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Effectiveness of trauma-focused psychological therapies compared to usual postnatal care for treating post-traumatic stress symptoms in women following traumatic birth: A systematic review protocol

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Abstract

Introduction: Maternal mental health has been largely neglected in the literature. Women, however, may be vulnerable to developing post-traumatic stress symptoms or post-traumatic stress disorder (PTSD), following traumatic birth. In turn, this may affect their capacity for child rearing, ability to form a secure bond with their baby and impact on the wider family. Trauma-focused psychological therapies (TFPT) are widely regarded as effective and acceptable interventions for PTSD in general and clinical populations. Relatively little is known about the effectiveness of TFPT for women post-partum who have post-traumatic stress symptoms.

Methods and analysis: We will conduct a review to assess the effectiveness of TFPT, compared with usual postpartum care, as a treatment for post-traumatic stress symptoms or PTSD for women following traumatic birth. Using a priori search criteria, we will search for randomised controlled trials in four databases, including Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PsycINFO and OpenGrey. We will use search terms that relate to the population, TFPT and comparators. Screening of search results, and data extraction, will be undertaken by two reviewers, independently. Risk of bias will be assessed in RCTs which meet the review criteria. Data will be potentially analysed using the following methods, as appropriate: narrative synthesis; meta-analysis; subgroup analysis; and meta-regression.

Dissemination and ethics: As this work comprises a synthesis of existing studies, ethical approvals are not required. Results will be disseminated at conferences and publications.

Strengths and limitations of this study

- With comprehensive literature search and synthesis, this systematic review will provide the best evidence available regarding the effectiveness of trauma-focused psychological therapies for women who have suffered a traumatic birth experience.
- The systematic review protocol was developed and published prior to conducting the review to avoid reporting bias.
- There may be some issues related to data (incorrect reporting, missing or insufficient data), but we will contact the original researchers to ask for the clarification, if necessary.

INTRODUCTION

Maternal mental health remains relatively underexplored despite the potential long-term impact and consequences for women, their babies, and the wider family network [1-4]. A recent confidential enquiry into maternal deaths and morbidity in the UK and Ireland[5] reported that mental health problems remain one of the leading causes of maternal death: from 2009 to 2013, 23% of deaths in women postpartum (ranging from six weeks to one year after pregnancy) were attributed to either suicide or accidental death (e.g. following substance misuse). The most common maternal mental health problem diagnosed during the postnatal period is depression.[6] It has been suggested, however, that the term 'postnatal depression' is overused in clinical practice as a label for any mental illness occurring postnatally.[7]

It is increasingly recognised that a traumatic birth can result in post-traumatic stress symptoms (i.e. symptoms that fall below the diagnostic threshold), or post-traumatic stress disorder (PTSD).[8 9] PTSD is a severe and debilitating mental disorder that an individual may develop in response to experiencing or witnessing a highly traumatic event (APA, 2013).[10] For some women, giving birth can be a frightening, anxiety-provoking, and traumatic experience. Perceptions of childbirth as traumatic arise when a woman believes that there is a serious or significant threat to her own life or the life of her baby.[11 12] PTSD symptoms that may occur in women after a traumatic birth include intrusive thoughts and images about the traumatic event (e.g. seeing severe blood loss, being rushed to hospital); avoidance of stimuli associated with the traumatic event (e.g., avoiding attending hospital appointments or sharing birth experiences with others; avoiding the baby who is a reminder of the trauma); blunting of affect (e.g., low mood); negative thoughts and beliefs about the self, others, or the world (e.g., 'I am going to die', 'I am not a good mother'); dissociative states, and emotional

dysregulation. PTSD symptoms can typically impede aspects of daily functioning, including social relationships and employment.

It is estimated that the proportion of women who suffer post-traumatic stress symptoms following 'normal' childbirth is about 3% to 6% at around six weeks postpartum, decreasing to about 1.5% at six months postpartum.[13] Prevalence rates appear to be higher for at-risk groups (e.g. women who have experienced obstetric complications, emergency caesarean sections, premature births, or stillbirths), and are estimated to be up to 44% within two years postpartum.[14] However, prevalence estimates vary widely, perhaps due to differences in study designs, sampling frames, sample sizes, diagnostic criteria employed and measurement instruments.[14-16] It is anticipated that the number of women who experience traumatic births is likely to rise, due to increasingly complex medical needs of women who become pregnant when older or obese.[17-20] There is, therefore, an urgent need to consider how best to support women who suffer from post-traumatic stress symptoms during the postnatal period.

