TECHNICAL COMMENTARY

NeuRA Discover. Conquer. Cure.

SCHIZOPHRENIA LIBRARY

Heart disease

Introduction

People with schizophrenia may show increased rates of co-occurring conditions, including heart disease. It is unclear if any increased risk is a consequence of the metabolic impact of antipsychotic administration 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 given priority for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist which describes a preferred way to present a meta-analysis[1]. 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 nine systematic reviews that met our inclusion criteria[3-11].

- Moderate quality evidence suggests small increases in rates of coronary heart disease and congestive heart failure in people with schizophrenia, with rates gained from both longitudinal and cross-sectional studies, and from data adjusted for potential confounding factors. Longitudinal studies with adjusted data also show small to medium-sized increases in rates of cardiovascular disease and death due to cardiovascular disease in people with schizophrenia.
- Moderate quality evidence suggests rates of myocarditis and cardiomyopathy are similar in people taking clozapine, with incidence of myocarditis 0.6% and cardiomyopathy 0.7%.

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

Heart disease

- Moderate to high quality evidence finds a large effect of reduced overall heart rate variability in people with schizophrenia. Chronic patients show a larger effect size than first-episode patients for reduced high-frequency heart rate variability, while first-episode patients showed a larger effect size for reduced root mean square of successive R-R interval differences RMSSD.
- Moderate to low quality evidence suggests a medium-sized effect of increased risk of myocardial infarction in patients taking antipsychotics compared to patients not taking antipsychotics.
- Moderate quality evidence suggests cardiac patients with schizophrenia may be less likely to have a cardiac procedure, including revascularisation, angiogram, or reperfusion than cardiac patients without schizophrenia. A small effect shows cardiac patients with schizophrenia may also be less likely to be prescribed an angiotensin converting enzyme/ angiotensin receptor blocker (ACE/ARBs). Schizophrenia patients diagnosed with heart disease also have an increased risk of mortality than mentally healthy people without heart disease.
- Moderate to high quality evidence suggests a medium effect size for people with schizophrenia receiving fewer revascularisation procedures compared with people without a mental illness following acute coronary syndrome.

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

Alvares GA, Quintana DS, Hickie IB, Guastella AJ

Autonomic nervous system dysfunction in psychiatric disorders and the impact of psychotropic medications: A systematic review and meta-analysis

Journal of Psychiatry and Neuroscience 2016; 41(2): 89-104

View review abstract online

Comparison	**Heart rate variability (low variability represents unhealthy autonomic nervous system output) in people with a schizophrenia spectrum disorder vs. controls.**
Summary of evidence	**Moderate to high quality evidence (unable to assess consistency, precise, direct, large samples) suggests a large effect of reduced heart rate variability in people with a schizophrenia spectrum disorder, with no effect of medications apart from clozapine and tricyclic antidepressants.**
Heart rate variability	
A large, significant effect of reduced heart rate variability in people with a schizophrenia spectrum disorder compared to controls, with similar effect sizes in medicated and non-medicated patients; All patients: 41 studies, N = 3,373, g = -0.952, 95%CI -1.105 to -0.800, $p < 0.001$ Non-medicated patients: 19 studies, N = 1,799, g = -0.901, 95%CI -1.210 to -0.592, $p < 0.05$ Medicated patients: 21 studies, N = 1,532, g = -1.058, 95%CI -1.353 to -0.763, $p < 0.05$ Assessment of individual antipsychotics indicated clozapine had a significant detrimental effect on heart rate variability (g = -0.643, $p < 0.001$), but not amisulpride, olanzapine or sertindole. Assessment of individual antidepressants indicated tricyclic antidepressants had a significant detrimental effect on heart rate variability (g = -0.454, $p < 0.01$), but not selective serotonin reuptake inhibitors or serotonin−norepinephrine reuptake inhibitors. Many people with a schizophrenia spectrum disorder also had a mood disorder. Authors report possible publication bias.	
Consistency in results‡	No measure of consistency is reported for the analysis on schizophrenia spectrum disorders.
Precision in results§	Precise
Directness of results‖	Direct

TECHNICAL COMMENTARY

Heart disease

Clamor A, Lincoln TM, Thayer JF, Koenig J

Resting vagal activity in schizophrenia: meta-analysis of heart rate variability as a potential endophenotype

