TECHNICAL COMMENTARY

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Amygdala

Introduction

The amygdala is located deep in the medial temporal lobe, and has reciprocal connections with many regions of the cortex, such as prefrontal and cingulate cortex, as well as sub-cortical regions such as the brainstem and hippocampus. The amygdala is implicated in the processing and memory of emotional responses, particularly emotional learning, as well as mediating the autonomic expression of emotion.

Schizophrenia has been associated with alterations in the amygdala. Understanding of brain alterations in people with schizophrenia may provide insight into changes in brain development associated with the illness onset or progression. The amygdala is often identified in imaging studies in conjunction with the hippocampus, due to their close spatial proximity. Reviews contained in this technical summary reflect both structural imaging investigations (MRI), and functional imaging investigations (fMRI, PET) of the amygdala 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 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 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 thirteen systematic reviews that met our inclusion criteria[3-15].

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Structural changes: MRI and DTI

- Moderate quality evidence suggests reduced amygdala and hippocampus-amygdala grey matter in people with schizophrenia, including child-onset patients, compared to healthy controls.
- Moderate to high quality evidence suggests no change in amygdala volume over time in people with schizophrenia compared to controls.
- Moderate quality evidence suggests that first degree relatives of people with schizophrenias and other people at high risk have reduced amygdala grey matter compared to healthy controls.
- Moderate to low quality evidence suggests reduced white matter integrity in the amygdala of patients.

Functional changes: fMRI and PET

- Moderate quality evidence suggests people with schizophrenia show functional hyperactivity in the amygdala during executive function tasks.
- Moderate to low quality evidence suggests people with schizophrenia have decreased activation in the amygdala during emotion processing tasks.
- Low quality evidence is unclear as to the direction of the changes in functional activity in the amygdala during cognitive tasks in individuals at high risk of developing schizophrenia.

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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	**Brain volume in first degree relatives of schizophrenia patients vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample size, direct, inconsistent, precise) suggests that first degree relatives of schizophrenia patients have reduced amygdala volume compared to healthy controls.**
Amygdala/hippocampus volume	
Medium combined effect size for decreased amygdala and hippocampus volume in first degree relatives compared to healthy controls; 12 studies, N = 1280, d = 0.52, 95%CI 0.16 to 0.89, $p < 0.05$, Q = 94.17, $p < 0.001$	
Consistency in results‡	Inconsistent
Precision in results§	Precise
Directness of results‖	Direct

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 1	**Grey matter changes in people at high risk of schizophrenia vs. healthy controls. People at high risk of schizophrenia were defined as first or second degree relatives of people with schizophrenia, those meeting the Personal Assessment and**

	Crisis Evaluation clinic criteria, or those with a modification of the catechol-O-methyltransferase gene.
Summary of evidence	**Moderate quality evidence (large sample size, direct, unable to assess consistency or precision) suggests high risk individuals have grey matter reductions in bilateral left amygdala compared to healthy controls and first episode schizophrenia patients.**
Grey matter changes in high risk individuals	
Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies; FWHM 10mm, FDR corrected at $p < 0.01$ 8 studies, N = 1031 Left amygdala: Talairach coordinates (-28, -8, -12), cluster 800mm^3, ALE 0.0112 Between group comparisons: subtraction analysis between high risk individuals and first episode schizophrenia *Compared to first episode patients, high risk subject showed greater grey matter reduction in;* Left amygdala: Talairach coordinates (-30, -8, -12), cluster 128mm^3, ALE -0.0097	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct
Comparison 2	**Grey matter changes in chronic schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample size, direct, unable to assess consistency or precision) suggests chronic schizophrenia have grey matter reductions in bilateral amygdala compared to healthy controls.**
Grey matter change in chronic schizophrenia	
Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies FWHM 10mm, FDR corrected at $p < 0.01$ *19 studies, N = 1664* Left amygdala: Talairach coordinates (-16, -6, -12), cluster 840mm^3, ALE 0.0247	