Description of the intervention

Systematic reviews have consistently concluded that trauma-focused psychological therapies (TFPTs) are effective treatments for PTSD in general population groups. These include different modes of exposure therapy such as narrative exposure therapy (NET), trauma-focused cognitive behavioural therapy (TFCBT), and eye-movement desensitisation and reprocessing (EMDR).[21-23] All TFPTs share some core treatment principles, in particular, an emphasis on supporting patients to make sense of and process memories of trauma, and cognitions and attributions of traumatic events.[24-26] EMDR[27] and CBT, in particular, are recommended by NICE guidance on PTSD for children and adults who have experienced a single traumatic event.[23]

How the intervention might work

Exposure therapy typically involves asking the individual to relive the trauma, either in their imagination or by writing (in NET) a trauma narrative to create a detailed account of the event. The individual is then asked repeatedly to revisit or read the narrative in order to become habituated to the post-traumatic stress symptoms that are generated.[24 28] TFCBT involves helping individuals to make sense of their experiences, identify ways or patterns of thinking that are negative, recognise thoughts and beliefs about the self, others or the world that are associated with the traumatic event, and finally, note behavioural or coping responses which may be helpful in the short term, yet perpetuate anxiety in the longer term. Individuals are encouraged to develop new ways of thinking about and appraising traumatic events (Ehlers, 2005). EMDR involves supporting individuals to identify and then focus on a traumatic image (e.g., finding oneself with heavy bleeding), an associated thought (e.g., 'My baby and I are going to die'), the emotion (e.g., extreme fear), and physical sensations, while receiving bilateral stimulation, most commonly in the form of eye movements.[27]

Importance of the review

Although trauma-focused psychological therapies (TFPT) are both effective and acceptable as treatments for PTSD in general and clinical populations, postpartum women are typically excluded from research studies, so the clinical utility of these interventions is yet to be established.[2] There is currently no systematic review that synthesises evidence regarding the effectiveness of TFPT for women who have suffered a traumatic birth. A Cochrane review of psychosocial and psychological interventions (e.g. CBT) for postnatal depression does exist,[29 30] but PTSD and trauma symptoms are not included as outcomes of interest. It is quite possible that PTSD following childbirth differs from PTSD that occurs in other contexts.[31]

Unlike typical stressors that contribute to PTSD, such as abuse, assault, torture, or war, childbirth is by and large deemed to be a positive event, while also concurrently seeming traumatic for some women. The implication is that women's needs may be misunderstood.[32] Behaviours indicative of PTSD, such as social withdrawal and avoidance, may be misattributed to needing to care for a baby, when in fact this is as a consequence of PTSD. It is also evident that for some women caring for a baby continues to be a reminder of traumatic experiences, which may in turn mediate the propensity for developing strong bonds and secure attachments between mother and child. Overall, it is likely to be clinically important to take account of the postnatal context when planning and delivering TFPT.

OBJECTIVES

The primary objective of this systematic review is to assess the effectiveness of TFPT, compared with usual postpartum care for PTSD or post-traumatic stress symptoms in women following traumatic birth.

Secondary objectives are to examine the effectiveness of these psychological interventions for common co-morbid symptoms including depression, anxiety or distress, as well as any adverse effects including an increase in PTSD symptoms or death.

METHOD AND ANALYSIS

Inclusion/exclusion criteria

Population

Women experiencing post-traumatic stress symptoms and/or the impact of these, who meet PTSD diagnostic threshold, or who have sub-threshold symptoms. Diagnostic assessment

could be made according to self-report, such as via a questionnaire (e.g. Impact of Events Scale [IES][33]), or via a clinician administered assessment (e.g. Structured Clinical Interview for DSM-IV [SCID][34 35]); Clinician-administered PTSD scale [CAPS][36]). There is no restriction on age, nationality or birth mode.

Intervention

Trauma-focused psychological therapies (TFPT) added to usual (standard) postnatal care to reduce symptoms of PTSD. Psychological interventions that will be included in this review are as follows:

1. Exposure therapy: Any individual therapy which involves guiding the individual to relive and process the trauma memory through creating a narrative using formats such as writing or audio-recording. During therapy, the patient will revisit the narrative repeatedly in order to habituate or develop tolerance of trauma symptoms.

