TECHNICAL COMMENTARY

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Infectious agents

Introduction

This topic summarises the available evidence on markers of infection (antibodies) in adults with schizophrenia. The physiological mechanisms of any association of these infectious agents with risk for schizophrenia are largely unclear.

The *Herpesviridae* are a family of viruses which cause latent, recurring, and sometimes lifelong infections. These include Herpes simplex virus (HHV1 & 2) which causes oral and/or genital herpes; the Varicella Zoster Virus (VZV,HHV3) which causes chicken pox, shingles and rarely, encephalitis; the Epstein-Barr Virus (EBV, HHV4) and Cytomegalovirus (CMV, HHV5) which cause neurological complications; and the Herpes lymphotropic virus (HHV6), which causes roseola (skin rash and fever).

Borna Disease Virus (BDV) is the key causative component of Borna disease, a neurological syndrome primarily affecting animals (particularly horses, cattle, sheep, dogs and cats). However, human infection with BDV has been linked to some psychiatric illnesses through its neurological interactions.

Human Endogenous Retroviruses (HERVs) are fragments of ancient viral infections that became embedded within the germ cells (sperm and eggs), and are passed on to subsequent generations, making up a large proportion of the human genome. HERVs are proposed to have involvement in some autoimmune diseases.

The Human T-lymphotropic virus Type I (HTLV-1) is a human retrovirus that integrates into immune cells and is associated with an increased risk of developing cancers such as adult T-cell leukemia, myeloma, and lymphoma.

The *Chlamydiaceae* family of bacteria can cause a range of infections in humans, including chlamydia and trachoma (*Chlyamydia trachomysis)* and pneumonia (*Chlamydophila pneumonia, Chlamydophila psittaci*).

Toxoplasma gondii is a parasitic protozoa, hosted by domestic cats and other warm-blooded animals including humans. Toxoplasma gondii infection is usually of minor consequence to an adult but can have serious implications for a foetus.

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 a schizophrenia spectrum disorder. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews with 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

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some reviews may have been limited by journal guidelines.

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

Results

We found six systematic reviews that met our inclusion criteria[3-8].

- Moderate to high quality evidence suggests greater levels of markers for Human Herpesvirus-2 (small effect); Borna Disease Virus (small to medium effect); Human Endogenous Retroviruses (HERV-W: large effect); Chlamydophila pneumoniae and Chlamydophila psittaci (large effects); and Toxoplasma gondii (small to medium effect).
- Moderate quality evidence indicates a medium-sized increase in antibodies to Toxoplasma gondii in people with recent-onset schizophrenia. There is also a small increase in antibodies to Toxoplasma gondii, prior to illness onset.

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Arias I, Sorlozano A, Villegas E, de Dios Luna J, McKenney K, Cervilla J, Gutierrez B, Gutierrez J

Infectious agents associated with schizophrenia: A meta-analysis

Schizophrenia Research 2012; 136(1-3): 128-136

View review abstract online

Comparison	**Rates of infection markers in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (direct, large samples, consistent, imprecise) suggests people with schizophrenia may have higher levels of markers for Human Herpesvirus-2 (small effect); Borna Disease Virus (small to medium-sized effect); Human Endogenous Retroviruses (HERV-W: large effect); Chlamydophila pneumoniae and Chlamydophila psittaci (large effects); and Toxoplasma gondii (small to medium-sized effect).**

Herpesviridae family

Human Herpesvirus-1

No differences were reported between people with schizophrenia and controls;

11 studies, N = 664, †OR = 1.37, 95%CI 0.78 to 2.39, p = 0.273, Q 11.69, p = 0.306, I^2 = 14.5%

Meta-regression suggested no differences in results due to detection technique.

Human Herpesvirus-2

Significant, small effect of an increase in markers in people with schizophrenia vs. controls;

6 studies, N = 2,288, OR = 1.34, 95%CI 1.09 to 1.70, p = 0.05, Q 4.27, p = 0.511, I^2 not reported

Note: The largest included study in this analysis was the only study showing a positive association and utilised blood samples from newly born babies (< 1 week after birth), so antibodies came from the mother.

