-guidelines (28% increase);* 3 studies, (N = not reported), 75.9%, 95%CI 37.3% to 98.7%, I^2 = 99.7%	
Blood pressure	
Suboptimal monitoring of blood pressure pre-guidelines; 14 studies, (N = not reported), 69.8%, 95%CI 50.9% to 85.8%, I^2 = 99.7% *Adequate monitoring of blood pressure post-guidelines (5.4% increase);* 3 studies, (N = not reported), 75.2%, 95%CI 45.6% to 95.5%, I^2 = 99.4%	
Glucose	
Inadequate monitoring of glucose pre-guidelines; 30 studies, (N = not reported), 44.3%, 95%CI 36.3% to 52.4%, I^2 = 99.9% *Suboptimal monitoring of glucose post-guidelines (11.8% increase);* 3 studies, (N = not reported), 56.1%, 95%CI 43.4% to 68.3%, I^2 = 99.8%	
Lipids	
Inadequate monitoring of lipids pre-guidelines; 23 studies, (N = not reported), 22.2%, 95%CI 16.4% to 28.7%, I^2 = 99.8% *Inadequate monitoring of lipids post-guidelines (15% increase);* 3 studies, (N = not reported), 37.2%, 95%CI 23.7% to 51.9%, I^2 = 99.8%	
Cholesterol	
Inadequate monitoring of cholesterol pre-guidelines; 7 studies, (N = not reported), 41.5%, 95%CI 18% to 67.3%, I^2 = 99.5%	
Triglycerides	

Suboptimal monitoring of triglycerides pre-guidelines; 5 studies, (N = not reported), 59.9%, 95%CI 36.6% to 81.1%, I^2 = 98.9%
Diabetes
Inadequate monitoring of diabetes pre-guidelines; 10 studies, (N = not reported), 16.0%, 95%CI 7.5% to 26.9%, I^2 = 99.5%

Consistency in results	Inconsistent
Precision in results	Unable to assess; not a standardised measure.
Directness in results	Direct

Mitchell AJ, Vancampfort D, De Hert A, Yu W, van Winkel R, Yu W, De Hert M

Is the Prevalence of Metabolic Syndrome and Metabolic Abnormalities Increased in Early Schizophrenia? A Comparative Meta-Analysis of First Episode, Untreated and Treated Patients

Schizophrenia Bulletin 2013; 39(2): 295-305

View review abstract online

Comparison	**Prevalence of metabolic syndrome in treated, untreated and first-episode patients.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) suggests increased rates of diabetes, metabolic syndrome, high triglycerides, low HDL, and hyperglycaemia > 100 mg/dl in medicated patients compared to people in their first-episode of psychosis, and compared to un-medicated patients with an established disorder. There was also increased prevalence of high blood pressure in first-episode patients compared to un-medicated patients, and increased waist size in un-medicated patients compared to first-episode patients.**
Metabolic syndrome	