British Journal of Psychiatry 2016; 208: 9-16

View review abstract online

Comparison	**Vagal parasympathetic activity in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests a large effect of lower vagal parasympathetic activity in people with schizophrenia. Chronic patients showed a larger effect size than first-episode patients for high-frequency heart rate variability, while first-episode patients showed a larger effect size for root mean square of successive R-R interval differences RMSSD.**
Vagal parasympathetic activity	
Large, significant effects of lower vagal parasympathetic activity in people with schizophrenia; High-frequency heart rate variability (HRV): 29 studies, N = 3,055, *g* = -0.98, 95%CI -1.56 to -0.41, *p* = 0.0008, I^2 = 98% Root mean square of successive R-R interval differences (RMSSD): 24 studies, N = 2,485, *g* = -0.91, 95%CI -1.19 to -0.62, *p* < 0.0001, I^2 = 88% Chronic patients showed a larger effect size than first-episode patients for HRV, while first-episode patients showed a larger effect size for RMSSD. There were no moderating effects of age, duration of illness, medication, study setting (inpatient or outpatient), or method of assessing vagal activity.	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P, Thapa-Chhetri N, Fornaro M, Gallicchio D, Collantoni E, Pigato G, Favaro A, Monaco F, Kohler C, Vancampfort D, Ward PB, Gaughran F, Carvalho AF, Stubbs B

Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls

World Psychiatry 2017; 16: 163-80

View review abstract online

Comparison	**Cardiovascular disease in people with schizophrenia vs. people without schizophrenia.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, mostly imprecise, direct) suggests small increases in rates of coronary heart disease and congestive heart failure in people with schizophrenia, with rates gained from both longitudinal and cross-sectional studies, and from data adjusted for potential confounding factors. Longitudinal studies with adjusted data also show small to medium-sized increases in rates of cardiovascular disease and death due to cardiovascular disease in people with schizophrenia.**

Cardiovascular disease

A small, significant increase in cardiovascular disease in people with schizophrenia in unadjusted and adjusted longitudinal data, but not in cross-sectional data;

Longitudinal studies

Unadjusted: 16 studies, N = 16,457,419, RR = 1.21, 95%CI 1.01 to 1.45, $p = 0.04$, $I^2 = 98\%$

Adjusted: 14 studies, N = 7,453,152, HR = 1.95, 95%CI 1.41 to 2.70, $p < 0.0001$, $I^2 = 99\%$

Cross-sectional studies

Unadjusted: 10 studies, N = 4,290,899, OR = 1.23, 95%CI 0.92 to 1.65, $p = 0.16$, $I^2 = 99\%$

Adjusted: 5 studies, N = 3,902,581, OR = 1.38, 95%CI 0.93 to 2.05, $p = 0.11$, $I^2 = 96\%$

Death due to cardiovascular disease

A medium-sized, significant increase in death due to cardiovascular disease in people with schizophrenia in adjusted, but not in unadjusted, longitudinal data;

Longitudinal studies

Unadjusted: 9 studies, N = 7,233,233, RR = 1.26, 95%CI 0.84 to 1.90, $p = 0.27$, $I^2 = 96\%$

Adjusted: 9 studies, N = 7,025,498, HR = 2.45, 95%CI 1.64 to 3.65, $p < 0.0001$, $I^2 = 96\%$

Coronary heart disease	
A small, significant increase in coronary heart disease in people with schizophrenia in adjusted, but not unadjusted, longitudinal and cross-sectional data; Longitudinal studies Unadjusted: 8 studies, N = 15,616,132, RR = 0.93, 95%CI 0.81 to 1.08, $p = 0.33$, $I^2 = 87\%$ Adjusted: 5 studies, N = 6,424,825, HR = 1.59, 95%CI 1.08 to 2.35, $p = 0.02$, $I^2 = 95\%$ Cross-sectional studies Unadjusted: 8 studies, N = 4,273,550, OR = 1.03, 95%CI 0.85 to 1.25, $p = 0.76$, $I^2 = 98\%$ Adjusted: 1 study, N = 120,443, OR = 1.52, 95%CI 1.48 to 1.56, $p < 0.001$, I^2 = N/A	
Congestive heart failure	
A small, significant increase in congestive heart failure in people with schizophrenia in unadjusted and adjusted longitudinal and cross-sectional data; Longitudinal studies Unadjusted: 3 studies, N = 9,135,562, RR = 1.80, 95%CI 1.35 to 2.79, $p = 0.009$, $I^2 = 84\%$ Cross-sectional studies Unadjusted: 5 studies, N = 3,784,415, OR = 1.71, 95%CI 1.36 to 2.15, $p < 0.001$, $I^2 = 92\%$ Adjusted: 3 studies, N = 5,749,899, OR = 1.60, 95%CI 1.06 to 2.40, $p = 0.02$, $I^2 = 97\%$	
Consistency in results	Inconsistent
Precision in results	Mostly imprecise
Directness of results	Direct

