TECHNICAL COMMENTARY

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Smoking

Introduction

Tobacco smoking is very common among people with schizophrenia, who often show particularly heavy usage. This poses considerable health risks, potential interference with the metabolism of antipsychotic medications, as well as financial burden for the individuals. Heavy cigarette use may contribute to the increased mortality and reduced life expectancy reported within the schizophrenia population. This topic considers the evidence for the prevalence of smoking among people with schizophrenia.

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. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. 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.

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 reporting less than 50% of items 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 or if there is a dose dependent response. We have also taken into account sample size and whether results are 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 inclusion criteria[3-11].

- Compared with the general population, moderate quality evidence finds higher rates of current smoking, heavy smoking, and lifetime smoking, and lower rates of smoking cessation in people with schizophrenia. People with first-episode psychosis, and those at ultra-high risk of psychosis also show higher rates of smoking, with rates of

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Smoking

~57% and ~33% respectively. There is also a medium-sized increased risk of psychotic disorders, and an earlier age of psychosis onset in smokers compared to non-smokers.

- Compared with people with other mental disorders, moderate quality evidence suggests people with schizophrenia show a small to medium-sized effect of higher rates of current smoking, and lower rates of smoking cessation.
- Moderate to high quality evidence found small effects of more severe positive symptoms and less severe extrapyramidal symptoms in smokers with schizophrenia compared to non-smokers with schizophrenia. There were no differences in negative symptoms, depression, anxiety, tardive dyskinesia, or parkinsonism.
- Moderate to low quality evidence finds lower serum clozapine levels in smokers compared to non-smokers, which may increase after smoking cessation.
- Moderate quality evidence suggests the most commonly reported reasons for smoking were; relaxation/stress reduction, dysphoria relief, sociability, craving/addiction. The most commonly reported reasons for quitting were; self-control, health concerns, social influence.
- Moderate quality evidence finds the following factors are barriers to smoking cessation: cravings and addiction, perceived risk of negative affect, social pressures, stress and boredom reduction, and weight management. Knowledge about health risks of smoking, physician advice and social pressures to quit helped facilitate smoking cessation.

Carney R, Cotter J, Bradshaw T, Firth J, Yung AR

Cardiometabolic risk factors in young people at ultra-high risk for psychosis: A systematic review and meta-analysis

Schizophrenia Research 2016; 170: 290-300

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Comparison	**Rates of smoking in people at ultra-high risk for psychosis vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, imprecise, inconsistent, direct) suggests a medium-sized increased odds of smoking in people at ultra-high risk for psychosis, with prevalence rates ~33%.**
Smoking prevalence	
Increased odds of smoking in people at ultra-high risk compared with controls; 17 studies, N = 938, OR = 2.30, 95%CI 1.48 to 3.48, $p < 0.05$, I^2 =78.8% Overall prevalence in people at ultra-high risk (N = 629) = 33%, 95%CI 0.24 to 0.42, I^2 = 82.4%	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

De Leon J, Diaz FJ

A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviours

Schizophrenia Research 2005; 76: 135-157

View review abstract online

Comparison 1	**Prevalence of smoking in people with schizophrenia vs. the general population.**
Summary of evidence	**Moderate quality evidence (large samples, imprecise, unable to assess consistency, direct) suggests people with schizophrenia**

