TECHNICAL COMMENTARY

Ventricular system

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SCHIZOPHRENIA LIBRARY

Introduction

The ventricular system of the brain functions to provide support to surrounding tissues with cerebrospinal fluid (CSF), produced in the choroid plexus tissue lining many of the ventricles. The system comprises the bilateral cerebral lateral ventricles, the midline third and fourth ventricles, and the central canal of the spinal cord. The lateral ventricles have four sections, the frontal (anterior) horns; temporal (inferior) horns; body; and occipital (posterior) horns. The interventricular foramen connects the lateral ventricles to the third ventricle, and the cerebral aqueduct connects the third ventricle to the fourth. The fourth ventricle is continuous with the central canal in the spinal cord, as well as three subarachnoid foramina allowing CSF to surround the brainstem and cortices.

Schizophrenia has been associated with altered ventricular volume. Understanding of brain alterations in people with schizophrenia may provide insight into changes in brain development associated with the illness onset or progression. Reviews contained in this table reflect structural imaging investigations of ventricular volume in 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. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, 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 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).

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Results

We found 11 systematic reviews that met our inclusion criteria[3-13].

- Moderate to high quality evidence found increases in ventricular volume (right and left lateral ventricles, and third ventricle) in both first episode and chronic patients compared to controls. Right and left temporal horn were also increased in people with schizophrenia. Moderate to low quality evidence suggests increased ventricular volume in children with schizophrenia.
- Moderate to high quality evidence suggests first-degree relatives of people with schizophrenia have decreased third ventricle volume compared to controls.
- Moderate to high quality evidence found better overall functioning was associated with smaller ventricle volumes.
- Moderate to high quality evidence found increases in lateral and third ventricle volume over time (4-520 weeks from baseline), which was not explained by antipsychotic use or duration of illness. There were no changes over time in cerebrospinal fluid.

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Boos HB, Aleman A, Cahn W, Hulshoff Pol H, Kahn RS

Brain volumes in relatives of patients with schizophrenia: a meta-analysis

Archives of General Psychiatry 2007; 64(3): 297-304

View review abstract online

Comparison	**Whole brain investigation in first-degree relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, direct, mostly consistent, precise) suggests first-degree relatives of people with schizophrenia have reduced third ventricle volume.**
Lateral ventricle volume	
No differences between groups; 7 studies, N = 779, *d* = 0.11 95%CI -0.05 to 0.27, *p* > 0.05, Q = 5.85, *p* = 0.44	
Third ventricle volume	
Small effect size of decreased third ventricle volume in relatives; 7 studies, N = 832, *d* = 0.21 95%CI 0.03 to 0.4, *p* < 0.05, Q = 8.31, *p* = 0.22	
Cerebral spinal fluid volume	
No differences between groups; 4 studies, N = 217, *d* = 0.61 95%CI 0.08 to 1.14, *p* > 0.05, Q = 9.81, *p* = 0.02	
Consistency in results‡	Consistent for third ventricle, inconsistent for spinal fluid.
Precision in results§	Precise
Directness of results‖	Direct

Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S

Progressive brain changes in schizophrenia related to antipsychotic

treatment? A meta-analysis of longitudinal MRI studies **Neuroscience and Biobehavioural Reviews 2013; 37: 1680-1691** View review abstract online	
Comparison	**Longitudinal brain changes in medicated people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (medium to large samples, consistent, precise, direct) showed increased cerebrospinal fluid and enlarged lateral ventricles in patients at baseline. Moderate to high quality evidence (inconsistent) found increases in lateral ventricle volume over time (4-520 weeks from baseline), which was not explained by antipsychotic use or duration of illness. There were no changes over time in cerebrospinal fluid.**
Baseline grey matter volume	
People with schizophrenia showed increased cerebrospinal fluid and enlarged lateral ventricles; Cerebrospinal fluid: 3 studies, N = 158, g = 0.451, 95%CI 0.088 to 0.813, p = 0.045, I^2 = 8% Lateral ventricles: 11 studies, N = 896, g = 0.309, 95%CI 0.144 to 0.467, p < 0.001, I^2 = 17%	
Changes in grey matter volume over time (4 - 520 weeks from baseline)	
People with schizophrenia showed increases in lateral ventricle volume over time, with controls showing no significant change; Schizophrenia: 12 studies, g = 0.207, 95%CI 0.075 to 0.339, p = 0.002 Controls: 12 studies, g = 0.129, 95%CI -0.025 to 0.283, p = 0.102 Q_B = 9.566, p = 0.029 Lateral ventricle changes were not associated with antipsychotic use or duration of illness. *There were no changes over time in cerebrospinal fluid over time in schizophrenia or controls;* Schizophrenia: 3 studies, g = 0.007, 95%CI -0.339 to 0.352, p = 0.970 Controls: 3 studies, g = 0.199, 95%CI -0.256 to 0.654, p = 0.391 Q_B = 1.759, p = 0.185	
Consistency in results	Consistent for baseline data, not reported for follow-up data.
Precision in results	Precise
Directness of results	Direct