2. *Trauma-focused cognitive behavioural therapy (TFCBT):* Any psychological therapy that predominantly employs trauma-focused cognitive, behavioural or cognitive-behavioural techniques, and that aim to support individuals to identify unhelpful thoughts or thinking styles, and behaviours, and develop new ways of thinking about or coping with trauma. Examples of therapies within this category are cognitive therapy,[37] cognitive processing therapy[38] and prolonged exposure.[39]

3. EMDR: A structured protocol-driven trauma-focused therapy, which relies on an adaptive information process model of PTSD.[40] EMDR comprises eight elements, including recall

of images, thoughts, emotions and bodily sensations associated with traumatic events, while receiving bilateral stimulation.

4. Any other psychological intervention that does not fit the above categories, but clearly describes the theoretical underpinning and is intended to target trauma symptoms and related distress in postpartum females.

Comparators

1. Standard postnatal care (which denotes the usual postnatal care provided within the first six weeks post-birth in settings which do not routinely offer TFPT).
2. Standard postnatal care, plus any non-specific supportive counselling or 'attention control' (e.g. befriending) provided by primary care/postnatal follow-up.

Types of outcome measures

1. Primary outcome

Recovery (dichotomous outcomes) from, or reduction (continuous outcomes) in PTSD or trauma symptoms as measured by validated scales e.g. IES,[33] CAPS.[36]

2. Secondary outcomes

- Recovery (dichotomous outcomes) from, or reduction (continuous outcomes) in depressive symptoms as measured by validated scales, e.g. Edinburgh Postnatal Depression Scale (EPDS),[41] Beck Depression Inventory (BDI),[42] State of Anxiety and Depression (SAD)[43]

- Recovery (dichotomous outcomes) from, or reduction (continuous outcomes) in anxiety symptoms as measured by validated scales, e.g. Beck Anxiety Inventory (BAI: Beck et al. 1988), Hospital Anxiety and Depression Scale[44]
- Well-being or quality of life, e.g. Short Form-36 (SF-36)[45]
- Adverse events or effects, e.g. increased PTSD or trauma symptom severity, death.

Types of studies

We will include all randomised controlled trials (RCTs), cluster RCTs, crossover trials that compare TFPT for PTSD symptoms in women following birth with usual postpartum care. Study populations which comprise non-postpartum individuals will be included if the subset of data specific to the women are published or obtainable from the paper/trialists. There will be no restriction based on the study sample size, language, study setting or publication status

Data sources and search strategy

We will carry out systematic searches in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PsycINFO, and OpenGrey using a search strategy developed in consultation with an information specialist at the academic institution where the first reviewer (MF) is based (Table 1). To maximise search sensitivity, we will use both index terms (e.g. Medical Subject Heading: MeSH) and free-text terms referring to population (e.g. 'pregnancy', 'postnatal') and interventions (e.g. 'Cognitive Therapy', 'Eye Movement Desensitization Reprocessing') without terms referring to outcomes. The terms for study design will be added if necessary to increase search specificity. No restrictions on date, language, or publication status will be applied to the searches. The electronic searches will be supplemented by a hand search of the reference lists of all included studies. The citations we

retrieve from the searches will be imported into the reference management software package EndNote X7.

Table 1 Searching strategy (Medline)

Population	AND	Intervention	AND	Study design[i)]
exp Pregnancy/		exp Cognitive Therapy/		exp Clinical Trial/
OR		*OR*		*OR*
exp Pregnancy Outcome/		CBT.mp.		exp Clinical Trial, Phase I/
OR		*OR*		*OR*
exp Delivery, Obstetric/		exp Eye Movement Desensitization Reprocessing/		exp Clinical Trial, Phase II/
OR		*OR*		*OR*
exp Parturition/		EMDR		exp Clinical Trial, Phase III/
OR		*OR*		*OR*
birth.mp		exp Behavior Therapy/		exp Clinical Trial, Phase IV/
OR		*OR*		*OR*
childbirth.mp		Behaviour* therapy.mp		exp Controlled Clinical Trial/
OR		*OR*		*OR*
exp Postnatal Care/		exp Psychotherapy/		exp Randomized Controlled Trial/
OR		*OR*		*OR*
postnatal.mp.		psychological.mp		exp Random Allocation/
OR		*OR*		*OR*
exp Postpartum Period/		exp Psychological Techniques/		randomised.mp
OR		*OR*		*OR*
postpartum.mp		exp Psychology, Experimental/		trial.mp
OR		*OR*		*OR*
exp Maternal Health Services/		Trauma focused.mp		RCT.mp
OR				
exp Infant, Newborn/				
OR				
exp Cesarean Section/				
OR				
caesarean				
OR				
exp Stillbirth/				
exp Intensive Care, Neonatal/				
OR				
exp Intensive Care Units, Neonatal/				

