TECHNICAL COMMENTARY

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Infectious agents

Introduction

Increased exposure to infections prior to the onset of schizophrenia has been recognised, which suggests infections may be involved in its aetiology. Potential mechanisms for this association include a direct impact of infections on the brain, immune activation, inflammatory cytokines, and alterations in the gut microbiota. This topic summarises the available evidence for the risk of developing schizophrenia following exposure to infectious agents, both before and after birth. Please also see the maternal illness risk factor topic and the infectious agents and immunological changes topics in the physical features section of the library.

Method

We have included only systematic reviews with detailed literature search, methodology, and inclusion/exclusion criteria that were published in full text, in English, from the year 2000. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Reviews with pooled data are prioritized for inclusion. Reviews reporting fewer than 50% of items on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA[1]) checklist have been excluded from the library. The evidence was graded guided by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach[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 to high quality evidence found a small increased risk of schizophrenia in people exposed to childhood infections where hospitalisation occurred. The effect sizes increased with increasing number of hospitalisations and decreased with increasing age of exposure (up to 10 years).
- Moderate to high quality evidence suggests a medium-sized increased risk of having had a central nervous system viral infection in childhood in people with schizophrenia compared to people without schizophrenia.
- Moderate quality evidence indicates cohort studies, but not case-control studies, showed a significant association between gastroenteritis exposure and later development of schizophrenia.
- Moderate quality evidence indicates a small increase in levels of Toxoplasma gondii antibodies in people who later develop schizophrenia, and a medium-sized increase in levels of Toxoplasma gondii antibodies in people with recent-onset schizophrenia. Toxoplasma gondii is a parasitic protozoa, hosted by domestic cats and other warm-blooded animals including humans.
- Moderate to high quality evidence suggests a small increased risk of psychotic disorders (mostly schizophrenia spectrum or non-affective psychosis) following exposure to herpes simplex type 2 in utero. Lower quality evidence suggests exposure to toxoplasma gondii or genitourinary infections in utero may also be associated with increased risk of psychotic disorders. No significant risk was found following exposure to herpes simplex type 1, influenza (in any trimester), or cytomegalovirus in utero.

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Davies C, Segre G, Estrade A, Radua J, De Micheli A, Provenzani U, Oliver D, Salazar de Pablo G, Ramella-Cravaro V, Besozzi M, Dazzan P, Miele M, Caputo G, Spallarossa C, Crossland G, Ilyas A, Spada G, Politi P, Murray RM, McGuire P, Fusar-Poli P

Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis

The Lancet Psychiatry 2020; 7: 399-410

View review abstract online

Comparison	**Risk of psychotic disorders (mostly schizophrenia spectrum or non-affective psychosis) in adulthood in people who were exposed to infection in utero vs. controls.**
Summary of evidence	**Moderate to high quality evidence (unclear sample size, consistent, precise, direct) suggests small increased risk of psychotic disorders (mostly schizophrenia spectrum or non-affective psychosis) following exposure to herpes simplex type 2 in utero. Lower quality evidence suggests toxoplasma gondii may also be associated with increased risk of psychotic disorders, however the results may be subject to publication bias. No associations were found for herpes simplex type 1, influenza (in any trimester), urinary tract infection, cytomegalovirus, or sexually transmitted infections.**

Maternal infection

Small effects of increased risk of psychotic disorders following exposure in utero to;

Overall maternal infections: 9 studies, N not reported, OR = 1.27, 95%CI 1.06 to 1.53, $p = 0.0099$, $I^2 = 50\%$, $p = 0.04$

Toxoplasma: 4 studies, N not reported, OR = 1.30, 95%CI 1.04 to 1.62, $p = 0.02$, $I^2 = 18\%$, $p = 0.30$

This result was not significant after adjustment for publication bias or after excluding studies using retrospective recall.

Herpes simplex type 2: 5 studies, N not reported, OR = 1.35, 95%CI 1.16 to 1.58, $p = 0.0002$, $I^2 = 0\%$, $p = 0.80$

No associations were found for herpes simplex type 1, influenza (any trimester), cytomegalovirus, urinary tract infection, or sexually transmitted infections.