Mitchell A, Lord O

Do deficits in cardiac care influence high mortality rates in schizophrenia? A systematic review and pooled analysis

Journal of Psychopharmacology 2010; 24(11): supplement 4: 69-80

View review abstract online

Comparison	**Adequacy of medical treatment in cardiac patients with schizophrenia vs. cardiac patients without schizophrenia.**

Heart disease

Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency, some imprecision, direct) suggests cardiac patients with schizophrenia may be less likely to have a cardiac procedure, including revascularisation, angiogram or reperfusion than cardiac patients without schizophrenia. A small effect shows cardiac patients with schizophrenia may also be less likely to be prescribed an angiotensin converting enzyme/ angiotensin receptor blocker (ACE/ARBs). Schizophrenia patients diagnosed with a cardiac disorder also have an increased risk of mortality.** **There were no difference between cardiac patients with a mental illness and those without a mental illness in the likelihood of being prescribed beta-blockers, aspirin, non-statin cholesterol-lowering agents and insulin.**

Cardiac procedures

3 of 7 studies (N = 906,768) reported that cardiac patients with schizophrenia were significantly less likely to undergo revascularization than cardiac patients without schizophrenia. Revascularisation included cardiac catheterisation, percutaneous transluminal coronary angioplasty and coronary artery bypass graft.

1 study (N = 4,340) reported that cardiac patients with schizophrenia were significantly less likely to undergo diagnostic angiogram; age adjusted RR = 0.90, 95%CI 0.83 to 0.98. 1 study (N = 14,194) reported no differences in the rate of procedures: SCZ 38.7% vs. control 40.3%, *p* = 0.14.

1 study (N = 88,241) reported that cardiac patients with schizophrenia were significantly less likely to receive reperfusion procedure following myocardial infarction.

Receipt of cardiac medication

Small effect size suggests psychiatric patients were significantly less likely to receive ACE/ARBs;

6 studies, N unclear, age adjusted OR = 0.779, 95%CI 0.638 to 0.950, *p* = 0.0137

Small effect size suggests psychiatric patients were significantly less likely to receive statins;

5 studies, N unclear, age adjusted OR = 0.604, 95%CI = 0.408 to 0.89, *p* = 0.0117

No difference between groups in likelihood of receiving beta-blockers;

9 studies, N unclear, age adjusted OR = 0.844, 95%CI 0.690 to 1.03, *p* = 0.1036

No difference between groups in likelihood of receiving aspirin;

7 studies, N unclear, age adjusted OR = 0.986, 95%CI 0.955 to 1.02, *p* = 0.381

No difference between groups in likelihood to receive non-statin cholesterol-lowering agents;

4 studies, N unclear, age adjusted OR = 1.55, 95%CI 1.04 to 2.32, *p* = 0.0312

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

No difference between groups in likelihood to receive insulin; 1 study, N = 3,808, OR = 1.44, 95%CI 0.96 to 2.16, *p* not reported
Rates of mortality
7 of 8 studies reported a significantly higher risk of mortality for schizophrenia patients and other patients with a mental illness; 1 study, N = 4,340, age adjusted OR = 1.25, 95%CI 1.00 to 1.53, $p < 0.05$ 1 population-based record-linkage study, N = 215,889, age-adjusted RR = 1.13, 95%CI 1.25 to 1.36, $p < 0.05$ 1 study, N = 345,195, schizophrenia patients < 65 years had higher inpatient mortality ($p < 0.001$) 1 record linkage study, N = 210,129, SMR = 1.91 for total ischemic heart disease and SMR = 1.71 for acute myocardial infarction 1 study, N = 14,194, 15.8% with SMI vs. 19.1% without SMI, $p < 0.001$ 1 study, N = 113,653, 12.8% of people with schizophrenia died within 30 days vs. 10.8% of people without a mental illness *1 study reported a significantly lower risk of mortality for schizophrenia patients;* 1 study, N = 345,195, patients > 65 years had 21% lower risk adjusted likelihood of death compared to those without a mental illness ($p < 0.001$)