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Huhtaniska S, Jaaskelainen E, Hirvonen N, Remes J, Murray GK, Veijola J, Isohanni M, Miettunen J

Long-term antipsychotic use and brain changes in schizophrenia - a systematic review and meta-analysis

Human Psychopharmacology 2017; 32: doi: 10.1002/hup.2574

View review abstract online

Comparison	**Association between long-term antipsychotic dose and changes in brain regions over time (>2 years) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, inconsistent, precise, direct) suggests no associations between antipsychotic dose and CSF/ventricle volume.**
Longitudinal changes in volume	
There were no associations between long-term antipsychotic use and; Cerebrospinal fluid and ventricles: 5 studies, N = 394, r = 0.13, 95%CI -0.08 to 0.34, p = 0.23, I^2 = 70% There were no moderating effects of antipsychotic type (first vs. second generation).	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Kempton MJ, Stahl D, Williams SCR, DeLisi LE

Progressive lateral ventricular enlargement in schizophrenia: A meta-analysis of longitudinal MRI studies

Schizophrenia Research 2010; 120(1): 54-62

View review abstract online

Comparison	**Longitudinal assessments of lateral ventricle volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample precise, inconsistent, direct) suggests showed an increased rate of enlargement in lateral ventricles over time in people with schizophrenia.**
Longitudinal changes in lateral ventricle volume	
A medium-sized increased rate of lateral ventricle dilation over time; 13 studies, N = 821, g = 0.449, 95%CI 0.192 to 0.707, p = 0.0006, Q = 37.3, p < 0.001, I^2 = 63% *Results were similar in first episode and chronic patients;* First-episode: 5 studies, g = 0.491, 95%CI −0.113 to 1.095, p = 0.11 Chronic: 9 studies, g = 0.407, 95%CI 0.134 to 0.679, p = 0.003 *Meta-regressions with clinical variables;* No significant association with mean patient interscan interval (13 studies, p = 0.49), mean patient age at baseline scan (13 studies, p = 0.79), percentage of female patients (11 studies, p = 0.27), mean duration of illness at baseline scan (13 studies, p = 0.61), and mean age of onset (13 studies, p = 0.31)	
Consistency in results	Inconsistent
Precision in results	Precise for all analyses except first episode subgroup analysis.
Directness of results	Direct

Lahuis B, Kemner C, Van Engeland H

Magnetic resonance imaging studies on autism and childhood-onset schizophrenia in children and adolescents – a review

Acta Neuropsychiatrica 2003; 15(3): 140-147

View review abstract online

Comparison	**Brain volume in childhood-onset schizophrenia (COS) vs. healthy controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess consistency or precision) suggests increased**

	ventricular volume in children with schizophrenia.
Ventricular volume	
12 studies, N unclear Increased volume was observed in the ventricles of COS.	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Olabi B, Ellison-Wright I, McIntosh AM, Wood SJ, Bullmore E, Lawrie SM

Are There Progressive Brain Changes in Schizophrenia? A Meta-Analysis of Structural Magnetic Resonance Imaging Studies

Biological Psychiatry 2011; 70(1): 88-96

View review abstract online

Comparison	**Progressive changes in ventricles in people with schizophrenia vs. healthy controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) found a medium-sized increase in lateral ventricles and a small increase in third ventricles over time in people with schizophrenia.**
Longitudinal changes in ventricle volume	
Progressive changes reported across longitudinal MRI scans over 1-10 years. 31 studies, N = 1,867 *Medium-sized increase was found over time in schizophrenia;* Lateral ventricles: 10 studies, N = 719, d = 0.530, 95%CI 0.28 to 0.78, $p < 0.0001$, I^2 = 51.7% *Small increase was found over time in schizophrenia;* Third ventricle: 6 studies, N = 466, d = 0.180, 95%CI -0.01 to 0.37, p = 0.059, I^2 = 0%	
Consistency in results	Consistent