Right amygdala: Talairach coordinates (18, -4, -12), cluster 584mm^3, ALE 0.0195	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Davidson LL, Heinrichs RW

Quantification of frontal and temporal lobe brain-imaging findings in schizophrenia: a meta-analysis

Psychiatry Research 2003; 122(2): 69-87

View review abstract online

Comparison	**Grey matter volume in schizophrenia patients vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample size, inconsistent, precise, direct) suggests grey matter volume is significantly reduced in the amygdala in schizophrenia.**
Amygdala volume	
Small to medium effect size suggests reduced volume in schizophrenia; Left amygdala: N = 970, *d* = -0.39, 95%CI -0.68 to -0.10, *p* not reported SD = 0.53, FSN = 44 Right amygdala: N = 1109, *d* = -0.38, 95%CI -0.72 to -0.04, *p* not reported SD = 0.67, FSN = 48	
Hippocampus/amygdala complex volume	
Left hippocampus/amygdala complex: N = 1302, *d* = -0.41, 95%CI -0.74 to -0.41, *p* not reported SD = 0.44, FSN = 71 Right hippocampus/amygdala complex: N = 1238, *d* = -0.36, 95%CI -0.54 to -0.18, *p* not reported SD = 0.40, FSN = 57	
Consistency in results	Significant heterogeneity reported in all outcomes.
Precision in results	Precise for all outcomes.
Directness of results	Direct

Ellison-Wright I, Glahn DC, Laird AR, Thelen SM, Bullmore E

The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis

American Journal of Psychiatry 2008; 165(8): 1015-23

View review abstract online

Comparison	**Grey matter volume in first episode schizophrenia patients vs. chronic schizophrenia patients vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample size, direct, unable to assess consistency or precision) suggests a reductions of bilateral amygdala grey matter in first episode schizophrenia, which are absent in chronic schizophrenia.**
Changes reported in first-episode schizophrenia patients	
Voxel-based morphometry whole brain grey matter volume reported at baseline N = 1556, 27 observational studies *Significant reductions of volume observed in the amygdala in first episode schizophrenia;* Left uncus/amygdala: Talairach coordinates (-18, -2, -22), cluster 2760mm^3, ALE 0.018, p < 0.0002 Right uncus/amygdala: Talairach coordinates (20, -4, -22), cluster 688mm^3, ALE 0.012, p < 0.0002	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

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

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Amygdala

Comparison	**Comparison of grey matter volume (GMV) and grey matter concentration (GMC, grey matter as a proportion of the whole brain volume) using voxel-based morphometry MRI analysis in schizophrenia patients vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess consistency or precision) suggests that concentration and volume measures of grey matter provide different accounts of the regions affected in schizophrenia. Volume measured clusters were generally smaller and more spatially dispersed while concentration measured regions remained consistent across all subsets tested, suggesting GMC values may be more robust. Significant volume reductions were reported in the amygdala/hippocampus.**
Clusters where GMC reductions were significantly more frequent than GMV reductions	
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 Left amygdala/hippocampus: Talairach coordinates (-18.33, -4.63, -15.34), Voxel cluster size 1592mm^3, ALE 0.98 x 10^{-3}	
GMC vs. GMV: multiple comparisons for reliability	
As GMC had fewer foci available for comparison, a random subset was initially selected for comparison with GMV. To increase validity of this comparison, four additional GMC/GMV contrasts were performed with different GMC subsets, and demonstrated high consistency between randomisations. *Both cluster size and ALE statistic were larger for comparisons using concentration measures compared to volume measures;* Cluster size t = 2.54, $p = 0.02$ ALE statistic t = 2.82, $p = 0.01$	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