	show a medium to large effect of higher rates of current smoking, heavy smoking, lifetime smoking, and lower rates of smoking cessation compared to the general population.
Smoking prevalence	
Medium to large effects show people with schizophrenia have higher rates of current smoking compared to the general population; Overall: 42 studies, N = 12,279, OR = 5.3, 95%CI 4.9 to 5.7, $p < 0.05$ Males: 32 studies, N = 6,210, OR = 7.2, 95%CI 6.1 to 8.3, $p < 0.05$ Females: 25 studies, N = 3,039, OR = 3.3, 95%CI 3.0 to 3.6, $p < 0.05$ *Medium to large effects show people with schizophrenia have higher rates of heavy smoking compared to the general population (≥ 20 cigarettes per day);* Overall: 6 studies, N = 979, OR range 1.9-6.4, all $p < 0.05$ Males: 3 studies, N = 418, OR range 2.0-7.4, all $p < 0.05$ Females: 3 studies, N = 174, OR range 2.0-8.8, all $p < 0.05$ *Medium to large effects show people with schizophrenia have lower rates of smoking cessation compared to the general population;* Overall: 6 studies, N = 1,107, OR = 0.19, 95%CI 0.14 to 0.24, $p < 0.05$ Males: 4 studies, N = 329, OR = 0.10, 95%CI 0.06 to 0.14, $p < 0.05$ Females: 3 studies, N = 113, OR = 0.46, 95%CI 0.23 to 0.69, $p < 0.05$ *Medium to large effects show people with schizophrenia have higher rates of lifetime smoking compared to the general population;* Overall: 9 studies, N = 2,929, weighted OR = 3.1, 95%CI 2.4 to 3.8, $p < 0.05$ Males: 2 studies, N = 676, weighted OR = 7.3, 95%CI 1.04 to 13.6, $p < 0.05$ Females: 3 studies, N = 231, weighted OR = 2.8, 95%CI 1.2 to 4.4, $p < 0.05$	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Imprecise
Directness of results	Direct
Comparison 2	**Prevalence of smoking in people with schizophrenia vs. people with other mental disorders.**

Summary of evidence	**Moderate quality evidence (large samples, imprecise, unable to assess consistency, direct) suggests a small to medium-sized effect of higher rates of current smoking, and lower rates of smoking cessation, in males and females with schizophrenia compared to people with other mental illnesses. A small to medium-sized effect suggests that males with schizophrenia (but not females) showed higher rates of lifetime smoking and more heavy smoking those people with other mental illnesses.**
Smoking prevalence	
Medium to large effects show people with schizophrenia have higher rates of current smoking compared to people with other mental illnesses; Overall: 18 studies, N = 5,197, OR = 1.9, 95%CI 1.7 to 2.1, $p < 0.05$ Males: 14 studies, N = 4,990, OR = 2.3, 95%CI 2.0 to 2.7, $p < 0.05$ Females: 8 studies, N = 1,770, OR = 1.8, 95%CI 1.5 to 2.3, $p < 0.05$ *Small to medium-sized effects show males with schizophrenia, but not females, showed higher rates of lifetime smoking compared to people with other mental illness;* Overall: 5 studies, N = 2,325, OR = 2.0, 95%CI 1.6 to 2.4, $p < 0.05$ Males: 4 studies, N = 1,156, OR = 2.0, 95%CI 1.5 to 2.7, $p < 0.05$ Females: 2 studies, N = 184, OR = 0.92, 95%CI 0.44 to 1.9, $p > 0.05$ *A small to medium-sized effect shows people with schizophrenia have lower rates of smoking cessation compared to people with other mental illness;* 4 studies, N = 734, OR = 0.55, 95%CI 0.33 to 0.90, $p < 0.05$ *A small effect was reported for males but not females, for heavy smoking (≥ 20 cigarettes per day);* Overall: 3 studies, N = 748, OR = 1.2, 95%CI 0.8 to 1.7, $p < 0.05$ Males: 5 studies, N = 973, OR = 1.5, 95%CI 1.0 to 2.2, $p < 0.05$ Females: 3 studies, N = 252, OR = 0.94, 95%CI 0.4 to 2.0, $p > 0.05$	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Imprecise
Directness of results	Direct

