



Parietal lobe

Introduction

The parietal cortex is located posterior to the frontal lobe. It is structurally divided into the superior, middle and inferior gyri. The most anterior portion of the parietal lobe forms the post-central gyrus, the somatosensory cortex. Posterior to this are the parietal association regions, and the visual regions of the posterior parietal cortex, involved in visuospatial processing.

Schizophrenia has been associated with altered structure and function of the parietal lobe. Understanding of any 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 technical summary reflect both structural (MRI, DTI), and functional imaging (fMRI, PET) studies, as well as metabolic investigations (MRS) of the parietal lobe 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-analysis¹. 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).

Results

We found twelve systematic reviews that met our inclusion criteria³⁻¹⁴.



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Structural changes: MRI and DTI

- Moderate quality evidence suggests grey matter reductions in the left inferior parietal gyrus in schizophrenia and bilateral post-central gyrus in chronic and first-episode schizophrenia compared to controls.
- Moderate to low quality evidence suggests reductions in white matter integrity in the parietal lobe, including temporo-parietal and parieto-occipital regions.
- High quality evidence suggests greater reductions over time in parietal white matter in schizophrenia than in controls.

Functional changes: fMRI, PET, MRS

- Moderate quality evidence suggests reduced functional activation of the right inferior parietal lobe in schizophrenia during episodic memory encoding and executive functioning tasks. Regions of the inferior parietal cortex and precuneus show increased activity during executive functioning tasks.
- Moderate to low quality evidence suggests abnormal activity (mostly increased) in the parietal cortex of first-degree relatives of people with schizophrenia during cognitive control, working memory and language processing tasks. No difference was reported in long-term memory tasks.
- Moderate to low quality evidence shows decreased N-acetyl aspartate levels in parietal cortex grey matter in schizophrenia compared to healthy controls.



Chan RCK, Di X, McAlonan GM, Gong Q

Brain Anatomical Abnormalities in High-Risk Individuals, First-Episode, and Chronic Schizophrenia: An Activation Likelihood Estimation Meta-analysis of Illness Progression

Schizophrenia Bulletin 2011; 37(1) 177-188

[View review abstract online](#)

Comparison	Grey matter changes in people with chronic or first-episode schizophrenia vs. healthy controls.
Summary of evidence	Moderate quality evidence (large sample size, direct, unable to assess consistency or precision) suggests people with first-episode schizophrenia have grey matter reductions in bilateral postcentral gyrus compared to healthy controls.
Grey matter volume	
<p>Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies.</p> <p style="text-align: center;">FWHM 10mm, FDR corrected at $p < 0.01$</p> <p style="text-align: center;"><i>Areas of reduced volume in first-episode schizophrenia;</i></p> <p style="text-align: center;">14 studies, N = 1082</p> <p>Right post central gyrus Talairach coordinates (52, -20, 44), cluster 216mm³, ALE 0.0115</p> <p>Left post central gyrus Talairach coordinates (-60, -18, 20), cluster 200mm³, ALE 0.0117</p> <p style="text-align: center;"><i>Areas of reduced volume in chronic schizophrenia;</i></p> <p style="text-align: center;">19 studies, N = 1664</p> <p>Right post central gyrus: Talairach coordinates (56, -20, 18), cluster 792mm³, ALE 0.0239</p> <p style="text-align: center;"><i>Subtraction analysis between chronic and first-episode schizophrenia showed greater grey matter reduction in the chronic group in;</i></p> <p>Right postcentral gyrus: Talairach coordinates (56, -22, 16), cluster 160mm³, ALE 0.0151</p>	
Consistency in results[‡]	No measure of consistency is reported.
Precision in results[§]	No confidence intervals are provided.



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Directness of results	Direct
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Fornito A, Yucel M, Patti J, Wood SJ, Pantelis C

Mapping grey matter reductions in schizophrenia: An anatomical likelihood estimation analysis of voxel-based morphometry studies

Schizophrenia Research 2009; 108(1-3): 104-113

[View review abstract online](#)

Comparison	Grey matter volume in schizophrenia patients vs. healthy controls.
Summary of evidence	Moderate quality evidence (large sample sizes, direct, unable to assess consistency or precision) suggests bilateral reductions in grey matter volume in the anterior cingulate/medial prefrontal cortex, the insula/operculum, the posterior cingulate, thalamus, medial temporal lobe, and subgenual cingulate; as well as lateralised differences in the left middle and inferior frontal gyri, the left fusiform gyrus, and left inferior parietal gyrus in people with schizophrenia.

Grey matter volume

Meta-analysis was performed using Activation Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies.