Varicella Zoster Virus

No differences were reported between people with schizophrenia and controls;

4 studies, N = 138, OR = 1.17, 95%CI 0.16 to 8.58, p = 0.877, I^2, p not reported

Epstein-Barr Virus

No differences were reported between people with schizophrenia and controls;

5 studies, N = 258, OR = 1.67, 95%CI 0.57 to 4.94, p = 0.352, Q 4.29, p = 0.306, I^2 = 31.6%

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Cytomegalovirus *No differences were reported between people with schizophrenia and controls;* 15 studies, N = 929, OR = 0.86, 95%CI 0.54 to 1.38, *p* = 0.544, Q *12.81, p* = 0.541, I^2 not reported Meta-regression suggested no differences in results due to detection technique *Human Herpesvirus-6* *No differences were reported between people with schizophrenia and controls;* 3 studies, N = 113, OR = 0.34, 95%CI 0.49 to 2.42, *p* = 0.283, Q, I^2, Q-test *p* not reported
Borna Disease Virus
Significant, small to medium sized effect of an increase in markers in people with schizophrenia vs. controls; 23 studies, N = 3,853, OR = 2.03, 95%CI 1.35 to 3.06, *p* < 0.01, Q 32.70, *p* = 0.086, I^2 = 29.7% Meta-regression suggested no differences in results due to detection technique
Human Endogenous Retroviruses
No differences were reported in HERV between people with schizophrenia and controls; 4 studies, N = 212, OR = 3.66, CI95% 0.79 to 16.95, *p* = 0.097 *Significant, large effect of an increase in HERV-W markers in people with schizophrenia vs. controls;* 5 studies, N = 519, OR = 19.31, 95%CI 6.74 to 55.29, *p* < 0.001, Q 5.42, *p* = 0.247, I^2 = 26.2%
Human T-cell Lymphotropic Virus
No differences were reported between people with schizophrenia and controls; 2 studies, N = 302, OR = 0.58, 95%CI 0.20 to 1.62, *p* = 0.297
Chlamydiaceae family
Chlamydia trachomatis *No differences were reported between people with schizophrenia and controls;* 2 studies, N = 422, OR = 4.39, 95%CI 0.03 to 571.24, *p* = 0.551 *Chlamydophila pneumonia* *Significant, large effect of an increase in markers in people with schizophrenia vs. controls;* 2 studies, N = 422, OR = 6.34, 95%CI 2.83 to 14.19, *p* < 0.001, Q, I^2, Q-test *p* not reported *Chlamydophila psittaci*

Significant, large effect of an increase in markers in people with schizophrenia vs. controls; 2 studies, N = 422, OR = 29.05, 95%CI 8.91 to 94.70, $p < 0.001$, Q, I^2, Q-test p not reported
Toxoplasma gondii
Significant, small to medium sized effect of an increase in markers in people with schizophrenia vs. controls; 8 studies, N = 2,381, OR = 2.70, 95%CI 1.34 to 4.42, $p = 0.005$, Q 33.89, $p < 0.001$, $I^2 = 79.3\%$ Authors state this heterogeneity was explained by detection technique, with results from DNA in brain biopsies (OR = 1.83 95%CI 0.03 to 97.01) being significantly different ($p < 0.001$) from results from serum antibodies (OR = 2.74, 95%CI 1.33 to 5.62).
Influenza virus
No differences were reported between people with schizophrenia and controls
Other infectious agents
Individual studies assessed: parvovirus B19, parvovirus AAV-2, John Cunningham (JC) virus, BK virus, HERV-K115, Human immunodeficiency virus (HIV) and Toxocara seroprevalence *Only Toxocara seroprevalence showed a large effect of increased markers in schizophrenia;* 1 study, N = 198, OR = 41.60, 95%CI 9.71 to 178.30, $p < 0.001$

Consistency in results‡	Consistent where reported. T.gondii heterogeneity explained by detection technique.
Precision in results§	Imprecise
Directness of results‖	Direct

Azami M, Jalilian FA, Khorshidi A, Mohammadi Y, Tardeh Z

The association between Borna Disease Virus and schizophrenia: A systematic review and meta-analysis

Asian Journal of Psychiatry 2018; 34: 67-73

View review abstract online

Comparison	**Borna disease virus makers in people with schizophrenia vs. controls.**