i) Search will be performed initially with sets of terms referring to population and interventions The terms referring to study design may be added if necessary, to increase search specificity.

Data collection and analysis

Selection of studies

Two reviewers will independently screen titles and abstracts of all potential studies identified through the search strategy, and they will code them as 'retrieve' (eligible or potentially

eligible/unclear) or 'do not retrieve.' The two reviewers will then independently read the full text of the studies retrieved to determine whether trials meet the inclusion criteria or to record reasons for excluding the ineligible studies. The third author will undertake a random check of 10% of results at each stage. Any disagreements will be resolved through discussion or, if required, through consultation with other review authors. The process of the study selection will be outlined in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram and 'characteristics of excluded studies' table.

Data extraction and management

Two review authors will independently extract data using a data extraction form designed for this review which include details about study eligibility; sample frame and size; diagnosis and diagnostic criteria used; nature, timing, and duration of intervention; number and frequency of sessions; professional background of trial therapists; outcomes (primary and secondary measures); and statistical analyses, duration of follow-up, and attrition. Attempts will be made to obtain missing and/or unpublished details, by contacting study authors. This process will involve contacting trialists for independent datasets of postnatal women, if they are included in trials that also include other trauma victims.

Risk of bias assessment

Two review authors will independently assess the risk of bias of all included studies, using the approach recommended in the *Cochrane Handbook for Systematic Review of Interventions*.[46] The Cochrane's risk-of-bias tool addresses six specific domains: (1) sequence allocation for randomization; (2) allocation concealment; (3) blinding of personnel and assessors; (4) incomplete outcome data; (5) selective reporting; and (6) any other notable risks of bias. For each item, one of the following three judgements will be made: 'low risk' of

bias (plausible bias – unlikely to seriously alter the results), 'high risk' of bias (plausible bias that seriously weakens confidence in the results), or 'unclear risk' of bias (plausible bias that raises some doubt about the results) when insufficient information was reported to permit judgment. The process for reaching judgments will be described in the risk-of-bias tables to ensure transparency.

Summary Assessments of Risk of Bias

The overall quality of the evidence for each outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[46 47] The overall quality of evidence for each outcome will be assigned to one of four levels – high, moderate, low, or very low – according to factors including within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias.[46 47]

Measures of treatment effect

For dichotomous outcomes, such as the presence of PTSD, depression or anxiety, the Mantel-Haenszel method for computing the pooled risk ratio (RR) with 95% confidence intervals (CI) will be used. For continuous data, the standardised mean difference (SMD) and 95% CI will be calculated, where different scales have been used. The weighted mean difference (WMD) and 95% CI will be calculated where all outcomes were measured using the same scale in the same way.

Multiplicity and unit of analysis issues

If a study reports data for more than one outcome or time-point, analyses will be conducted separately for each outcome/time point (short, medium, long term), or select single

outcomes/time point (e.g. at the end of the trial), following discussion with content experts. For trials with multiple arms of treatment in a study, the appropriateness of combining data to create a single pair-wise comparison will be considered if therapies are sufficiently similar. Alternatively, data from the arms of the trial which fit closest to the review objectives will be used. Where studies have adopted a cross-over design, only outcome data from the first randomisation period will be included. If cluster-randomised trials are identified, sample sizes will be adjusted using an estimate of the intra-cluster correlation co-efficient (ICC) from the trial or from a study of a similar population, based on statistical advice.