FWHM 12mm, FDR corrected at $p < 0.05$

37 studies, N = 3336

Decreased grey matter was reported in the left inferior parietal gyrus.

Pooled analysis identified 15 clusters of reduced grey matter, encompassing foci in the frontal, temporal, limbic and subcortical regions.

Clusters where volume reductions were significantly more frequent than grey matter concentration reductions (grey matter as a proportion of the whole brain volume);

Right pre and post-central gyri: Talairach coordinates (52.97, -24.28, 43.55), Voxel cluster size 408mm^3 , ALE -0.54×10^{-3}

Fusar-Poli P, Perez J, Broome M, Borgwardt S, Placentino A, Caverzasi E, Cortesi



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M, Veggiotti P, Politi P, Barale F, McGuire P

Neurofunctional correlates of vulnerability to psychosis: A systematic review and meta-analysis

Neuroscience & Biobehavioral Reviews 2007; 31(4): 465-484

[View review abstract online](#)

Comparison 1	Functional activation in people following their first episode of schizophrenia and people at high-risk of psychosis vs. healthy controls
Summary of evidence	Low quality evidence (one small study per outcome) is unclear as to the direction of the changes in functional activity in the parietal cortex during information processing tasks.
Functional activation during Information processing paradigm	
1 study, N = 23 Reduced activation of parietal lobe ($d = 1.34$) in medication naïve first-episode schizophrenia patients compared to controls.	
Working memory paradigm	
1 study, N = 41 Medium effect size suggests increased activation of inferior parietal lobe ($d = 0.58$) in siblings of people with schizophrenia compared to controls for working memory tasks.	
1 study, N = 40 Small effect size suggests increased activation of inferior parietal lobe ($d = 0.48$) in siblings of people with schizophrenia compared to controls for working memory tasks	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals reported
Directness of results	Direct

Glahn DC, Laird AR, Ellison-Wright I, Thelen SM, Robinson JL, Lancaster JL, Bullmore E, Fox PT

Meta-analysis of gray matter anomalies in schizophrenia: application of



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anatomic likelihood estimation and network analysis

Biological Psychiatry 2008; 64(9): 774-781

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Comparison	Grey matter density in people with schizophrenia vs. healthy controls.
Summary of evidence	Moderate quality evidence (large sample sizes, direct, unable to assess consistency or precision) suggests schizophrenia is associated with significant grey matter reductions in the post central gyrus.
Grey matter volume	
<p>Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies.</p> <p style="text-align: center;">FWHM 12mm, FDR corrected at $p < 0.05$</p> <p style="text-align: center;">13 studies, N = 2457</p> <p><i>Clusters where density reductions were more frequent in people with schizophrenia than in controls;</i></p> <p>Left post central gyrus: Talairach coordinates (-62, -16, 18), Voxel cluster size 608mm³, $p < 0.01$, ALE = 0.012</p>	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Goghari MV

Executive functioning-related brain abnormalities associated with the genetic liability for schizophrenia: an activation likelihood estimate meta-analysis

Psychological Medicine 2001; 41: 1239-1252

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Comparison	Functional activation in relatives of people with schizophrenia
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	vs. controls during an executive functioning task.
Summary of evidence	Moderate quality evidence (unable to assess consistency or precision, direct) suggests that regions of the inferior parietal cortex and precuneus show increased activity during executive functioning tasks.
Activation during executive functioning tasks	
<p>All VBM studies, including those assessing voxel-based activation in <i>a priori</i> regions of interest, were included in this analysis.</p> <p style="text-align: center;">17 studies, N = 456</p> <p><i>Increased activity in relatives of people with schizophrenia compared to controls in;</i></p> <p>Left inferior parietal gyrus: Talairach coordinates (-40/-40, -64/-60, 46/44), cluster volume 192 mm³</p> <p>Left precuneus: Talairach coordinates (-2, -80, 44), cluster volume 368 mm³</p> <p>Subgroup analysis of studies that assessed whole-brain voxel-based activation.</p> <p><i>Increased activity in relatives of people with schizophrenia compared to controls in;</i></p> <p>Left inferior parietal cortex: Talairach coordinates (-40/-40, -64/-60, 46/44), cluster volume 264 mm³</p> <p>Left precuneus: Talairach coordinates (-2, -80, 44), cluster volume 384 mm³</p> <p><i>Decreased activity in relatives of people with schizophrenia compared to controls in;</i></p> <p>Right parietal cortex: Talairach coordinates (24, -48, 42), cluster volume 144 mm³</p>	
Activation during a working memory task	
<p><i>Increased activity in relatives of people with schizophrenia compared to controls in;</i></p> <p>Left inferior parietal cortex: Talairach coordinates (-40/-40, -64/-60, 46/44), cluster volume 264 mm³</p> <p>Left precuneus: Talairach coordinates (-2, -80, 46), cluster volume 368 mm³</p>	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct



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Kanaan RA, Kim JS, Kaufmann WE, Pearlson GD, Barker GJ, McGuire PK

Diffusion tensor imaging in schizophrenia

Biological Psychiatry 2005; 58(12): 921-929

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Comparison	White matter fractional anisotropy (FA) in people with schizophrenia vs. healthy controls
Summary of evidence	Moderate quality evidence (large sample size, direct, unable to fully assess precision and consistency) suggests no significant difference in FA in the parietal cortex.
Functional activity	
19 studies, N = 640 Temporo-parietal cortex; parieto-occipital cortex report no significant difference in FA between schizophrenia patients and controls.	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Kyriakopoulos M, Bargiotas T, Barker GJ, Frangou S

Diffusion tensor imaging in schizophrenia

European Psychiatry: the Journal of the Association of European Psychiatrists 2008; 23(4): 255-273

[View review abstract online](#)

Comparison	White matter integrity, assessed by voxel-based analysis, in people with schizophrenia vs. healthy controls.
Summary of evidence	Moderate to low quality evidence (sample size unclear, direct, unable to assess precision and consistency) suggests reduced FA in the parietal lobe of people with schizophrenia.



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Functional activity	
15 studies, N = unclear Parietal lobe illustrated decreased FA in four studies between schizophrenia patients and controls.	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct
Comparison 2	Regions of reduced white matter integrity, assessed by region-of-interest analysis, in schizophrenia patients vs. healthy controls
Summary of evidence	Moderate to low quality evidence (sample size unclear, direct, unable to assess precision and consistency) suggests reduced white matter integrity in the parietal lobe using region-of-interest analysis.
Functional activity	
17 studies, N = unclear 3 studies show decreases in parietal regions in schizophrenia patients.	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

MacDonald AW, Thermenos HW, Barch DM, Seidman L.

Imaging genetic liability to schizophrenia: systematic review of fMRI studies of patients' nonpsychotic relative.

Schizophrenia Bulletin 2009; 35(6): 1142-1162

[View review abstract online](#)

Comparison	Functional activation in first-degree relatives of people with schizophrenia vs. healthy controls.
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<p>Summary of evidence</p>	<p>Moderate to low quality evidence (large sample size, direct, unable to assess precision or consistency) suggests that functional activity during cognitive control, working memory and language processing tasks shows abnormal activity (mostly increased) in the parietal cortex of relatives. No difference was reported for long-term memory tasks.</p>
<p align="center">Functional activity during cognitive control tasks</p>	
<p align="center"><i>7 studies investigated functional activity during cognitive control tasks, N = 308;</i> 6 studies investigated the parietal cortex, 3/6 showed increased bilateral activity compared to controls. Activity (hyper- and hypo-) was abnormal in 67% of reports.</p>	
<p align="center">Functional activity during working memory tasks</p>	
<p align="center"><i>4 studies (5 independent samples) investigated functional activity during working memory tasks, N = 239;</i> 5 studies investigated the parietal cortex, 3/5 showed increased activity compared to controls. Activity (hyper- and hypo-) was abnormal in 67% of reports.</p>	
<p align="center">Functional activity during long-term memory tasks</p>	
<p align="center"><i>3 studies investigated functional activity during episodic long term memory tasks, N = 195;</i> 3 studies investigated the parietal cortex, 3/3 showed no group differences.</p>	
<p align="center"><i>1 study investigated functional activity during procedural long term memory tasks, N = 27</i> Reduced activity in relatives was shown in parietal cortex.</p>	
<p align="center">Functional activity during language processing studies</p>	
<p align="center"><i>4 studies investigated functional activity during language processing tasks, N = 164;</i> 3/4 showed increased activity in the right parietal cortex, 1/3 also showed increased activity in the left parietal.</p>	
<p>Consistency in results</p>	<p>No measure of consistency is reported.</p>
<p>Precision in results</p>	<p>No measure of precision reported</p>
<p>Directness of results</p>	<p>Direct</p>



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Minzenberg MJ, Laird AR, Thelen S, Carte, CS, Glahn DC

Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia

Archives of General Psychiatry 2009; 66(8): 811-822

[View review abstract online](#)