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

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	**Comparison of functional activation in individuals at high risk of developing schizophrenia vs. healthy controls.**
Summary of evidence	**Low quality evidence (one small observational study) is unclear as to the direction of the changes in functional activity in the amygdala during cognitive tasks in individuals at high risk of developing schizophrenia.**
Functional activation during emotional face processing paradigm	
1 study, N = 39 Medium effect size suggests reduced activation of amygdala (d = 1.05) in non-psychotic relatives of schizophrenia patients compared to controls for emotional face processing tasks.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
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	**Comparison of 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 amygdala.
Regions of altered FA: ROI	
No regions showed consistent FA changes across all studies; 17 studies, N = unclear 8 studies report decreased FA in temporal regions (amygdala) between schizophrenia patients and controls.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
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 (sample sizes unclear, direct, unable to assess consistency or precision) suggests child-onset schizophrenia patients exhibit volume reductions in the amygdala.**
Regions of reduced volume on MRI in COS	
12 studies, N unclear Reduced volume was reported in the amygdala.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.

Directness of results	Direct comparison of whole brain volume in childhood-onset schizophrenia to healthy controls

Li H, Chan R, McAlonan G, Gong Q-Y

Facial emotion processing in schizophrenia: A meta-analysis of functional neuroimaging data

Schizophrenia Bulletin 2010; 36(5): 1029-1039

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Comparison	**Comparison of functional activation in people with schizophrenia vs. controls during a facial emotion processing task.**
Summary of evidence	**Moderate to low quality evidence (small sample, direct, unable to assess consistency or precision) suggests that people with schizophrenia show decreased activation during emotion processing tasks in amygdala.**

Activation during a facial emotion processing task

Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis.

10 studies, N = 133, reported activation foci for control subjects alone.

Left parahippocampal gyrus/amygdala: Talairach coordinates (-21, -5, -10), 8 foci, 784mm^3, 0.102 ALE

8 studies, N = 95, reported activation for people with schizophrenia.

Left parahippocampal gyrus/amygdala: Talairach coordinates (-21, -8, -14), 5 foci, 480mm^3, 0.068 ALE

Right parahippocampal gyrus/amygdala: Talairach coordinates (23, -5, -14), 4 foci, 424mm^3, 0.061 ALE

Subtraction meta-analysis suggests these activations were significantly larger in controls than in people with schizophrenia.

Left parahippocampal gyrus/amygdala: Talairach coordinates (-22, -5, -9), 8 foci, 464mm^3, 0.091 ALE

Direct between-group contrasts examined regions of differential activation between people with schizophrenia and controls.

13 studies reported reduced activation in people with schizophrenia compared to controls during an

emotion perception task. Right parahippocampal gyrus/amygdala: Talairach coordinates (26, -8, -12), 4 foci, 368mm^3, 0.052 ALE Left parahippocampal gyrus/amygdala: Talairach coordinates (-26, -10, -13), 3 foci, 272mm^3, 0.060 ALE <u>Subgroup analysis assessed the studies by task type: explicit emotion and implicit emotion</u> Subtraction meta-analysis of activation during an explicit emotional task found decreased activation in people with schizophrenia compared to controls. Left amygdala: Talairach coordinates (-21, -7, -8), 6 foci, 368mm^3, 0.091 ALE Subtraction meta-analysis of activation during an implicit emotional task suggesting decreased activation in people with schizophrenia compared to controls. Left parahippocampal gyrus/amygdala: Talairach coordinates (-26, -10, -14), 3 foci, 280mm^3, 0.060 ALE Right left parahippocampal gyrus/amygdala: Talairach coordinates (24, -8, -12), 3 foci, 280mm^3, 0.051 ALE	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Minzenberg MJ, Laird AR, Thelen S, Carter 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	**Comparison of functional activation in individuals with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample size, direct, unable to assess precision or consistency) suggests patients with schizophrenia show increased activity in the amygdala during executive function tasks.**

Activation following executive function tasks: schizophrenia > controls	
41 observational studies, N = 1217 ALE analysis – FWHM 12mm, False Discovery Rate (FDR) corrected model Significantly increased activity in schizophrenia patients compared to controls Right amygdala: Talairach centre of mass (18, -4, -12), cluster volume 592mm^3	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
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