Consistency in results	Consistent, apart from overall maternal infections
Precision in results	Precise

Directness of results	Direct

Jiang HY, Zhang X, Pan LY, Ma YC

Childhood infection and subsequent risk of psychotic disorders in adults: A systematic review and meta-analysis

Asian Journal of Psychiatry 2020; 54: 102275

View review abstract online

Comparison	**Risk of schizophrenia in adulthood in people who had an infection in childhood vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) found a small effect of increased risk of schizophrenia in people exposed to childhood infections where hospitalisation occurred. The effect sizes increased with increasing number of hospitalisations and decreased with increasing age of exposure (up to 10 years). The effect size was similar in the analyses of CNS infection exposure.**
Childhood infections	
A small increased risk of any psychotic disorder following hospital exposure to any infection in childhood; 5 studies, 3,772,628, OR = 1.27, 95%CI 1.13 to 1.44, $p < 0.001$, $I^2 = 84$ % The effect sizes increased with increasing number of hospitalisations. The effect sizes decreased with increasing age (up to 10 years). The effect sizes were similar in the analyses of schizophrenia outcome and CNS infection exposure.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Khandaker G, Zimbron J, Dalman C, Lewis G, Jones P

Childhood infection and adult schizophrenia: A meta-analysis of

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population-based studies

Schizophrenia Research 2012; 139(1-3): 161-168

View review abstract online

Comparison	**Risk of schizophrenia in adulthood in people who had an infection in childhood vs. general population rates.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, imprecise, direct) suggests a medium-sized effect of increased risk of schizophrenia in people exposed to childhood CNS viral infections.**

All childhood CNS infections

A significant, small effect of increased risk of schizophrenia in people with a history of any childhood CNS infection;

2 studies, N = 1,198,507, RR = 1.80, 95%CI 1.04 to 3.11, $p = 0.03$, $I^2 = 55\%$, Q$p = 0.10$

A significant, medium-sized effect of increased risk of schizophrenia in people with a history of a viral childhood CNS infection;

2 studies, N = 1,198,507, RR = 2.12, 95%CI 1.17 to 3.84, $p = 0.01$, $I^2 = 70\%$, Q$p = 0.07$

No difference in the risk of schizophrenia following exposure to childhood bacterial infections;

2 studies, N = 1,198,507, RR = 0.72, 95%CI 0.14 to 3.54, $p = 0.68$, I^2 and Qp-value not reported

Specific childhood CNS infections

Viral infections

A significant effect of increased risk of schizophrenia in people with a history of CBV-5 meningitis in childhood;

1 study, N = 11,017, cumulative incidence = 12.5%, 95%CI -4.90% to 29.90%, $p < 0.05$

A significant, large effect of increased risk of non-affective psychosis in people with a history of cytomegalovirus in childhood;

1 study, N = 1,187,571, RR = 16.60, 95%CI 4.30 to 65.10, $p < 0.05$

A significant, medium-sized effect of increased risk of non-affective psychosis in people with a history of mumps in childhood;

1 study, N = 1,187,571, RR = 2.70, 95%CI 1.20 to 6.20, $p < 0.05$

Bacterial infections

A significant, large effect of increased risk of schizophrenia in people with a history of tuberculosis in childhood;

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1 study, N = 12,074, RR = 15.00, 95%CI 2.00 to 120.00, $p < 0.05$	
Consistency in results	Consistent where applicable (> 1 RCT).
Precision in results	Imprecise, particularly for specific infections.
Directness of results	Direct

Khandaker G, Zimbron J, Dalman C, Lewis G, Jones P

Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population based studies

Psychological Medicine 2013; 43(2): 239-257

View review abstract online

Comparison	**Exposure to prenatal maternal infections in adults with schizophrenia vs. population controls.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) suggests there may be an increased risk of schizophrenia following exposure to herpes simplex virus or Toxoplasma gondii in utero. Low quality evidence (no blood tests) is unclear about the relationships with other maternal infections.**

Prenatal maternal infections

Serum assays

Herpes simplex virus (HSV);

3/5 studies (N = 1,200) reported a significant increased risk of schizophrenia (~ 50%) after exposure to HSV-2 infection during pregnancy. 1 study (N = 110) reported a non-significant, 30% increase in risk of schizophrenia spectrum disorder following HSV-2 exposure, and 1 study (N = 648) reported no increase in risk of schizophrenia following HSV-1 or HSV-2 exposure.