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Imprecise for revascularisation procedures, statins, aspirin, non-statins cholesterol-lowering agents, insulin and high mortality. Precise for all other measures.
Directness of results	Direct

Mitchell A, Lawrence D

Revascularisation and mortality rates following acute coronary syndromes in people with severe mental illness: comparative meta-analysis

British Journal of Psychiatry 2011; 198: 434-441

View review abstract online

Comparison	**Revascularisation procedures and mortality rates in people with schizophrenia vs. people without a mental illness following**

	acute coronary syndrome.
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests a medium effect size for people with schizophrenia receiving fewer revascularisation procedures compared with people without a mental illness, following acute coronary syndrome. A small, non-significant effect was reported for increased mortality rates in patients with a mental illness (including schizophrenia).**
Revascularisation procedure rates following acute coronary syndrome	
Significant, medium effect size of reduced rates of revascularization procedures in people with schizophrenia compared to people without a mental illness; All procedures: 3 studies, N = 567,692, RR = 0.53, 95%CI 0.44 to 0.64, $p < 0.0002$, $I^2 = 77.6\%$ CABG: RR = 0.69, 95%CI 0.55 to 0.85, $p < 0.05$ PTCA/PCI: RR = 0.50, 95%CI 0.34 to 0.75, $p < 0.05$ Note; only 1 study adjusted for demographic and clinical characteristics (age, gender, number of days hospitalised, residence, hospital transfer, cardiovascular risk factors and other medical comorbidity).	
Mortality rates following acute coronary syndrome	
Very small effect size of increased coronary mortality rates in people with a mental illness (schizophrenia not reported separately) compared to people without a mental illness; 6 studies, N = 847,822, RR = 1.11, 95%CI 1.00 to 1.29, $p = 0.05$, $I^2 = 91.6\%$	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Shao M, Tian H, Wang L, Jiang D, Ji F, Zhuo C

Mortality risk following acute coronary syndrome among patients with schizophrenia: A meta-analysis

Progress in Neuro-Psychopharmacology & Biological Psychiatry 2020; 96: 109737

View review abstract online

Comparison	**Risk of mortality risk in people with schizophrenia with acute coronary syndrome vs. people without schizophrenia with acute coronary syndrome.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests a small effect of higher risk of mortality in people with schizophrenia with acute coronary syndrome than people without schizophrenia with acute coronary syndrome.**
Mortality	
A small effect showed acute coronary syndrome was associated with a significantly higher risk of mortality in people with schizophrenia; 9 studies, N = 3,611,343, RR = 1.66, 95%CI 1.33 to 2.09, $p < 0.001$, $I^2 = 93\%$ Subgroup analyses of duration of follow-up and adjustment for revascularization treatments showed similar results.	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Shao M, Zhuo C, Gao X, Chen C, Xu Y, Tian H, Li G, Jiang D, Wang W

Reduced rate of revascularization in schizophrenic patients with acute myocardial infarction: A systematic review and meta-analysis

Progress in Neuro-Psychopharmacology and Biological Psychiatry 2020; 99: 109870

View review abstract online

Comparison	**Rates of revascularization in people with schizophrenia and acute myocardial infarction vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a medium-sized effect of lower rates of revascularization in people with schizophrenia.**
Revascularization	

A medium-sized effect showed rates of revascularization was significantly lower in acute myocardial infarction; 6 studies, N = 3,260,754, OR = 0.48, 95%CI 0.38 to 0.62, $p < 0.001$, $I^2 = 93\%$ Results were adjusted for demographic characteristics, comorbidities, and hospital and regional factors.