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Comparison	**Progressive changes in whole brain grey matter volume in schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to high quality evidence (large sample sizes, inconsistent, precise, direct) suggests no change in amygdala volume over time in schizophrenia compared to controls.**
Grey matter volume	
Progressive changes in grey matter volume reported across longitudinal MRI scans over 1-10 years. 31 studies, N = 1867 *No differences between patients and controls;* Right hippocampal/amygdala complex: N = 153, 5 studies, d = -0.060, 95%CI -0.38 to 0.26, p = 0.716, I^2 = 0% Right amygdala: N = 235, 5 studies, d = -0.138, 95%CI -0.43 to 0.16, p = 0.362, I^2 = 12.5% Left hippocampal/amygdala complex: N = 153, 5 studies, d = 0.107, 95%CI -0.22 to 0.43, p = 0.518, I^2 = 0%	

Left amygdala: N = 235, 5 studies, *d* = 0.019, 95%CI -0.24 to 0.28, *p* = 0.887, I^2 = 0%	
Consistency in results	Consistent for hippocampal/amygdala complex only.
Precision in results	Precise
Directness of results	Direct

Vita A, De Peri L, Silenzi 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

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Comparison	**Brain volume in people with first-episode schizophrenia vs. healthy controls.**
Summary of evidence	**High quality evidence (large sample sizes, precise, consistent, direct) suggests no difference in amygdala volume between first-episode schizophrenia and controls.**
Amygdala volume	
No significant difference were found for; Right amygdala: 4 studies, N = 203, *d* = 0.088, 95%CI -0.193 to 0.369, *p* = 0.537, Q = 2.51, *p* = 0.47 Left amygdala: 4 studies, N = 203, *d* = 0.195, 95%CI -0.086 to 0.476, *p* = 0.173, Q = 1.49, *p* = 0.68	
Consistency in results	Consistent
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

Amygdala

American Journal of Psychiatry 2000; 157(1): 16-25 View review abstract online	
Comparison	**Brain volume in people with schizophrenia vs. healthy controls.**
Summary of evidence	**High quality evidence (large sample size, consistent, precise, direct) suggests non-significant reductions of amygdala and hippocampus-amygdala volume in people with schizophrenia compared to healthy controls.**
Amygdala volume	
Average volume of schizophrenia amygdala 91% of control volume; Left amygdala: 7 studies, N = 283, *d* = -0.72, no CIs reported; *p* = 0.30 (average volume 91% of control volume, 95%CI 87 to 94%) Right amygdala: 7 studies, N = 283, *d* = -0.69, no CIs reported; *p* = 0.14 (average volume 91% of control volume, 95%CI 87 to 95%) *Average volume of schizophrenia hippocampus-amygdala 95% of control volume;* Left hippocampus-amygdala: 15 studies, N =731, *d* = -0.24, no CIs reported; *p* = 0.10 (average volume 95% of control volume, 95%CI 92 to 99%) Right hippocampus-amygdala*:* 15 studies, N = 731, *d* = -0.28, no CIs reported; *p* = 0.50 (average volume 94% of control volume, 95%CI 92 to 97%)	
Consistency in results	Consistent
Precision in results	Precise – volume CI range does not exceed 10% in either direction.
Directness of results	Direct

Explanation of acronyms

ALE = activation/anatomical likelihood estimate, Activation refers to functional magnetic resonance imaging (MRI) while Anatomical refers to structural MRI, CI = Confidence Interval, COS = child onset schizophrenia, *d* = Cohen's *d* and *g* = Hedges' *g* = standardized mean differences (see below for interpretation of effect size), FDR = false discovery rate correction for multiple comparisons, fMRI = functional magnetic resonance imaging, FSN = fail-safe N, FWHM = full-width half maximum (smoothing kernel), GMC = grey matter concentration, GMV = grey matter volume, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic (chi-square) for test of heterogeneity, SD = standard deviation, 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[16].

† 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[16].

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[17]. lnOR 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 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 which are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives which 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[18].

‖ 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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