Dealing with missing data

Dealing with missing data may include imputing outcomes for the missing participants to facilitate an intention-to-treat (ITT) analysis.[46] This can involve a sensitivity analysis by imputing outcomes for the missing participants with the most optimistic and the most pessimistic scenarios and then comparing the results of these two analyses. The sensitivity analysis may also be conducted to facilitate comparisons of the ITT with imputations from 'available case analysis' (i.e. analyse data with participants whose outcomes are known).[46] If these analyses yield similar results in the same direction of the effects of the treatment (indicating participants with missing outcomes are safely excluded), the results of available case analysis will be used for meta-analysis. The impact of including these studies in the overall assessment of treatment effect (summary effect) will be further assessed with additional sensitivity analysis comparing the results of meta-analyses with and without trials which are rated as high risk bias due to missing data (see Sensitivity analysis).

Assessment of reporting biases

When sufficient studies are available (n=10 or more), we will construct funnel plots and scrutinised them for signs of asymmetry [46].

Data synthesis

Random effects meta-analyses will be performed which will produce the average effect size of the intervention across studies, allowing for differences in the treatment effect from study to study. Random effects meta-analyses is a conservative option and more appropriate for this study than a fixed-effect model (which assumes that there is one true effect) because the population and setting are likely to be slightly different, therefore the effects are likely to be slightly different. However, if there are only few studies (2-4 studies), it may be inadequate to accurately estimate of the width of the distribution of intervention effects.[46 48] In this case a fixed-effect analysis will be performed. Then, the results obtained from these two methods random effects and fixed-effect models will be compared to seek potential bias and heterogeneity. Analyses will be conducted by a statistician (ESWN) using a statistical software, STATA 14.

Heterogeneity

Heterogeneity will be assessed within each comparison. When clinical heterogeneity (ie. variation in study settings and delivery mode of the intervention) is discovered, we will conduct subgroup analyses, whereas when methodological heterogeneity (ie. variation in study designs and risk of bias) is discovered, we will perform sensitivity-analyses. If comparable studies are not available with great clinical heterogeneity, extracted data will be synthesised into a narrative summary.

Where meta-analyses are performed, tests of statistical heterogeneity will be carried out using I^2 and Chi² statistics,[46] as well as visual inspection of the forest plots. If heterogeneity is identified (e.g. the I² is greater than 30%, and the *p* value is less than 0.10 in the Chi² test for heterogeneity or different direction of the effects), pre-specified subgroup analysis and meta-regression analyses will be conducted to identify important determinants of heterogeneity when sufficient data are available.

Subgroup analysis and meta-regression

If possible, subgroup analyses will be undertaken as follow:

1. Study setting (high-income versus middle income versus low income countries)
2. Delivery mode of the intervention which shares the same theoretical modality (e.g. face-to-face versus web-based TFCBT)

Meta-regression analysis:

1. Intervention frequency (e.g. numbers of session)
2. Methodological heterogeneity of trial (e.g. ways of dealing with missing data, whether effect estimates from 'per-protocol' analyses differ compared with 'ITT' analyses)

Sensitivity analysis

Sensitivity analyses will be conducted to assess the effects of quality of trial methodology by comparing the results of meta-analyses with and without trials that are judged to have a high risk of bias for one or more of the domains of random sequence generation, allocation concealment, blinding of outcome assessment or incomplete outcome.

A sensitivity analysis will also be conducted to examine potential bias caused by missing data, by comparing results from different methods of dealing with missing data (e.g. available case analysis, ITT analysis using imputation of outcomes, assuming that all missing participants had positive outcome or that all missing participant had negative outcomes). Results of sensitivity will be reported in a Summary of Findings table.

Ethics and dissemination

Ethical approval is not required to conduct systematic reviews. The protocol will be registered in PROSPERO. The findings of the review will be presented at relevant national and international conferences, and submitted to a peer-reviewed journal.

DISCUSSION

There is a lack of acknowledgement that women postpartum may be at risk of developing symptoms of trauma or PTSD. This means that their mental health needs likely remain undetected and unmet and, importantly, symptoms may impact on childcare and rearing. Women are not routinely included in studies investigating the effectiveness of psychological interventions for PTSD, and therefore we know little about whether these interventions are effective and acceptable to this population. We believe that this systematic review will be a valuable contribution to improving women's mental health and well-being following childbirth.