Significantly higher prevalence of metabolic syndrome was reported in medicated patients who were not in their first-episode of psychosis, compared to first-episode patients and un-medicated patients ($p < 0.0001$). No differences were reported between the latter two groups ($p = 0.9755$); Medicated established patients: 78 studies, N = 24,892, 35.3%, 95%CI 32.8% to 37.8% First-episode patients: 14 studies, N = 1,104, 9.9% 95%CI 6.1% to 14.5% Un-medicated patients: 11 studies, N = 702, 9.8%, 95%CI 5.3% to 15.6%
Waist size in males > 102cm, females > 88cm
Significantly higher prevalence of increased waist size was reported in medicated patients who were not in their first-episode of psychosis, compared to first-episode patients and un-medicated patients ($p < 0.0001$). Significantly higher prevalence of increased waist size was reported in un-medicated patients compared to first-episode patients ($p < 0.0072$); Medicated established patients: 58 studies, N = 17,474, 52.7%, 95%CI 48.9% to 56.5% First-episode patients: 17 studies, N = 2,127, 22.0%, 95%CI 15.6% to 29.1% Un-medicated patients: 10 studies, N = 837, 26.6%, 95%CI 15.9% to 38.9%
Blood pressure > 130/85
Significantly higher prevalence of high blood pressure was reported in medicated patients who were not in their first-episode of psychosis, compared to first-episode patients and un-medicated patients ($p < 0.0001$). Significantly higher prevalence of high blood pressure was reported in first-episode patients compared to un-medicated patients ($p < 0.0154$); Medicated established patients: 64 studies, N = 18,202, 39.7%, 95%CI 36.4% to 43.1% First-episode patients: 11 studies, N = 979, 30.4% 95%CI 21.3% to 40.3% Un-medicated patients: 7 studies, N = 454, 24.3%, 95%CI 11.2% to 40.5%
Triglycerides > 150 mg/dl
Significantly higher prevalence of high triglycerides was reported in medicated patients who were not in their first-episode of psychosis, compared to first-episode patients and un-medicated patients ($p < 0.0001$). No differences were reported between the latter two groups ($p = 0.1063$); Medicated established patients: 69 studies, N = 19,388, 41.4%, 95%CI 36.5% to 45.7% First-episode patients: 17 studies, N = 1,950, 19.6% 95%CI 13.1% to 27.0% Un-medicated patients: 9 studies, N = 730, 16.9%, 95%CI 7.6% to 29.0%
HDL in males < 40 mg/dl, females < 50 mg/dl

Significantly higher prevalence of low HDL was reported in medicated patients who were not in their first-episode of psychosis, compared to first-episode patients and unmedicated patients (p < 0.0001). No differences were reported between the latter two groups (p = 0.4043); Medicated established patients: 68 studies, N = 18,837, 44.7%, 95%CI 41.2% to 48.2% First-episode patients: 16 studies, N = 1,950, 21.9% 95%CI 15.6% to 28.9% Un-medicated patients: 9 studies, N = 730, 20.4%, 95%CI 9.8% to 33.7%
Hyperglycaemia > 110 mg/dl
Significantly higher prevalence of hyperglycaemia (> 110 mg/dl) was reported in medicated patients who were not in their first-episode of psychosis, compared to first-episode patients (p < 0.0001); Medicated established patients: 41 studies, N = 13,214, 18.1%, 95%CI 15.5% to 20.7% First-episode patients: 5 studies, N = 240, 6.9% 95%CI 5.0% to 19.9%
Hyperglycaemia >100 mg/dl
Significantly higher prevalence of hyperglycaemia (> 100 mg/dl) was reported in medicated patients who were not in their first-episode of psychosis, compared to first-episode patients and unmedicated patients (p < 0.0001). No differences were reported between the latter two groups (p = 0.162); Medicated established patients: 26 studies, N = 6,798, 27.8%, 95%CI 23.0% to 32.9% First-episode patients: 7 studies, N = 788, 8.7% 95%CI 5.2% to 12.9% Un-medicated patients: 3 studies, N = 390, 6.4%, 95%CI 2.2% to 12.7%
Diabetes
Significantly higher prevalence of diabetes was reported in medicated patients who were not in their first-episode of psychosis, compared to first-episode patients and unmedicated patients (p < 0.0001). No differences were reported between the latter two groups (p = 0.31); Medicated established patients: 12 studies, N = 2,098, 12.8%, 95%CI 8.44% to 17.9% First-episode patients: 9 studies, N = 8,075, 1.3% 95%CI 0.4% to 2.4% Un-medicated patients: 4 studies, N = 7,618, 2.1%, 95%CI 0.5% to 4.8%

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; not a standardised measure.
Directness in results	Direct

Perry BI, McIntosh G, Weich S, Singh S, Rees K

The association between first-episode psychosis and abnormal glycaemic control: systematic review and meta-analysis

