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Introduction

For a person to be diagnosed with PTSD, at least one stressor is required. Stressors as determined by the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) include being exposed to threatened death, actual or threatened serious injury, or actual or threatened sexual violence. Examples are direct exposure, witnessing the trauma, or learning that a relative or close friend was exposed to trauma.

This summary table presents the evidence for risk of PTSD at different levels of trauma severity.

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 2010 that report results separately for people with PTSD. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. When multiple copies of reviews were found, only the most recent version was included. We prioritised reviews with pooled data 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-analysis¹. Reviews with less than 50% of items checked have been excluded from the library. 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 (<u>GRADE</u>) 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 or if there is a dose dependent response. We have also taken into account sample size and whether results are 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 14 systematic reviews that met our inclusion criteria³⁻¹⁶.

- Moderate quality evidence found people with advanced-stage cancer had higher rates of PTSD than those in earlier stages (11.4% vs. 4.2%).
- Moderate quality evidence finds the prevalence of PTSD in people with chronic pain is around 9.7%, with the prevalence higher in people with chronic widespread pain (20.5%).
- Moderate quality evidence found risk factors associated with PTSD following a burn injury include (in descending order of effect); more threat perception, pain, negative life emotions or distress, acute stress symptoms, being injured by an explosion, more body surface area affected, longer hospitalisation stay, and having more surgeries.
- Moderate to high quality found associations between PTSD symptoms after a spinal cord injury and more distress and pain severity.
- Moderate to high quality evidence found a large effect of more PTSD symptoms in

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parents of chronically ill children than in parents of healthy children. Rates were highest in parents of children with increased illness severity and longer treatment duration and intensity.

- Moderate quality evidence found the incidence of PTSD was lowest in people exposed to mild flood severity (4.41%) and highest in people who experience severe flood intensity (20.06%).
- Moderate quality evidence found small to medium-sized associations between increased disaster death toll and increased PTSD symptoms (dose-dependent). Closer proximity to the disaster, more threat to self, and more general distress all showed medium-sized associations with increased PTSD symptoms, while loss of a loved one showed a small association.
- Moderate quality evidence found a mediumsized effect of fewer PTSD symptoms in older adults than younger adults following exposure to man-made disasters. Older people who had the greatest level of exposure were even less likely than young people to report PTSD symptoms (medium to large effect).
- Moderate quality evidence found the prevalence of PTSD in adults exposed to an earthquake ranged from 4% to 67%, and prevalence of PTSD in children exposed to earthquake ranged from 2.5% to 60%. Being trapped, experiencing fear, injury, or bereavement, and witnessing injury/death during the earthquakes were related to greater risk of PTSD (medium-sized effects).
- Moderate to high quality evidence found a small association between greater level of exposure to mass shootings (closer proximity, longer duration) and increased PTSD symptoms.
- Moderate to high quality found the prevalence of PTSD in war-affected refugees and citizens was around 31%. Rates were highest in samples exposed to recent conflict, to torture, to more potentially traumatic events, to political terror, and in



people from Cambodia, Bosnia, Kosovo, and Africa.

- Moderate quality evidence found the risk factors associated with most risk of PTSD in military personnel and veterans were (in descending order of effect) discharging a weapon, witnessing someone being wounded or killed, experiencing severe trauma, and having longer and more deployments.
- Moderate quality evidence found a mediumsized association between exposure to increased trauma severity in children and adolescents and increased risk of PTSD.
- Moderate quality evidence finds the prevalence of PTSD in civilians with a traumatic brain injury is around 15.6%. There were no differences in rates of PTSD between people with mild or moderate to severe TBI.