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Summary of evidence	**Moderate quality evidence (large samples, mostly inconsistent, imprecise, direct) suggests a small increase in Borna Disease Virus markers in people with schizophrenia compared to controls using western blotting, reverse transcriptase polymerase chain reaction, and electrochemiluminescent immunoassay methods.**
Borna Disease Virus markers	
A small, significant effect of increased Borna Disease Virus antibodies in people with schizophrenia; 30 studies, N = 6,537, OR = 2.72, 95%CI 1.75 to 4.20, $p < 0.05$, $I^2 = 59.4\%$, $p < 0.0001$ *The effect was significant using the following methods;* Western blotting: 5 studies, N = 1,244, OR = 4.99, 95%CI 1.80 to 13.85, $p < 0.05$, $I^2 = 27.1\%$, $p = 0.249$ Reverse transcriptase polymerase chain reaction: 13 studies, N = 1,872, OR = 3.83, 95%CI 1.59 to 9.20, $p < 0.05$, $I^2 = 59.3\%$, $p = 0.003$ Electrochemiluminescent immunoassay: 1 study, N = 1,262, OR = 2.88, 95%CI 1.38 to 6.01, $p < 0.05$ *The effect was not significant using the following methods;* Enzyme immunoassay: 3 studies, N = 654, OR = 2.26, 95%CI 0.48 to 10.64, $p > 0.05$, $I^2 = 65\%$, $p = 0.057$ Relative luciferase activity: 3 studies, N = 562, OR = 1.67, 95%CI 0.50 to 5.56, $p > 0.05$, $I^2 = 36.6\%$, $p = 0.206$ Indirect fluorescent antibody: 4 studies, N = 488, OR = 1.27, 95%CI 0.23 to 7.12, $p > 0.05$, $I^2 = 81.4\%$, $p = 0.001$ *The effect was significant using all sources of markers;* Brain: 3 studies, OR = 7.89, 95%CI 1.75 to 35.53, $p < 0.05$, $I^2 = 0\%$, $p = 0.588$ White blood cell: 10 studies, OR = 3.31, 95%CI 1.19 to 9.25, $p < 0.05$, $I^2 = 66.9\%$, $p = 0.001$ Serum: 10 studies, OR = 2.21, 95%CI 1.17 to 4.17, $p < 0.05$, $I^2 = 72.4\%$, $p = 0.003$ Plasma: 8 studies, OR = 2.21, 95%CI 1.03 to 4.73, $p < 0.05$, $I^2 = 9\%$, $p = 0.360$	
Consistency in results	Consistent for western blotting, relative luciferase activity, brain, and plasma subgroup analyses only.
Precision in results	Imprecise
Directness of results	Direct

Monroe JM, Buckley PF, Miller BJ

Meta-Analysis of Anti-Toxoplasma gondii IgM Antibodies in Acute Psychosis

Schizophrenia Bulletin 2015; 41(4): 989-998

View review abstract online

Comparison	**Toxoplasma gondii antibodies in people with acute psychosis vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, some inconsistencies, imprecise, direct) suggests a medium-sized, increased risk of toxoplasma gondii IgM antibodies in chronic patients with acute psychosis compared to controls.**

Toxoplasma gondii IgM antibodies

Significant, medium sized increased risk of positive T. gondii IgM antibodies in people with acute psychosis compared with controls, with no differences for first-episode patients;

Any psychosis: 16 studies, N = 4,060, OR = 1.68, 95%CI 1.23 to 2.27, $p = 0.001$, $I^2 = 41.1\%$, $p = 0.055$

After removing two studies with the highest seroprevalence of positive IgM antibodies in patients and controls, the association was stronger and the heterogeneity was no longer significant;

OR = 2.81, 95%CI 1.80 to 4.37, $p < .001$, $I^2 = 30.5\%$, $p = 0.148$

Meta-regression analyses showed increased risk in studies from Asia, Europe, and South America (regions with a lower prevalence of T. gondii IgM positive controls), than in studies from Africa and the Middle East. There were no differences according to age, sex, or publication year.

Relapsed, chronic schizophrenia: 10 studies, OR = 2.54, 95%CI 1.63 to 3.96, $p < .001$, $I^2 = 48.5\%$, $p = 0.05$

After excluding one study, the association was large and the heterogeneity was not significant;

OR = 6.89, 95%CI 3.10 to 15.34, $p < 0.001$, $I^2 = 24.8\%$, $p = 0.232$

First-episode psychosis: 4 studies, OR = 1.47, 95%CI 0.84 to 2.58, $p = 0.181$, I^2 5.9%, $p = 0.363$

Authors report no evidence of publication bias.