Lancet Psychiatry 2016; 3: 1049-58

View review abstract online

Comparison	**Prediabetic markers in drug-naive or drug-free (30 days) people with first-episode psychosis compared to people without a psychiatric and/or physical illness.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, some imprecision, direct) suggests a large effect of more impaired glucose tolerance in people with first-episode psychosis compared to people without a psychiatric and/or physical illness. There may also be more insulin resistance in first-episode patients, with no differences in fasting plasma glucose.**
Prediabetic markers	
People with first-episode psychosis showed more; Impaired glucose tolerance: 7 studies, N = 630, OR = 5.44, 95%CI 2.63 to 11.27, $p < 0.0001$, I^2 = 0% Insulin resistance: 8 studies, N = 681, MD = 0.30, 95%CI 0.18 to 0.42, $p < 0.01$, I^2 = 19% *There were no significant differences in fasting plasma glucose;* 12 studies, N = 1,115, SMD = 0.06, 95%CI -0.05 to 0.18, $p > 0.05$, I^2 = 21%	
Consistency in results	Consistent
Precision in results	Imprecise for OR, precise for SMD, unable to assess MD (not standardised).
Directness of results	Direct

Pillinger T, Beck K, Stubbs B, Howes OD

Cholesterol and triglyceride levels in first-episode psychosis: Systematic

review and meta-analysis

British Journal of Psychiatry 2017; 211: 339-49

View review abstract online

Comparison	**Cholesterol and triglyceride levels in people with first-episode psychosis vs. controls.** **63.9% of the patients were antipsychotic-naïve, and the remainder had received antipsychotic medication for up to 14 days.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly inconsistent, precise, direct) suggests small effects of reduced total and LDL cholesterol, and increased triglycerides in people with first-episode psychosis, with no changes in HDL cholesterol or leptin levels.**
Cardiometabolic parameters	
Significant, small effects of reduced total and LDL cholesterol in first-episode patients matched to controls for age and gender; Total cholesterol: 15 studies, N = 1,886, g = -0.19, 95%CI -0.32 to -0.06, p = 0.005, I^2 = 42%, p = 0.04 LDL cholesterol: 13 studies, N = 1,681, g = -0.22, 95%CI -0.35 to -0.09, p = 0.001, I^2 = 29%, p = 0.16 These effects remained significant in studies matched for BMI. The total cholesterol effect size was not significant in studies matched for ethnicity. *Significant, small effect of increased triglycerides in patients matched to controls for age;* 17 studies, N = 1,825, g = 0.14, 95%CI 0.00 to 0.28, p = 0.05, I^2 = 48%, p = 0.02 The effect remained significant in studies matched for dietary intake or gender. The effect was not significant in studies matched for BMI or ethnicity. *There were no significant differences in HDL cholesterol or leptin levels;* HDL cholesterol: 16 studies, N = 2,021, g = -0.19, 95%CI -0.39 to 0.02, p = 0.07, I^2 = 77%, p < 0.01 Leptin: 5 studies, N = 326, g = 0.05, 95%CI -0.31 to 0.42, p = 0.78, I^2 = 59%, p = 0.03	
Consistency in results	Inconsistent, apart from LDL cholesterol.
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 naıve, 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 cardio-metabolic parameters (risk factors for cardiovascular disease) in multi-episode patients with 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 patients with multi-episode schizophrenia have increased rates of abdominal obesity, hypertension, hypertriglyceridemia, and low HDL cholesterol compared to age and gender-matched population controls.** **Patients with multi-episode schizophrenia also have increased rates of abdominal obesity, hypertriglyceridemia, and low HDL cholesterol compared to first-episode and drug-naive patients.**

Abdominal obesity

Multi-episode patients with schizophrenia were at increased risk for abdominal obesity compared to matched population controls.

5 studies, N = 7,500, OR = 4.43, 95%CI 2.52 to 7.82, $p < 0.001$

Multi-episode patients (N = 19,043) had significant increased rates of abdominal obesity compared to drug-naive patients (N = 444): 50.0% vs.16.6%, $p < 0.001$. There were not enough studies reporting abdominal obesity in first-episode patients to assess differences for this group.