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Abbey G, Thompson SB, Hickish T, Heathcote D

A meta-analysis of prevalence rates and moderating factors for cancerrelated post-traumatic stress disorder

Psycho-Oncology 2015; 24: 371-81

View review abstract online

Comparison	PTSD in people with early (I-II) vs. advanced-stage (III-IV) cancer.
Summary of evidence	Moderate quality evidence (large samples, appears imprecise, direct) found people with advanced-stage cancer had higher rates of PTSD than those in earlier stages (11.4% vs. 4.2%).
	Cancer
People with advanced	-stage cancer had higher rates of PTSD than those in earlier stages;
Early stage (I-II)	: 8 studies, N = 737, prevalence = 4.2%, 95%Cl 2.1% to 8.1%
Advanced stage (III-	-IV): 1 study, N = 989, prevalence = 11.4%, 95%CI 9.6% to 13.5%
Consistency in results	No measure of consistency is reported for these subgroups.
Precision in results	Appears imprecise
Directness of results	Direct

Chen L, Liu A

The Incidence of Posttraumatic Stress Disorder After Floods: A Meta-Analysis

Disaster Medicine and Public Health Preparedness 2015; 9: 329-33

View review abstract online

Comparison	PTSD after mild vs. moderate vs. severe floods.
Summary of evidence	Moderate quality evidence (large samples, appears imprecise, direct) found the incidence of PTSD was lowest in people exposed to mild flood severity (4.41%) and highest in people who experience severe flood intensity (20.06%).
	Floods

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PTSD was lowest with mild flood intensity and highest with severe flood intensity;	
Mild: 4 studies, N = 15,718, incidence = 4.41%, 95%CI 2.24% to 7.25%	
Moderate: 3 studies, N = 9,646, incidence = 12.82%, 95%CI 12.16% to 13.50%	
Severe: 9 studies, N = 14,521, incidence = 20.06%, 95%CI 12.55% to 28.78%	
Consistency in results	No measure of consistency is reported for these subgroups.
Precision in results	Appears imprecise
Directness of results	Direct

Furr JM, Comer JS, Edmunds JM, Kendall PC

Disasters and youth: a meta-analytic examination of posttraumatic stress

Journal of Consulting and Clinical Psychology 2010; 78: 765-80

View review abstract online

Comparison	PTSD symptoms in youth (≤18 years) after disasters.
Summary of evidence	Moderate quality evidence (large samples, direct) found small to medium-sized associations between increased disaster death toll and increased PTSD symptoms. Closer proximity to the disaster, more threat to self, and more general distress all showed medium-sized associations with increased PTSD symptoms, while loss of a loved one showed a small association.
	Disasters
PTSD symptoms increa	ase as disaster death toll increases (small to medium-sized effects);
Death	n toll <25: 12 studies, N = 4,169, <i>r</i> = 0.09, <i>p</i> > 0.05
Death toll 2	6 to 100 deaths: 4 studies, N = 1,251, r = 0.12, p < 0.05
Death toll 10	01 to 999 deaths: 6 studies, N = 5,978, r = 0.19, p < 0.01
Death toll ≥ ²	1,000 deaths: 19 studies, N = 21,418, <i>r</i> = 0.22, <i>p</i> < 0.001
The following risk factors w	ere also associated with more PTSD symptoms (medium-sized effects);
Closer proxin	nity to disaster: 14 studies, N = 14,834, <i>r</i> = 0.33, <i>p</i> < 0.001
Threat	t to self: 13 studies, N = 11,593, <i>r</i> = 0.34, <i>p</i> < 0.001
General/unsp	ecified distress: 14 studies, N = 12,347, <i>r</i> = 0.38, <i>p</i> < 0.001
	Loss of a loved one showed a small effect;

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Loss of a loved one: 22 studies, N = 7,763, r = 0.16, p < 0.001	
Consistency in results	No measure of between study heterogeneity was reported.
Precision in results	No CIs are reported
Directness of results	Direct

Giannoni-Pastor A, Eiroa-Orosa FJ, Fidel Kinori SG, Arguello JM, Casas M

Prevalence and Predictors of Posttraumatic Stress Symptomatology Among Burn Survivors: A Systematic Review and Meta-Analysis