Comparison	Whole brain comparison of functional activation in individuals with schizophrenia vs. healthy controls: ALE analysis
Summary of evidence	Moderate quality evidence (observational, large sample) suggests people with schizophrenia show regions of reduced activity in the right inferior parietal region and increased activity in the left inferior parietal region during executive functioning tasks.
Functional activation during executive functioning tasks	
<p>41 studies, N = 1217</p> <p>ALE analysis – FWHM 12mm, False Discovery Rate (FDR) corrected model</p> <p><i>Significantly reduced activity in schizophrenia compared to controls in;</i></p> <p>Right inferior parietal lobule: Talairach centre of mass (36, -58, 42), cluster volume 792mm³</p> <p><i>Significantly increased activity in schizophrenia patients compared to controls in;</i></p> <p>Left inferior parietal lobule: Talairach centre of mass (-54, -42, 42), cluster volume 1200mm³</p> <p><i>Fractional similarity network subanalysis – regions of co-occurring hyperactivation where increases in schizophrenia are larger than in controls;</i></p> <p>Left anterior cingulate cortex: Talairach centre of mass (-2, 10, 40), cluster volume 1256mm³</p> <p>Left inferior parietal lobule: Talairach centre of mass (-54, -42, 42), cluster volume 584mm³</p>	
Consistency in results	No measure of consistency is reported.
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	Grey and white matter volume in people with schizophrenia vs. healthy controls
Summary of evidence	High quality evidence (large sample sizes, inconsistent, precise, direct) suggests no change in parietal grey over time but greater reductions of parietal white matter in people with schizophrenia compared to controls.
Grey and white matter volume	
<p>Progressive changes in grey matter volume reported across longitudinal MRI scans over 1-10 years 31 studies, N = 1867</p> <p><i>Significantly greater reductions were reported over time in schizophrenia compared to controls in;</i></p> <p>Parietal grey matter: N = 364, 7 studies, $d = -0.161$, 95%CI -0.50 to 0.18, $p = 0.352$, $I^2 = 52.6\%$</p> <p>Parietal white matter: N = 227, 4 studies, $d = -0.533$, 95%CI -0.84 to -0.23, $p = 0.001$, $I^2 = 4.0\%$</p>	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Ragland JD, Laird AR, Ranganath C, Blumenfeld RS, Gonzales SM, Glahn DC
Prefrontal activation deficits during episodic memory in schizophrenia

American Journal of Psychiatry 2009; 166(8): 863-874

[View review abstract online](#)

Comparison	Functional activation during episodic memory tasks in people with schizophrenia vs. healthy controls.
Summary of evidence	Moderate quality evidence (large sample, direct) suggests



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	activity during episodic memory encoding is reduced in the right inferior parietal gyrus of schizophrenia patients compared to controls
Functional activity during episodic memory encoding	
<p>ALE analysis – FWHM 12mm, False Discovery Rate (FDR) corrected model $p < 0.05$ <i>Significantly decreased activity in people with schizophrenia than in controls;</i> Right inferior parietal gyrus: cluster volume 1056mm³, Talairach centre of mass (50, -48, 36)</p>	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Steen RG, Hamer RM, Lieberman JA

Measurement of brain metabolites by ¹H magnetic resonance spectroscopy in patients with schizophrenia: a systematic review and meta-analysis

Neuropsychopharmacology 2005; 30(11): 1949-1962

[View review abstract online](#)

Comparison	N-acetyl aspartate (NAA) activity (measured by ¹ H-MRS) in grey and white matter regions in people with schizophrenia vs. healthy controls.
Summary of evidence	Low quality evidence (sample size unclear, direct inconsistent, unable to assess precision) is unclear of NAA levels in the parietal cortex in people with schizophrenia.
NAA	



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<p><u>Grey matter</u> 1 study, N unclear Patient average 94.0% of control levels</p> <p><u>White matter</u> 2 studies, N unclear Patient average 99.0% of control levels</p>	
Consistency in results	Significant heterogeneity reported, $p < 0.0001$
Precision in results	No confidence intervals are provided.
Directness of results	Direct comparison of NAA levels

Explanation of acronyms

ALE = activation likelihood estimate, CI = Confidence Interval, d = Cohen's d and g = Hedges' g = standardized mean differences (see below for interpretation of effect size), DTI = diffusion tensor imaging, FA = fractional anisotropy, FDR = false discovery rate correction for multiple comparisons, FWHM = full-width at half maximum smoothing kernel, fMRI = functional magnetic resonance imaging, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, NAA = N-acetyl aspartate, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PET = positron emission tomography, Q = Q statistic (chi-square) for the test of heterogeneity, 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 small¹⁵.

† 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 effect¹⁵.

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 ¹⁶. InOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios



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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 unforeseen 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 relaxed¹⁷.

|| 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 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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