Hypertension

Multi-episode patients with schizophrenia were at increased risk for hypertension compared to matched population controls;

4 studies, N = 735,375, OR = 1.36, 95%CI 1.21 to 1.53, $p < 0.001$

There were no differences in hypertension rates between multi-episode (N = 112,167; 37.3%), first-episode (N = 488; 41.1%), or drug-naive patients (N = 631; 31.6%), $p = 0.64$.
Hypertriglyceridemia
Multi-episode patients with schizophrenia were at increased risk for hypertriglyceridemia compared to matched population controls; 2 studies, N = 6,663, OR = 2.73, 95%CI 1.95 to 3.83, $p < 0.001$ Multi-episode patients (N = 19,152; 39%) had significant increased rates of hypertriglyceridemia compared to drug-naive (N = 538; 23.3%), or compared to first-episode patients (N = 1,150; 10.5%), $p < 0.001$. Although rates of hypertriglyceridemia were higher in drug-naive patients (23.3%) than in first-episode patients (10.5%), this difference was not significant.
Low HDL cholesterol
Multi-episode patients with schizophrenia were at increased risk for low HDL cholesterol compared to matched population controls; 2 studies, N = 6,663, OR = 2.35; 95%CI 1.78 to 3.10, $p < 0.001$ Multi-episode patients (N = 19,063; 41.7%) had significant increased rate of HDL cholesterol compared to drug-naive (N = 538; 24.2%), or compared to first-episode patients (N = 1,306; 16%), $p < 0.001$. Although rates of HDL cholesterol were higher in drug-naive patients (24.2%) than in first-episode patients (16%), this difference was not significant.

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

Vancampfort D, Stubbs B, Mitchell AJ, Wampers M, Ward PB, Rosenbaum S, Correll CU

Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis

World Psychiatry 2015; 14: 339-347

View review abstract online

Metabolic abnormalities

Comparison	**Rates of metabolic syndrome in people with schizophrenia vs. bipolar disorder vs. major depression.** **Note that the metabolic syndrome component results are not reported separately for schizophrenia, and thus are not reported here.**
Summary of evidence	**Moderate to low quality evidence (inconsistent, imprecise, large samples, direct) suggests people with schizophrenia and related psychotic disorders have a small increased risk of metabolic syndrome when compared to controls. There is a similar increased risk with bipolar disorder and major depression.**

Metabolic syndrome

Prevalence rates of metabolic syndrome are around 30-35%.

Schizophrenia: 93 studies, N = 29,596, prevalence = 33.4%, 95%CI 30.8% to 36.0%, Q_W = 1955.0, $p < 0.001$

Related psychotic disorders: 13 studies, N = 2,850, prevalence = 34.6%, 95%CI 29.3% to 40.0%, Q_W = 110.2, $p < 0.001$

Bipolar disorder: 33 studies, N = 5,827, prevalence = 31.7%, 95%CI 27.3% to 36.3%, Q_W = 843.5, $p < 0.001$

Major depressive disorder: 19 studies, N = 5,415, prevalence = 31.3%, 95%CI 27.3% to 35.5%, Q_W = 142.7, $p < 0.001$

Significant, small effects of increased prevalence of metabolic syndrome when compared to controls across all disorders.

Schizophrenia and related psychotic disorders combined: 11 studies, N = 51,413, RR 1.87, 95%CI 1.53 to 2.29, $p < 0.001$, Q_W = 18.3, $p = 0.03$

Bipolar disorder: 6 studies, N = 1,125, RR = 1.58, 95%CI 1.24 to 2.03, $p < 0.001$, Q_W = 6.6, $p = 0.25$

Major depressive disorder: 17 studies, N = 5,267, RR = 1.57, 95%CI 1.38 to 1.79, $p < 0.001$, Q_W = 19.0, $p = 0.263$

Multiple meta-regression revealed greater body mass index and older age were significant predictors of increased risk of metabolic syndrome, with no significant differences according to diagnosis, sex, or smoking status.