Journal of Burn Care and Research 2016; 37: e79-89

View review abstract online

Comparison	PTSD symptoms following a burn injury.
Summary of evidence	Moderate quality evidence (large samples, direct) found risk factors associated with PTSD following a burn injury include (in descending order of effect); more life threat perception, pain, negative emotions or distress, acute stress symptoms, being injured by an explosion, more body surface area affected, longer hospitalisation stay, and having more surgeries.
	Burn injury
The following risk factors v	vere associated with increased PTSD symptoms following a burn injury (in descending order of effect);
More	e life threat perception: 1 study, N = 428, $r = 0.98$
	Pain: 2 studies, N = 287, <i>r</i> = 0.39
Negativ	ve emotions or distress: 6 studies, $N = 445$, $r = 0.32$
Acu	te stress symptoms: 4 studies, N = 645, $r = 0.29$
I	njured by explosion: 1 study, $N = 60$, $r = 0.26$
Tota	I body surface area: 4 studies, N = 452, $r = 0.26$
Leng	th of hospitalisation: 4 studies, N = 561, $r = 0.23$
Ν	umber of surgeries: 1 study, N = 178, $r = 0.20$
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

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Pinquart M

Posttraumatic Stress Symptoms and Disorders in Parents of Children and Adolescents With Chronic Physical Illnesses: A Meta-Analysis

Journal of Traumatic Stress 2019; 32: 88-96

View review abstract online

Comparison	PTSD in parents of children with a chronic physical illness (cancer, burns, heart disease, diabetes, epilepsy, and asthma) vs. community norms or parents of healthy children.
Summary of evidence	Moderate to high quality evidence (large sample, consistent, imprecise, direct) found a large effect of more PTSD symptoms in parents of chronically ill children than in parents of healthy children. Rates were highest in parents of children with increased illness severity and longer treatment duration and intensity.
Pa	rents of children with chronic physical illness

184 studies, N = 30,068

A large effect of more PTSD symptoms in parents of chronically ill children than in parents of healthy children;

OR = 7.12, 95%CI 6.01 to 8.44, *p* < 0.001, Q*p* = 0.151

Parental PTSD symptoms were most prevalent among parents of children with increased illness severity (r = 0.18), and more treatment duration/intensity (r = 0.21).

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

Pollock K, Dorstyn D, Butt L, Prentice S

Posttraumatic stress following spinal cord injury: a systematic review of risk and vulnerability factors

Spinal Cord 2017; 55: 800-11

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Comparison	Risk factors associated with PTSD following spinal cord injury.
Summary of evidence	Moderate to high quality evidence (large samples, mostly consistent, precise, direct) found associations between PTSD symptoms after a spinal cord injury and more distress and pain severity.
	Spinal cord injury
The following risk factors	were associated with increased PTSD symptoms following a spinal cord injury (in descending order of effect);
Distress: 2 stud	ies, N = 512, r = 0.57, 95%Cl 0.50 to 0.62, p < 0.001, l ² = 0%
Pain severity: 4 studies	s, N = 493, r = 0.35, 95%Cl 0.27 to 0.43, p < 0.01, p < 0.001, l^2 = 0%
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Sigveland J, Hussain A, Lindstrom JC, Ruud T, Hauff E

Prevalence of posttraumatic stress disorder in persons with chronic pain: A meta-analysis

Frontiers in Psychiatry 2017; 8: 164

View review abstract online

ComparisonPTSD in people with chronic pain.Summary of evidenceModerate quality evidence (large sample, inconsistent, appeal imprecise, direct) finds the prevalence of PTSD in people with chronic pain is around 9.7%, with the prevalence higher in people with chronic widespread pain (20.5%).	
21 studies, N =	6,750, prevalence = 9.7%, 95%Cl 5.2% to 17.1%, l ² = 98.6%
PTSD prevalence	e was higher in people with chronic widespread pain (20.5%).
Consistency in results	Inconsistent
Precision in results	Appears imprecise
Directness of results	Direct

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Siskind DJ, Sawyer E, Lee I, Lie DC, Martin-Khan M, Farrington J, Crompton D, Kisely S

The mental health of older persons after human-induced disasters: A systematic review and meta-analysis of epidemiological data

American Journal of Geriatric Psychiatry 2016; 24: 379-88

View review abstract online

Comparison	PTSD symptoms in older adults vs. younger adults (>60 years) after human-induced disasters.
Summary of evidence	Moderate quality evidence (large sample, inconsistent, imprecise, direct) found a medium-sized effect of fewer PTSD symptoms in older adults than younger adults following exposure to man-made disasters. Older people who had the greatest level of exposure were even less likely than young people to report PTSD symptoms (medium to large effect).
	Human-induced disasters
A mediun	n-sized effect of fewer PTSD symptoms in older adults;
7 studies, $N = 2$	23,924, OR = 2.85, 95%Cl 1.42 to 5.70, <i>p</i> = 0.003, l ² = 89%
Older people who had the	e greatest level of exposure were even less likely than young people to report PTSD symptoms (OR = 3.70).
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Steel Z, Chey T, Silove D, Marnane C, Bryant RA, van Ommeren M