Toxoplasma Gondii;

2 studies (N = 771) reported significant increased risk of schizophrenia (ORs 1.79 and 2.61) after exposure to elevated levels of maternal IgG antibodies to T. gondii. One study found no association between T. gondii exposure and non-affective psychosis but was limited by a very small sample of psychosis (N = 40).

Influenza;

2 studies (N = 372) reported increased risk of schizophrenia after exposure to influenza, but neither

study reported significant differences compared to controls.

Clinically diagnosed infections

General infections;

1 study (N = 1,119,474) reported maternal hospitalisation for any infection during second trimester of pregnancy was associated with increased risk of schizophrenia in offspring (RR 1.72, 95% CI 1.15 to 2.46). 1 study (N = 7,941) reported bacterial infection during the first trimester was reported to be associated with a twofold increased risk of schizophrenia at follow-up at both age 34 and 47 years. Risk was also increased, but not statistically significant for second trimester exposure. No significant increase in risk after prenatal exposure to viral infections.

Respiratory infection;

2 studies (N = 16,964) reported that maternal upper respiratory tract infection during the second trimester was reported to be associated with a two to threefold increased risk of schizophrenia in adult offspring by age 47 years.

Genital, reproductive and urinary infection;

3/4 studies reported increased risk of schizophrenia following exposure to infections, mostly during the early stages of gestation. 1 study (N = 7,794) reported that maternal genital or reproductive infection during the peri-conceptional period (30 days before and after the last menstrual period) was associated with a fivefold increased risk schizophrenia in adult offspring, with no increase in risk during pregnancy. 1 study (N = 1,119,474) reported that hospital admission for genital infection during pregnancy was associated with a twofold increased risk of schizophrenia in adult offspring. 1 study (N = 7,941) reported that maternal gonococcal infection during pregnancy was associated with a threefold increased risk of schizophrenia by age 47 years.

1 study (N = 23,404) reported no association between maternal hospitalization with pyelonephritis during pregnancy and risk of schizophrenia in the offspring.

Interaction between prenatal maternal infection and other risk factors;

1 study (N = 23,404) reported a fivefold increased risk of schizophrenia in offspring exposed to maternal pyelonephritis during pregnancy who also have a family history of schizophrenia.

1 study (N = 744) reported that mother's sexual behaviour prior to and during pregnancy was relevant to HSV-2 seropositivity and subsequent increased risk of schizophrenia.

6 studies (N = 532) reported that exposure to maternal infection or increased inflammatory cytokines during pregnancy were associated with significant deficits in executive functioning, childhood and adult verbal IQ, and greater IQ decline during the pre-morbid period and increased ventricular volume, increased length of the cavum septum pallucidum, and reduced cortical volume in offspring who developed schizophrenia.

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

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Saatci D, van Nieuwenhuizen A, Handunnetthi L

Maternal infection in gestation increases the risk of non-affective psychosis in offspring: a meta-analysis

Journal of Psychiatric Research 2021; 139: 125-31

View review abstract online

Comparison	**Rates of schizophrenia following exposure to maternal infections in utero vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, imprecise, direct) suggests a small, increased risk of schizophrenia following exposure to maternal infections during pregnancy.**
Any maternal infection during pregnancy	
A small, increased risk of schizophrenia following exposure to maternal infections during pregnancy; 5 large prospective studies, RR = 1.65, 95%CI 1.23 to 2.22, $p = 0.0008$, $I^2 = 0\%$ Exposure in the second trimester of pregnancy was associated with the greatest risk of any non-affective psychosis. Serologically detected maternal exposure to herpes simplex virus 2 increased the risk of any non-affective psychosis. There were no associations with other infectious agents.	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Selten JP, Frissen A, Lensvelt-Mulders G, Morgan VA