Gurillo P, Jauhar S, Murray RM, MacCabe JH

Does tobacco use cause psychosis? Systematic review and meta-analysis **Lancet Psychiatry 2015; 2: 718-725** View review abstract online	
Comparison 1	**Prevalence and odds of smoking in people with a first episode of psychosis vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, imprecise, inconsistent, direct) finds the prevalence of tobacco smoking in people with first-episode psychosis is around 57%, and a medium-sized increased odds of tobacco smoking is found in patients compared to controls.**
Tobacco smoking	
Overall 61 studies, N = 13,145 *Medium-sized effect of increased odds of smoking tobacco in people with first-episode psychosis vs. controls;* 11 case-control studies, OR = 3.22, 95%CI 1.63 to 6.33, $p = 0.001$, $I^2 = 82.1\%$, $p < 0.05$ 34 studies, prevalence rate = 0.57, 95%CI 0.52 to 0.62, $p < 0.0001$, $I^2 = 88.0\%$, $p < 0.05$ Authors report possible publication bias.	
Consistency in results	Inconsistent
Precision in results	Imprecise for odds ratio
Directness of results	Direct
Comparison 2	**Risk of psychotic disorders in smokers vs. non-smokers.**
Summary of evidence	**Moderate quality evidence (large samples, imprecise, inconsistent, direct) suggests a medium-sized increased risk of psychotic disorders in smokers compared to non-smokers.**
Psychotic disorders	
Significant, medium-sized increased risk of psychotic disorders in daily smokers vs. non-smokers; 5 prospective studies, RR = 2.18, 95%CI 1.23 to 3.85, $p = 0.007$, $I^2 = 97.7\%$, $p < 0.05$ Authors report possible publication bias.	
Consistency in results	Inconsistent

Precision in results	Imprecise
Directness of results	Direct
Comparison 3	**Age of psychosis onset in smokers vs. non-smokers.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, unable to assess precision, direct) suggests an earlier age of psychosis onset in smokers vs. non-smokers.**
Age of psychosis onset	
Earlier age of psychosis onset in smokers vs. non-smokers; 23 studies, 24 years vs. 26 years, WMD -1.04, 95%CI -1.82 to -0.26, $p = 0.009$, $I^2 = 66.3\%$, $p < 0.05$ Subgroup analysis showed this difference was only observed in studies from Europe, North America, Australia, Finland, Spain, and Sweden, and not Egypt, Japan, or Turkey. No significant differences were found for age at initiation of smoking cigarettes between people with psychosis and controls. Authors report no evidence of publication bias.	
Consistency in results	Inconsistent
Precision in results	Unable to assess precision (not standardised).
Directness of results	Direct

Huang H, Dong M, Zhang L, Zhong B-L, Ng CH, Ungvari GS, Yuan Z, Xiangfei M, Xiang Y

Psychopathology and extrapyramidal side effects in smoking and non-smoking patients with schizophrenia: Systematic review and meta-analysis of comparative studies

Progress in Neuro-Psychopharmacology & Biological Psychiatry 2019; 92: 476-82

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Comparison	**Effects of smoking in people with schizophrenia vs. non-smokers with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent,**

	precise, direct) suggests small effects of more severe positive symptoms and less severe extrapyramidal symptoms in smokers with schizophrenia. There were no differences in negative, depression, anxiety, tardive dyskinesia, or parkinsonism symptoms.
Symptoms	
Positive symptoms *Small effect showed smokers had more severe positive symptoms;* 24 studies, N = 4,641, SMD = 0.33, 95%CI 0.16 to 0.50, *p* = 0.0002, I^2 = 85% This effect was increased in non-European and non-Western Pacific regions, and in lower socioeconomic regions. Younger age and shorter illness duration also increased the effect size. There were no moderating effects of gender, diagnostic or outcome assessment tools used, or inpatient vs. outpatient status. Negative symptoms *There were no significant differences between groups;* 24 studies, N = 5,048, SMD = 0.14, 95%CI -0.01 to 0.29, *p* = 0.06, I^2 = not reported Younger age increased the effect size. There were no other moderating factors. Depression symptoms *There were no significant differences between groups;* 4 studies, N not reported, SMD = 0.11, 95%CI -0.06 to 0.28, *p* = 0.06, I^2 = not reported Anxiety symptoms *There were no significant differences between groups;* 2 studies, N = not reported, SMD = 0.06, 95%CI -0.27 to 0.38, *p* = 0.73, I^2 = not reported	
Extrapyramidal side effects	
Any extrapyramidal side effect *Small effect showed smokers had less severe extrapyramidal symptoms* 7 studies, N = 2,602, SMD = -0.20, 95%CI -0.38 to -0.02, *p* = 0.03, I^2 = 70% This effect increased with more males in the study. There were no other moderating factors. Tardive dyskinesia *There were no significant differences between groups;* 4 studies, N = not reported, SMD = -0.01, 95%CI -0.13 to 0.11, *p* = 0.89, I^2 = not reported Parkinsonism	