Association of torture and other potentially traumatic events with mental health outcomes among populations exposed to mass conflict and displacement: a systematic review and meta-analysis

Jama 2009; 302: 537-49

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Comparison	Risk of PTSD in war-affected citizens and refugees.	
Summary of evidence	Moderate to high quality evidence (large sample, inconsistent, appears precise, direct) found the prevalence of PTSD in war- affected refugees and citizens was around 31%. Rates were highest in samples exposed to recent conflict, to torture, to more potentially traumatic events, to political terror, and in people from Cambodia, Bosnia, Kosovo, and Africa.	
War-affected citizens and refugees		
145 studies, N = 6	4,332, prevalence = 30.6%, 95%Cl 26.3% to 35.2%, l ² = 99%	
more potentially traumatic e samples exposed to recen	est in samples exposed to torture (OR = 2.01), in samples exposed to vents (OR = 1.52), in samples exposed to political terror (OR = 1.60), in t conflict (OR = 0.77), and in Cambodian (OR = 3.89), Bosnian (OR = sovon (OR = 4.15), and African (OR = 4.52) samples.	
self-report rather than diagr	gher in smaller rather than larger samples (OR = 3.49), in studies using nostic interviews to assess PTSD (OR = 1.62), and in studies reporting int rather than period prevalence (OR = 0.42).	
Consistency in results	Inconsistent	
Precision in results	Appears precise	
Directness of results	Direct	

Tang B, Deng Q, Glik D, Dong J, Zhang L

A Meta-Analysis of Risk Factors for Post-Traumatic Stress Disorder (PTSD) in Adults and Children after Earthquakes

International Journal of Environmental Research and Public Health 2017; 14: 1537

View review abstract online

Comparison	PTSD after earthquakes.
Summary of evidence	Moderate quality evidence (large sample, inconsistent, imprecise, direct) found the prevalence of PTSD in adults exposed to an earthquake ranged from 4% to 67%, and prevalence of PTSD in children exposed to earthquake ranged from 2.5% to 60%. Being trapped, experiencing fear, injury, or bereavement, and witnessing injury/death during the earthquakes were related to greater risk of PTSD (medium-sized effects).

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Earthquakes

15 studies, N = 22,931

Adults

The prevalence of PTSD in adults after earthquakes ranged from 4.10% to 67.07%.

Adults who experienced being trapped (OR = 1.81, 95%Cl 1.47 to 2.24), experienced fear (OR = 2.97, 95%Cl 1.78 to 4.95), injury (OR = 2.06, 95%Cl 1.33 to 3.19), or bereavement (OR = 2.49, 95%Cl 2.04 to 3.04) were more likely to have PTSD (medium-sized effects).

<u>Children</u>

The prevalence of PTSD in children after earthquakes ranged from 2.50% to 60.00%.

Children who experienced being trapped (OR = 1.94, 95%Cl 1.52 to 2.47), experienced fear (OR = 2.24, 95%Cl 1.52 to 3.32), injury (OR = 2.05, 95%Cl 1.67 to 2.52), witnessed injury/death (OR = 201, 95%Cl 1.44 to 2.80), or experienced bereavement (OR = 2.24, 95%Cl 1.95 to 2.56) were more likely to have PTSD (medium-sized effects).