Schizophrenia and 1957 Pandemic of Influenza: Meta-analysis

Schizophrenia Bulletin 2010; 36(2): 219-228

View review abstract online

Comparison 1	**The number of cases of schizophrenia among people born after the 1957 influenza pandemic compared to the number of cases of schizophrenia among people born in surrounding years (between 1 and 6 years on either side of 1957). Studies considered infants**

	born in the first month after the peak as having been exposed during the ninth month of pregnancy and classified the other months accordingly to assess first, second and third trimester exposure.
Summary of evidence	**Moderate to high quality evidence (large samples, precise, some inconsistency, direct) suggests no association between exposure to influenza during pregnancy and risk of schizophrenia in the offspring.**
Maternal influenza during pregnancy	
Studies were conducted in the United States, Europe, and Australia where the 1957 pandemic came in one wave and where approximately 50% of the population reported having had influenza. *No significant differences in the number of cases of schizophrenia between people potentially exposed to influenza prenatally and those potentially not exposed;* 6 population-level studies, OR = 0.99, 95%CI 0.96 to 1.03, $p > 0.05$, $Qp < 0.05$ For males only: OR = 0.95, 95%CI 0.87 to 1.04, $p > 0.05$, $Qp < 0.05$ For females only: OR = 0.96, 95%CI 0.85 to 1.09, $p > 0.05$, $Qp > 0.05$	
No significant differences in the number of cases of schizophrenia between people potentially exposed to influenza prenatally during any trimester and those potentially not exposed; First trimester: OR = 0.91, 95%CI 0.85 to 0.98, $p > 0.05$, $Qp > 0.05$ For males only: OR = 0.88, 95%CI 0.75 to 1.04, $p > 0.05$, $Qp > 0.05$ For females only: OR = 0.80, 95%CI 0.63 to 1.00, $p > 0.05$, $Qp > 0.05$ Second trimester: OR = 1.00, 95%CI 0.93 to 1.07, $p > 0.05$, $Qp > 0.05$ For males only: OR = 0.99, 95%CI 0.85 to 1.16, $p > 0.05$, $Qp < 0.05$ For females only: OR = 1.07, 95%CI 0.87 to 1.30, $p > 0.05$, $Qp > 0.05$ Third trimester: OR = 1.05, 95%CI 0.98 to 1.12, $p > 0.05$, $Qp < 0.05$ For males only: OR = 0.99, 95%CI 0.84 to 1.16, $p > 0.05$, $Qp > 0.05$ For females only: OR = 1.04, 95%CI 0.85 to 1.28, $p > 0.05$, $Qp > 0.05$	
Maternal influenza during pregnancy	
Studies were conducted in Japan where the 1957 pandemic came in two waves and where approximately 50% of the population reported having had influenza. *No significant differences in the number of cases of schizophrenia between people in Japan potentially exposed to influenza prenatally and people in Japan potentially not exposed;* 3 population-level studies, RR = 0.98 (CI not reported) For Japanese men: RR = 0.92, 95%CI 0.81 to 1.04, $p > 0.05$, Qp not reported For Japanese women: RR = 1.08, 95%CI 0.92 to 1.26, $p > 0.05$, Qp not reported	

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Consistency in results	Some inconsistency
Precision in results	Precise
Directness of results	Direct
Comparison 2	**Studies examining the risk of schizophrenia among people born to mothers who were pregnant during the pandemic and reported having had influenza compared to mothers who were pregnant during the pandemic and reported not having had influenza.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency, imprecise, direct) suggests no association between exposure to the 1957 influenza pandemic during pregnancy and risk of schizophrenia in the offspring.**
Maternal influenza during pregnancy	
No differences in the number of cases of schizophrenia between people whose mothers reported having had influenza during the pandemic and mothers who reported not having had influenza during the pandemic; 2 studies, N = 16,529, RR = 1.20, 95%CI 0.59 to 2.42, $p > 0.05$, Qp not reported	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Imprecise
Directness of results	Direct

Sutterland AL, Fond G, Kuin A, Koeter MWJ, Lutter R, van Gool T, Yolken R, Szoke A, Leboyer M, de Haan L