Consistency in results	Consistent with studies removed.
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 in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) indicates that people prior to onset of schizophrenia, or those with chronic schizophrenia may have a small increase in antibodies to Toxoplasma gondii, while people with recent onset schizophrenia may have a medium-sized increase.**

Toxoplasma gondii antibodies

Significant, small effect of increased Toxoplasma gondii antibodies in people with schizophrenia vs. controls;

42 studies, N ~60,000, OR = 1.81, 95%CI 1.51 to 2.16, $p < 0.00001$, $I^2 = 82\%$

Results adjusted for publication bias: OR = 1.43 95%CI 1.21 to 1.70, $p < 0.05$

Significant, medium effect of increased Toxoplasma gondii antibodies in people with recent onset schizophrenia vs. controls;

10 studies, N not reported, OR = 2.18, 95%CI 1.58 to 3.01, $p < 0.00001$, $I^2 = 43\%$

Significant, small effect of increased Toxoplasma gondii antibodies in people with chronic schizophrenia vs. controls;

28 studies, N not reported, OR = 1.88, 95%CI 1.46 to 2.42, $p < 0.000001$, $I^2 = 83\%$

Significant, small effect of increased Toxoplasma gondii antibodies prior to onset of schizophrenia vs. controls;

7 studies, N ~49,000, OR = 1.30, 95%CI 1.05 to 1.61, $p = 0.01$, $I^2 = 42\%$

The differences in magnitude of these ORs was significant (Q_B $p = 0.01$)

Subgroup analysis of serointensity revealed a between significant group effect ($Q_B = 11.2$, $p = 0.001$), with unpublished studies showing no effect (OR 0.79) and published studies a significant effect (OR 2.17). A significant between group effect was found depending on region of study ($Q_B = 17.3$, $p = 0.004$), with a higher ORs in Africa, South America, the Middle East and Asia and more

modest ORs in Europe and North America. No differences in results according to study quality, study mean age, and sex.	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Torrey EF, Bartko JJ, Lun ZR, Yolken RH

Antibodies to Toxoplasma gondii in patients with schizophrenia: a meta-analysis

Schizophrenia Bulletin 2007; 33(3): 729-736

View review abstract online

Recent update:

Torrey EF, Bartko JJ, Lun ZR, Yolken RH

Toxoplasma gondii and Other Risk Factors for Schizophrenia: An Update

Schizophrenia Bulletin 2012; 38(3): 642-647

View review abstract online

Comparison	**Assessment of results from serological assay that measure Toxoplasma gondii antibodies in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency, imprecise, direct) indicates that people with chronic or first episode schizophrenia may have increased antibodies to Toxoplasma gondii, depending on the assay used.**
Differences between the number of people with schizophrenia with positive antibody test compared to the number of controls with positive antibody tests	
2012 analysis *Significantly higher odds of having a positive antibody test (ELIZA, CF, IHA or dye test) in people with schizophrenia compared to controls;*	

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38 observational studies, N = 14,773, OR = 2.73, 95%CI 2.21 to 3.38, $p < 0.000001$, Q test and I^2 not reported	
2007 analysis: Subgroup analysis to investigate differences between people with chronic and first episode schizophrenia *No differences between chronic and first episode schizophrenia;* Chronic patients vs. controls; 16 observational studies, N = 8,918, OR = 2.79 First episode schizophrenia patients vs. controls; 7 observational studies, N = 1,999, OR = 2.54	
Subgroup analysis to investigate differences between studies using different serological tests *Significant differences between results of studies using different serological tests;* CF; 3 observational studies, N = 1,414 , OR = 1.38 ELISA; 14 observational studies, N = 6,087, OR = 2.61 Dye test, 3 observational studies, N = 2,460, OR = 2.54 IHA; 3 observational studies, N = 958, OR = 8.27 $X^2 = 25.3$, $p < 0.0001$	
Subgroup analysis to investigate differences between published and unpublished data *Significant differences between results of published and unpublished data – studies with a higher OR are more likely to have been published;* Published; 17 observational studies, N = 9,563, OR = 2.97 Unpublished; 6 observational studies, N = 1,356, OR = 2.16 $X^2 = 4.8$, $p < 0.03$	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

CF = complement fixation, CI = Confidence Interval, ELIZA = enzyme-linked immunosorbent assay, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), IgG = immunoglobulin G, IHA = immune hemagglutination, N = number of participants, OR = odds ratio, p = probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic (chi-square) for the test of heterogeneity, vs. = versus X^2 = chi-squared test

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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[9].

† 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[9].

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[10]. 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[11].

‖ 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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