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

Siskind D, Sidhu A, Cross J, Chua YT, Myles N, Cohen D, Kisely S

Systematic review and meta-analysis of rates of clozapine-associated myocarditis and cardiomyopathy

Australian and New Zealand Journal of Psychiatry 2020; 54(5): 467-481

View review abstract online

Comparison	**Rates of myocarditis and cardiomyopathy in people with schizophrenia taking clozapine.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, unable to assess precision, direct) suggests rates of myocarditis and cardiomyopathy are similar in people taking clozapine, with incidence between 0.6 and 0.7%.**
Myocarditis and cardiomyopathy	
Myocarditis: 24 studies, N = 256,635, 0.007 (incidence = 0.7%), 95%CI 0.003 to 0.016, $I^2 = 98\%$ Cardiomyopathy: 16 studies, N = 220,493, 0.006, (incidence = 0.6%), 95%CI 0.002 to 0.023, $I^2 = 98\%$	
Consistency in results	Inconsistent
Precision in results	Unable to assess (CIs not standardised).
Directness of results	Direct

Heart disease

Yu Z-H, Jiang H-Y, Shao L, Zhou Y-Y, Shi H-Y, Ruan B

Use of antipsychotics and risk of myocardial infarction: a systematic review and meta-analysis

British Journal of Clinical Pharmacology 2016; 82: 624-32

View review abstract online

Comparison	**Myocardial infarction in patients with schizophrenia taking antipsychotics vs. patients not taking antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, inconsistent, imprecise, direct) suggests a medium-sized effect of increased risk of myocardial infarction in patients taking antipsychotics.**
Myocardial infarction	
A medium-sized, significant increased risk of myocardial infarction in people taking antipsychotics; 3 studies, N = unclear, OR = 2.48, 95%CI 1.66 to 3.69, $p < 0.05$, $I^2 = 95\%$	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, CABG = coronary artery bypass graft, CI = confidence interval, HR = hazard ratio, 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), PCI = percutaneous coronary intervention, PTCA = percutaneous transluminal coronary angioplasty, Q = Q statistic (chi-square) for the test of heterogeneity, RR = relative risk, SCZ = schizophrenia, SMD = standardised mean difference, SMI = severe mental illness, SMR = standardised mortality rate, vs. = versus

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

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[12].

† 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 randomised 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[12].

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[13]. 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[12];

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

§ 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[14].

‖ 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, Lord O (2010): Do deficits in cardiac care influence high mortality rates in schizophrenia? A systematic review and pooled analysis. *Journal of Psychopharmacology* 24: 69-80.
4. Mitchell AJ, Lawrence D (2011): Revascularisation and mortality rates following acute coronary syndromes in people with severe mental illness: comparative meta-analysis. *British Journal of Psychiatry* 198: 434-41.
5. Clamor A, Lincoln TM, Thayer JF, Koenig J (2016): Resting vagal activity in schizophrenia: meta-analysis of heart rate variability as a potential endophenotype. *British Journal of Psychiatry* 208: 9-16.
6. Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P*, et al.* (2017): Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry* 16: 163-80.
7. Yu Z-H, Jiang H-Y, Shao L, Zhou Y-Y, Shi H-Y, Ruan B (2016): Use of antipsychotics and risk of myocardial infarction: a systematic review and meta-analysis. *British journal of clinical pharmacology* 82: 624-32.
8. Alvares GA, Quintana DS, Hickie IB, Guastella AJ (2016): Autonomic nervous system dysfunction in psychiatric disorders and the impact of psychotropic medications: A systematic review and meta-analysis. *Journal of Psychiatry and Neuroscience* 41: 89-104.
9. Shao M, Tian H, Wang L, Jiang D, Ji F, Zhuo C (2020): Mortality risk following acute coronary syndrome among patients with schizophrenia: A meta-analysis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 96: 109737.
10. Shao M, Zhuo C, Gao X, Chen C, Xu Y, Tian H*, et al.* (2020): Reduced rate of revascularization in schizophrenic patients with acute myocardial infarction: A systematic review and meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 99: 109870.
11. Siskind D, Sidhu A, Cross J, Chua YT, Myles N, Cohen D*, et al.* (2020): Systematic review and meta-analysis of rates of clozapine-associated myocarditis and cardiomyopathy. *Australian and New Zealand Journal of Psychiatry* Jan: doi: 10.1177/0004867419898760.
12. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
13. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
14. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*