There were no significant differences between groups; 2 studies, N = not reported, SMD = 0.17, 95%CI -0.54 to 0.88, p = 0.65, I^2 = not reported	
Consistency in results	Inconsistent where reported.
Precision in results	Precise
Directness of results	Direct

Lowe EJ, Ackman ML

Impact of tobacco smoking cessation on stable clozapine or olanzapine treatment

Annals of Pharmacotherapy 2010; 44: 727-732

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Comparison	**Clozapine or olanzapine response in people with schizophrenia who do or do not smoke.**
Summary of evidence	**Moderate to low quality evidence (small to large samples, unable to assess consistency or precision, direct) finds lower serum clozapine levels in smokers compared to non-smokers, which may increase after smoking cessation.**
Medication response	
2 studies (N = 2,692) reported significantly lower serum clozapine levels in smokers compared to non-smokers. 1 study (N = 11) found that smoking cessation was associated with increased clozapine serum concentrations. 1 study (N = 59) found no difference between smokers and non-smokers. 1 study (N = 17) found that, following treatment with olanzapine, non-smokers had greater improvements in BPRS symptom severity score compared to smokers, but were also more likely to experience adverse effects.	
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

Lum A, Skelton E, Wynne O, Bonevski B

A systematic review of psychosocial barriers and facilitators to smoking cessation in people living with schizophrenia

Frontiers in Psychiatry 2018; 9: 565

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Comparison	**Barriers and facilitators of smoking cessation in people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (large overall sample, unable to assess precision or consistency, direct) finds the following factors are barriers to smoking cessation: cravings and addiction, perceived risk of negative affect, social pressures, stress and boredom reduction, and weight management. Knowledge about health risks of smoking, physician advice and social pressures to quit helped facilitate smoking cessation.**
Smoking cessation	
23 studies, N = 3,557 *Barriers to smoking cessation;* 9 studies reported cravings and addiction 7 studies reported a perceived increased risk of negative affect 7 studies reported social pressures 5 studies reported stress reduction 5 studies reported boredom reduction 5 studies reported stimulation 4 studies reported weight management *Facilitators to smoking cessation;* 8 studies reported health risks 7 studies reported physician advice 2 studies reported social pressures to quit	
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

Mitchell AJ, Vancampfort D, De Hert M, Stubbs S

Do people with mental illness receive adequate smoking cessation advice? A systematic review and meta-analysis

General Hospital Psychiatry 2015; 37: 14-23

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Comparison	**Receipt of smoking cessation advice in people with schizophrenia vs. people without a mental disorder.** **Note: results are for schizophrenia samples only.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests no difference in smoking cessation advice between people with schizophrenia and people without a mental illness.**
Smoking cessation advice rates	
No significant difference in smoking cessation advice rates between those with and without schizophrenia; 3 studies, N = 542,129, RR = 1.09, 95%CI 0.68 to 1.70, Q_w = 109, $p < 0.001$ Authors report no evidence of publication bias.	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Myles N, Newell HD, Curtis J, Nielssen O, Shiers D, Large M

Tobacco Use Before, At and After First-Episode Psychosis: A Systematic Meta-Analysis