Beyond the association. Toxoplasma gondii in schizophrenia, bipolar disorder, and addiction: systematic review and meta-analysis

Acta Psychiatrica Scandinavica 2015; 132: 161-179

View review abstract online

Comparison	**Toxoplasma gondii antibodies prior to the onset of schizophrenia and in people with recent-onset schizophrenia vs. controls.**
Summary of evidence	**Moderate quality (large samples, inconsistent, imprecise, direct) evidence indicates a small increase in levels of Toxoplasma gondii antibodies in people who later develop schizophrenia, and a medium-sized increase in levels of Toxoplasma gondii**

	antibodies in people with recent-onset schizophrenia.
Toxoplasma gondii antibodies	
Significant, small effect of increased Toxoplasma gondii antibodies prior to onset of schizophrenia; 7 studies, N ~49,000, OR = 1.30, 95%CI 1.05 to 1.61, p = 0.01, I^2 = 42% *Significant, medium-sized effect of increased Toxoplasma gondii antibodies in people with recent onset schizophrenia;* 10 studies, N not reported, OR = 2.18, 95%CI 1.58 to 3.01, p < 0.00001, I^2 = 43%	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Yi W, Wei Q, Pan R, Song S, Gao J, Xu Z, Duan J, He Y, Tang C, Liu X, Zhou Y, Su H

Gastroenteritis exposure and the risk of schizophrenia onset: A systematic review and meta-analysis

Journal of Psychosomatic Research 2020; 134: 110136

View review abstract online

Comparison	**Gastroenteritis prior to the onset of schizophrenia and in people with recent-onset schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, mostly inconsistent, imprecise, direct) indicates no consistent association between gastroenteritis exposure and risk of schizophrenia. However, as cohort studies but not case-control studies showed a significant association, there may be a link between the two.**
Gastroenteritis	
Overall, no association was found between gastroenteritis exposure and rates of schizophrenia; 11 studies, N = 13,830,871, RR = 1.06, 95%CI 0.81 to 1.39, p > 0.05, I^2 = 88%, p < 0.01 *Large, prospective cohort studies showed a small effect, while case-control studies showed no effect;* Cohort studies: 7 studies, N not reported, RR = 1.27, 95%CI 1.05 to 1.53, p < 0.05, I^2 = 48%, p =	

0.07 Case-control studies: 4 studies, N not reported, RR = 0.73, 95%CI 0.47 to 1.11, $p > 0.05$, $I^2 = 79\%$, $p < 0.01$ Increased risk was observed in studies from America and Australia, but not Europe or Asia. Increased risk was observed in studies adjusting for ≥2 confounders (county, parental educational level, ages of mother and father at delivery, birth outcomes and/or socioeconomic status) than in studies adjusting for <2 confounders.	
Consistency in results	Inconsistent, apart from cohort studies analysis
Precision in results	Imprecise
Directness of results	Direct

Zhou YY, Zhang WW, Chen F, Hu SS, Jiang HY

Maternal infection exposure and the risk of psychosis in the offspring: A systematic review and meta-analysis

Journal of Psychiatric Research 2021; 135: 28-36

View review abstract online

Comparison	**Rates of schizophrenia following exposure to maternal infections in utero vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests a small, increased risk of schizophrenia following exposure to maternal infections during pregnancy, particularly herpes simplex virus 2 and genitourinary infection.**
Any maternal infection during pregnancy	
A small, increased risk of schizophrenia following exposure to maternal infections during pregnancy; 7 large studies, OR = 1.28, 95%CI 1.04 to 1.58, $p < 0.05$, $I^2 = 75\%$ Subgroup analysis found only herpes simplex virus 2 and genitourinary infection increased the risk of any non-affective psychosis. There were no associations with other infectious agents.	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

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Explanation of acronyms

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* = probability of obtaining that result ($p < 0.05$ generally regarded as significant), RR = risk ratio, vs. = versus.

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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).

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 medium effect, and 0.8 and over represents a large treatment 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, an 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. An 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 are an 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 dependent 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 treatment 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 substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

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

§ 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, this 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 so is 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.

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