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AUTHORS' CONTRIBUTIONS

- MF: Proposing and designing the review, protocol development. Will contribute to: abstract screening, paper screening, data extraction, quality appraisal of papers, writing to authors of papers for additional information, analysis and interpretation of data, and writing the review.
- DS: Design of the review and protocol development. Will contribute to: abstract screening, paper screening, data extraction, quality appraisal of papers, interpretation of data, and writing the review.
- DB: Design of the review and protocol development. Will contribute to: quality appraisal of papers, interpretation of data, and writing the review.
- ESWN: Design of the review and protocol development. Will contribute to: checking accuracy of data extraction and conducting statistical analysis and reviewing the final report.
- JS: Proposing and designing the review, protocol development. Will contribute to: abstract screening, paper screening, data extraction, quality appraisal of papers, analysis and interpretation of data, and writing the review.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page #
ADMINISTRATIVE INFORMATION			
Title:			p. 1
Identification	1a	Identify the report as a protocol of a systematic review	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	We will register the protocol in PROSPERO
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Contact: p. 1 Email: submission system
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Contribution: p. 21
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			p. 21
Sources	5a	Indicate sources of financial or other support for the review	
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	p. 4-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	p. 7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Inclusion/exclusion criteria: p. 7-10
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	p. 10 ‘Data sources and search strategy’

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	p. 10-11 'Data sources and search strategy'
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	p. 10-11 (11a). To manage record, we will use the reference management software package EndNote X7 as described in 'Data sources and search strategy'.
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	p. 11 (11b) 'Selection of study'
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	p. 11 (11c, 12) 'Data extraction and management'
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	p.9 'Types of outcome measures'
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	p. 12 'Risk of bias assessment'
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	p. 15-16 (15a, 15b) 'Data synthesis' and 'Heterogeneity'
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	p. 16 (15c) 'Subgroup analysis and meta-regression' and 'Sensitivity analysis'
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	p. 15 (15d). Under the section of 'Heterogeneity', we described that "If comparable studies are not available with great clinical heterogeneity, extracted data will be synthesised into a narrative summary."
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	p. 13 'Summary Assessments of Risk of Bias' p. 14 'Assessment of reporting biases'
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	p. 13. We will use the GRADE approach as described in 'Summary Assessments of Risk of Bias'.

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Effectiveness of trauma-focused psychological therapies compared to usual postnatal care for treating post-traumatic stress symptoms in women following traumatic birth: A systematic review protocol

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Effectiveness of trauma-focused psychological therapies compared to usual postnatal care for treating post-traumatic stress symptoms in women following traumatic birth: A systematic review protocol

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Effectiveness of trauma-focused psychological therapies compared to usual postnatal care for treating post-traumatic stress symptoms in women following traumatic birth: A systematic review protocol

Abstract

Introduction: Maternal mental health has been largely neglected in the literature. Women, however, may be vulnerable to developing post-traumatic stress symptoms or post-traumatic stress disorder (PTSD), following traumatic birth. In turn, this may affect their capacity for child rearing and ability to form a secure bond with their baby, and impact on the wider family. Trauma-focused psychological therapies (TFPT) are widely regarded as effective and acceptable interventions for PTSD in general and clinical populations. Relatively little is known about the effectiveness of TFPT for women post-partum who have post-traumatic stress symptoms.

Methods and analysis: We will conduct a review to assess the effectiveness of TFPT, compared with usual postpartum care, as a treatment for post-traumatic stress symptoms or PTSD for women following traumatic birth. Using a priori search criteria, we will search for randomised controlled trials (RCT) in four databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PsycINFO and OpenGrey. We will use search terms that relate to the population, TFPT and comparators. Screening of search results and data extraction will be undertaken by two reviewers, independently. Risk of bias will be assessed in RCTs which meet the review criteria. Data will be analysed using the following methods, as appropriate: narrative synthesis; meta-analysis; subgroup analysis; and meta-regression.

Dissemination and ethics: As this work comprises a synthesis of existing studies, ethical approvals are not required. Results will be disseminated at conferences and in publications.

Strengths and limitations of this study

- Using a comprehensive literature search and synthesis, this systematic review will provide the best evidence available regarding the effectiveness of trauma-focused psychological therapies for women who have suffered a traumatic birth experience.
- The systematic review protocol was developed and published prior to conducting the review to avoid reporting bias.
- There may be some issues related to data (incorrect reporting, missing or insufficient data), but we will contact the original researchers to ask for the clarification, if necessary.