Journal of Clinical Psychiatry 2012; 104: 719-733 View review abstract online	
Comparison	**Prevalence of smoking in first-episode psychosis vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests the prevalence of smoking in first-episode psychosis is around 60%, with the odds of smoking being 6 times greater than in people without first-episode psychosis.**
Smoking prevalence	
A large increase in the rate of smoking in people with first episode psychosis; 10 samples, N = 1,299, OR = 6.04, 95%CI 3.03 to 12.02, $p < 0.05$, $I^2 = 80\%$ *Prevalence of smokers with first-episode psychosis is around 60%;* 31 samples, N = 4,082, prevalence = 58.9%, 95%CI 54.3% to 63.4%, $I^2 = 86.7\%$ *Initiation was around 5.3 years prior to onset of psychosis;* 14 samples, N = 1,618, SMD = -0.85, 95%CI -0.97 to -0.72, $p < 0.05$, $I^2 = 47.5\%$ Prevalence rates varied by region ($p = 0.014$), with the highest smoking prevalence being reported in Australia (72%), with Britain, Europe, USA and Canada reporting similar rates (51%-59%). No differences in prevalence rates were found according to different recruitment methods, measurement of tobacco use, diagnostic criteria, proportion of males, proportion of affective subtypes, age, or year of study.	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Thornton LK, Baker AL, Johnson MP, Lewin TJ

Attitudes and perceptions towards substances among people with mental disorders: a systematic review

Acta Psychiatrica Scandinavica 2012; 126: 87-105

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Comparison	**Attitudes towards substances in people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (medium to large samples, unable to assess consistency or precision, direct) suggests the most commonly reported reasons for smoking were; relaxation/stress reduction, dysphoria relief, sociability, craving/addiction. The most commonly reported reasons for quitting were; self-control, health concerns, social influence.**
Attitudes to substances	
5 studies (N = 959) reported that people with schizophrenia who smoked cited reasons for use including: relaxation/stress reduction, dysphoria relief, sociability, craving/addiction. 1 study (N = 298) reported reasons for quitting were; self-control, health concerns, social influence.	
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

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CI = Confidence Interval, 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), Q = Q statistic for the test of heterogeneity, RCT = randomised controlled trial, RR = relative risk, SMD = standardised mean difference, vs. = versus, WMD = weighted mean difference

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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).

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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 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 measure the effect of an explanatory variable on the hazard or risk of an event.

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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. Unstandardised (*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. Standardised 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.

§ 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. de Leon J, Diaz FJ (2005): A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophrenia Research* 76: 135-57.
4. Lowe EJ, Ackman ML (2010): Impact of tobacco smoking cessation on stable clozapine or olanzapine treatment. *Annals of Pharmacotherapy* 44: 727-32.
5. Myles N, Newall HD, Curtis J, Nielssen O, Shiers D, Large M (2012): Tobacco use before, at, and after first-episode psychosis: a systematic meta-analysis. *Journal of Clinical Psychiatry* 73: 468-75.
6. Thornton LK, Baker AL, Johnson MP, Lewin TJ (2012): Attitudes and perceptions towards substances among people with mental disorders: A systematic review. *Acta Psychiatrica Scandinavica* 126: 87-105.
7. Mitchell AJ, Vancampfort D, De Hert M, Stubbs B (2015): Do people with mental illness receive adequate smoking cessation advice? A systematic review and meta-analysis. *General Hospital Psychiatry* 37: 14-23.
8. Gurillo P, Jauhar S, Murray RM, MacCabe JH (2015): Does tobacco use cause psychosis? Systematic review and meta-analysis. *The Lancet Psychiatry* 2: 718-25.
9. Carney R, Cotter J, Bradshaw T, Firth J, Yung AR (2016): Cardiometabolic risk factors in young people at ultra-high risk for psychosis: A systematic review and meta-analysis. *Schizophrenia Research* 170: 290-300.
10. Lum A, Skelton E, Wynne O, Bonevski B (2018): A systematic review of psychosocial barriers and facilitators to smoking cessation in people living with schizophrenia. *Frontiers in Psychiatry* 9: 565.
11. Huang H, Dong M, Zhang L, Zhong B-L, Ng CH, Ungvari GS*, et al.* (2019): Psychopathology and extrapyramidal side effects in smoking and non-smoking patients with schizophrenia: Systematic review and meta-analysis of comparative studies. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 92: 476-82.
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*