Precision in results	Precise
Directness of results	Direct

Sommer I, Aleman A, Ramsey N, Bouma A

Handedness, language lateralisation and anatomical asymmetry in schizophrenia: meta-analysis

British Journal of Psychiatry 2001; 178: 344-351

View review abstract online

Comparison	**Differences in anatomical asymmetry in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (medium to large samples, inconsistent, imprecise, direct) suggest both people with schizophrenia and controls showed right asymmetry in the temporal horn of the lateral ventricle.**

Anatomical asymmetry of the temporal horn of the lateral ventricle

Significant right asymmetry in both controls and people with schizophrenia;

Controls: 12 studies, N = 303, d = -0.25, 95%CI -0.41 to -0.09, $p < 0.01$, Q = 9.32, $p = 0.59$

Schizophrenia: 12 studies, N = 324, d = -0.42, 95%CI -0.88 to -0.04, $p = 0.04$, Q = 92.5, $p < 0.01$

No significant difference in degree of asymmetry of the temporal horn between people with schizophrenia and controls;

12 studies, N = 629, d = -0.11, 95%CI -0.61 to 0.4, $p = 0.34$, Q = 106.83, $p < 0.01$

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

Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA

Brain volume in first-episode schizophrenia: systematic review and meta-

analysis of magnetic resonance imaging studies **British Journal of Psychiatry 2006; 188(6): 510-8** View review abstract online	
Comparison	**Whole brain volume in people with first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests the ventricular volume is significantly increased in people with first-episode schizophrenia.**
Ventricular volume	
Significant increase in average ventricular volume in first-episode schizophrenia; 9 studies, N = 587 The average schizophrenia patient's left lateral ventricle volume was 33.7% larger than controls. The average schizophrenia patient's right lateral ventricle volume was 24.7% larger than controls. The average schizophrenia patient's third ventricle volume was 25.3% larger than controls.	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Vita A, De Peri L, Silenz, C, Dieci M

Brain morphology in first-episode schizophrenia: A meta-analysis of quantitative magnetic resonance imaging studies

Schizophrenia Research 2006; 82(1): 75-88

View review abstract online

Comparison	**Ventricular volume in people with first-episode schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large sample, precise, consistent, direct) suggests medium-sized increases in ventricular volume (right and left lateral ventricles, and third ventricle) of people with first-**

	episode schizophrenia.
Ventricular volume	
Right lateral ventricle *Medium effect size suggests increased right lateral ventricle volume in schizophrenia;* 8 studies, N = 447, *d* = -0.467 95%CI -0.659 to -0.275, *p* = 0.000, Q = 1.33, *p* = 0.98 Left lateral ventricle *Medium effect size suggests increased left lateral ventricle volume in schizophrenia;* 8 studies, N = 447, *d* = -0.608, 95%CI -0.802 to -0.414, *p* = 0.000, Q = 4.25, *p* = 0.74 Third ventricle *Medium effect size suggests increased third ventricle volume in schizophrenia;* 6 studies, N = 366, *d* = -0.591, 95%CI -0.804 to -0.377, *p* = 0.000, Q = 3.63, *p* = 0.6	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Wojtalik JA, Smith MJ, Keshavan MS, Eack SM

A Systematic and Meta-analytic Review of Neural Correlates of Functional Outcome in Schizophrenia

Schizophrenia Bulletin 2017; 43: 1329-47

View review abstract online

Comparison	**Association between functional outcomes and ventricular volume in people with schizophrenia.** **Functional outcomes include global functioning, social functioning, resource needs, quality of life, socioeconomic status, independent living, employment, and role functioning.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests better overall functioning was associated with smaller ventricle volumes.**

Ventricle volume and functional outcome	
37 studies, N = 1,187 *Better functioning was associated with smaller volumes in;* Ventricles: 10 studies, *r* = -0.31, 95%CI -0.41 to -0.21, *p* < 0.0001, Q = 45.09, *p* < 0.05	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET

Meta-analysis of regional brain volumes in schizophrenia

American Journal of Psychiatry 2000; 157(1): 16-25

View review abstract online

Comparison	**Ventricular volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (medium to large samples, consistent, imprecise, direct) suggests medium-sized increases in ventricular volume in the lateral ventricles, temporal horn and third ventricles of people with schizophrenia. No differences in fourth, frontal horn, occipital horn, or body ventricles.**
Ventricular volume	
Increased ventricle system in schizophrenia for; Left lateral ventricle 18 studies, N = 1053 *Medium effect size - average volume of schizophrenia ventricle 130% of control volume, 95%CI 120% to 141%;* *d* = 0.51 No CIs reported, *p* = 0.01 Right lateral ventricle 18 studies, N = 1053 *Small effect size – average volume of schizophrenia ventricle 120% of control volume, 95%CI 113% to*	

128%;

d = 0.39, no CIs reported, *p* = 0.17

Left temporal horn

13 studies, N = 791

Medium effect size – average volume of schizophrenia ventricle 134% of control volume, 95%CI 118% to 153%;

d = 0.53, no CIs reported, *p* < 0.01

Right temporal horn

13 studies, N = 791

Medium effect size – average volume of schizophrenia ventricle 119% of control volume, 95%CI 109% to 131%;

d = 0.40, no CIs reported, *p* = 0.01

Third ventricle

22 studies, N = 1143

Medium effect size – average volume of schizophrenia ventricle 126% of control volume, 95%CI 119% to 134%;

d = 0.59, no CIs reported, *p* = 0.01

No differences between groups for;

Left frontal horn

3 studies, N = 129

Small effect size – average volume of schizophrenia ventricle 113% of control volume, 95%CI 97% to 132%;

d = 0.29, no CIs reported, *p* = 0.25

Right frontal horn

3 studies, N = 129

Small effect size – average volume of schizophrenia ventricle 117% of control volume, 95%CI 105% to 132%;

d = 0.36, no CIs reported, *p* = 0.49

Left body ventricle

3 studies, N = 129

Large effect size – average volume of schizophrenia ventricle 147% of control volume, 95%CI 124% to 174%;

d = 0.78, no CIs reported, *p* = 0.82

Right body ventricle

Ventricular system

3 studies, N = 129 *Large effect size – average volume of schizophrenia ventricle 148% of control volume, 95%CI 126% to 174%;* *d* = 0.86, no CIs reported, *p* = 0.42 <u>Left occipital horn</u> 3 studies, N = 129 *Medium effect size – average volume of schizophrenia ventricle 129% of control volume, 95%CI 113% to 147%;* *d* = 0.58, no CIs reported, *p* = 0.91 <u>Right occipital horn</u> 3 studies, N = 129 *Medium effect size – average volume of schizophrenia ventricle 128% of control volume, 95%CI 110% to 149%;* *d* = 0.57, no CIs reported, *p*= 0.42 <u>Fourth ventricle</u> 5 studies, N = 253 *Small effect size – average volume of schizophrenia ventricle 107% of control volume, 95%CI 96% to 119%;* *d* = 0.21, no CIs reported, *p* = 0.23 <u>Total ventricles</u> 30 studies, N =1896 *Medium effect size – average volume of schizophrenia ventricle 126% of control volume, 95%CI 120% to 132%* *d* = 0.49, no CIs reported, *p* = 0.11	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, COS = child-onset schizophrenia, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect sizes), I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MRI = magnetic resonance imaging, N = number of participants, *p* = statistical probability of

obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic (chi-square) for the test of heterogeneity in results across studies, vs. = versus

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[14].

† Different effect measures are reported by different reviews.

ALE analysis (Anatomical Likelihood Estimate) refers to a voxel-based meta-analytic technique for structural imaging in which each point of statistically significant structural difference is spatially smoothed into Gaussian distribution space, and summed to create a statistical map estimating the likelihood of difference in each voxel, as determined by the entire set of included studies. Incorporated with the Genome Scan Meta-analysis (GSMA), the meta-analysis of coordinates from multiple studies can be weighted for sample size to create a random effect analysis. The ALE statistic (if reported) represents the probability of a group difference occurring at each voxel included in the analysis.

Fractional similarity network analysis refers to a network analysis technique in which secondary networks are identified within the larger framework of activity, creating a matrix for regional co-activity.

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) which 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[14].

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[15]. 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.

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 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.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).

‡ 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[16].

‖ 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, which allows indirectcomparisons 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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