Consistency in results	Authors report data are inconsistent.
Precision in results	Imprecise
Directness of results	Direct

Trickey D, Siddaway AP, Meiser-Stedman R, Serpell L, Field AP

A meta-analysis of risk factors for post-traumatic stress disorder in children and adolescents

Clinical Psychology Review 2012; 32: 122-38

View review abstract online

Comparison	Risk of PTSD in children and adolescents.
Summary of evidence	Moderate quality evidence (unclear sample size, inconsistent, precise, direct) found a medium-sized association between exposure to increased trauma severity in children and adolescents and increased risk of PTSD.
	Any trauma in children

A medium-sized association was found between increased trauma severity and increased PTSD; 41 studies, N not reported, r = 0.29, 95%CI 0.24 to 0.35, p < 0.001, Qp < 0.001

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

Van Praag DLG, Cnossen MC, Polinder S, Wilson L, Maas AIR

Post-Traumatic Stress Disorder after Civilian Traumatic Brain Injury: A Systematic Review and Meta-Analysis of Prevalence Rates

Journal of Neurotrauma 2019; 36: 3220-32

View review abstract online

Comparison	Prevalence of PTSD in civilians with a traumatic brain injury (TBI).
Summary of evidence	Moderate quality evidence (large sample, direct) finds the median prevalence of PTSD in civilians with a traumatic brain injury is around 15.6%. There were no differences in rates of PTSD between people with mild or moderate/severe TBI.
	Traumatic brain injury
31 studies N = not re	ported, prevalence = 15.64%, 95%CI 12.88% to 18.40%, I ² = 82%
There were no difference	es in rates of PTSD between people with mild or moderate/severe TBI (13.5% vs. 11.8%).
Consistency in results	Inconsistent
Precision in results	Appears imprecise
Directness of results	Direct

Wilson LC

Mass shootings: a meta-analysis of the dose-response relationship

Journal of Traumatic Stress 2014; 27: 631-8

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Comparison	PTSD symptoms following exposure to mass shootings (an
	incident occurring in a public place, during which the primary

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	weapon is a firearm, the event involves four or more victim deaths, the victims are indiscriminately selected, and there is no identifiable socio-political motivation).
Summary of evidence	Moderate to high quality evidence (large sample size, inconsistent, precise, direct) found a small association between greater level of exposure to mass shootings (closer proximity, longer duration) and increased PTSD symptoms. There were no moderating effects of time since shooting.
	Mass shootings
A small association was	found between greater level of exposure to mass shootings (proximity, duration) and more PTSD symptoms;
11 studies, N	I = 8,047, <i>r</i> = 0.19, 95%CI 0.13 to 0.25, <i>p</i> < 0.001, I ² = 88%
There were	no moderating effects of sex, age, or time since shooting.
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Xue C, Ge Y, Tang B, Liu Y, Kang P, Wang M, Zhang L

A meta-analysis of risk factors for combat-related PTSD among military personnel and veterans

PLoS ONE 2015; 10: e0120270

View review abstract online

Comparison	Risk of PTSD in military personnel and veterans.
Summary of evidence	Moderate quality evidence (large samples, inconsistent, some imprecision, direct) found the risk factors associated with increased risk of PTSD in military personnel and veterans were (in descending order of effect) discharging a weapon, witnessing someone being wounded or killed, experiencing severe trauma, and having longer and more deployments.
	Military personnel and veterans
	32 studies, N = 413,580
Factors associated w	ith increased risk of PTSD were (in descending order of effect size);

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Discharging a weapon: OR = 4.32, 95%CI 2.60 to 7.18, I ² = 90%	
Witnessing someone being wounded or killed: OR = 3.12 , 95% Cl 2.40 to 4.06, $l^2 = 56\%$	
Severe trauma: OR = 2.91, 95%Cl 1.85 to 4.56, l ² = 97%,	
Longer deployments: OR = 1.28, 95%CI 1.13 to 1.45, I ² = 71%	
More deployments: OR = 1.24, 95%Cl 1.10 to 1.39, $l^2 = 63\%$	
Consistency in results	Inconsistent
Precision in results	Some imprecision
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, p = probability of a statistically significant effect, r = correlation coefficient, vs. = versus

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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 small¹⁷.

† 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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect¹⁷.

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^{18} . InOR stands for logarithmic OR where a InOR 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

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between variables. They can provide an indirect 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 а strona 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.

‡ Inconsistency refers to differing estimates of 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. I² 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 considerable heterogeneity and over this is considerable heterogeneity. l² can be calculated from Q (chi-square) for the test of heterogeneity with the following formula¹⁷;

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

§ 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, these criteria should be relaxed¹⁹.

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 В. 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 and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-tohead comparisons of A and B.

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