Subgroup analyses revealed that the prevalence of metabolic syndrome was significantly higher in Australia and New Zealand compared with all other regions. There was a trend effect for lower prevalence in patients receiving one type of medication compared to two or more types. The prevalence of metabolic syndrome was lowest in antipsychotic-naive patients, and among those receiving antipsychotics, patients taking aripiprazole had the lowest prevalence, whilst patients taking clozapine had the highest prevalence. Patients treated with olanzapine had significantly higher prevalence than those treated with amisulpride, aripiprazole, risperidone or first-generation

antipsychotics. Authors report some publication bias, however the trim-and fill method demonstrated that adjusting for publication bias had little effect on the pooled estimate.	
Consistency in results	Inconsistent for schizophrenia and related disorders, consistent for bipolar disorder and depression.
Precision in results	Imprecise for schizophrenia and related disorders and bipolar disorder, precise for depression.
Directness of results	Direct

Explanation of acronyms

ATP III = adult treatment plan III of the national cholesterol education program, ATP III-A = adapted adult treatment plan, AUC = area under the curve, mg/dl = milligrams per deciliter, CI = confidence interval, *d* and *g* = Cohen's d and Hedge's g, standardised mean differences, HDL = high-density lipoprotein, I^2 = proportion of heterogeneity, IDF = international diabetes federation, MD = mean difference, N = number of participants, NCEP = national cholesterol education program, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = statistic for heterogeneity, RR = relative risk, SMD = standardised mean difference, vs. = versus

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 small[13].

† Different effect measures are reported by different reviews.

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. Standardised 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 effect, 0.5 a moderate effect, and 0.8 and over represents a large effect[13].

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[14]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

measure the effect of an explanatory variable on the hazard or risk of an event.

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 unforseen 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 formula[13];

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

§ 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 relaxed[15].

‖ 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.

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M (2011): Prevalence of Metabolic Syndrome and Metabolic Abnormalities in Schizophrenia and Related Disorders—A Systematic Review and Meta-Analysis. *Schizophrenia Bulletin*.
4. 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 naıve, first-episode and multi-episode patients with schizophrenia versus general population controls. *World Psychiatry* 12: 240-50.
5. Mitchell AJ, Vancampfort D, De Herdt A, Yu W, De Hert M (2013): Is the Prevalence of Metabolic Syndrome and Metabolic Abnormalities Increased in Early Schizophrenia? A Comparative Meta-Analysis of First Episode, Untreated and Treated Patients. *Schizophrenia Bulletin* 39: 295-305.
6. Mitchell A, Delaffon V, Vancampfort D, Correll C, De Hert M (2012): Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: Systematic review and meta-analysis of screening practices. *Psychological Medicine* 42: 125-47.
7. Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB*, et al.* (2015): Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: A systematic review and meta-analysis. *World Psychiatry* 14: 339-47.
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. Bruins J, Jorg F, Bruggeman R, Slooff C, Corpeleijn E, Pijnenborg M (2014): The effects of lifestyle interventions on (long-term) weight management, cardiometabolic risk and depressive symptoms in people with psychotic disorders: A meta-analysis. *PLoS ONE* 9.
10. Perry BI, McIntosh G, Weich S, Singh S, Rees K (2016): The association between first-episode psychosis and abnormal glycaemic control: systematic review and meta-analysis. *Lancet Psychiatry* 3: 1049-58.
11. Pillinger T, Beck K, Stubbs B, Howes OD (2017): Cholesterol and triglyceride levels in first-episode psychosis: Systematic review and meta-analysis. *British Journal of Psychiatry* 211: 339-49.
12. Misiak B, Stanczykiewicz B, Laczmanski L, Frydecka D (2017): Lipid profile disturbances in antipsychotic-naive patients with first-episode non-affective psychosis: A systematic review and meta-analysis. *Schizophrenia Research* 190: 18-27.
13. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
14. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
15. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*