INTRODUCTION

Maternal mental health remains relatively underexplored despite the potential long-term impact and consequences for women, their babies, and the wider family network [1-4]. A recent confidential enquiry into maternal deaths and morbidity in the UK and Ireland[5] reported that mental health problems remain one of the leading causes of maternal death: from 2009 to 2013, 23% of deaths in women postpartum (ranging from six weeks to one year after pregnancy) were attributed to either suicide or accidental death (e.g. following substance misuse). The most common maternal mental health problem diagnosed during the postnatal period is depression.[6] It has been suggested, however, that the term 'postnatal depression' is overused in clinical practice as a label for any mental illness occurring postnatally.[7]

It is increasingly recognised that a traumatic birth can result in post-traumatic stress symptoms (i.e. symptoms that fall below the diagnostic threshold), or post-traumatic stress disorder (PTSD).[8 9] PTSD is a severe and debilitating mental health disorder that an individual may develop in response to experiencing or witnessing a highly traumatic event (APA, 2013).[10] For some women, giving birth can be a frightening, anxiety-provoking, and traumatic experience. Perceptions of childbirth as traumatic arise when a woman believes that there is a serious or significant threat to her own life (eg. anticipated or unexpected obstetric complications, emergency caesarean section) or the life of her baby (eg. premature labour, stillbirth).[11 12] PTSD symptoms that may occur in women after a traumatic birth include intrusive thoughts and images about the traumatic event (e.g. seeing severe blood loss, being rushed to hospital); avoidance of stimuli associated with the traumatic event (e.g., avoiding attending hospital appointments or sharing birth experiences with others; avoiding the baby who is a reminder of the trauma); blunting of affect (e.g., low mood); negative thoughts and

beliefs about the self, others, or the world (e.g., 'I am going to die', 'I am not a good mother'); dissociative states, and emotional dysregulation. PTSD symptoms can typically impede aspects of daily functioning, including social relationships and ability to find and sustain employment.

It is estimated that the proportion of women who suffer post-traumatic stress symptoms following 'normal' childbirth is about 3% to 6% at around six weeks postpartum, decreasing to about 1.5% at six months postpartum.[13] Prevalence rates appear to be higher for at-risk groups (e.g. women who have experienced obstetric complications, emergency caesarean sections, premature births, or stillbirths), and are estimated to be up to 44% within two years postpartum.[14] However, prevalence estimates vary widely, perhaps due to differences in study designs, sampling frames, sample sizes, diagnostic criteria employed and measurement instruments.[14-16] It is anticipated that the number of women who experience traumatic births is likely to rise, due to increasingly complex medical needs of women who become pregnant when older or obese.[17-20] There is, therefore, an urgent need to consider how best to support women who suffer from post-traumatic stress symptoms during the postnatal period.

Description of the intervention

Systematic reviews have consistently concluded that trauma-focused psychological therapies (TFPT) are effective treatments for PTSD in general population groups. These include different modes of exposure therapy such as narrative exposure therapy (NET), trauma-focused cognitive behavioural therapy (TFCBT), and eye-movement desensitisation and reprocessing (EMDR).[21-23] All TFPT share some core treatment principles, in particular, an emphasis on supporting patients to make sense of and process memories of trauma, and cognitions and attributions relating to traumatic events.[24-26] EMDR[27] and CBT, in particular,

are recommended by NICE guidance on PTSD for children and adults who have experienced a single traumatic event.[23]

How the intervention might work

Exposure therapy typically involves asking the individual to relive the trauma, either in their imagination or by writing (in NET) a trauma narrative to create a detailed account of the event. The individual is then asked repeatedly to revisit or read the narrative in order to become habituated to the post-traumatic stress symptoms that are generated.[24 28] TFCBT involves helping individuals to make sense of their experiences, identify ways or patterns of thinking that are negative, recognise thoughts and beliefs about the self, others or the world that are associated with the traumatic event, and finally, note behavioural or coping responses which may be helpful in the short term, yet perpetuate anxiety in the longer term. Individuals are encouraged to develop new ways of thinking about and appraising traumatic events (Ehlers, 2005). EMDR involves supporting individuals to identify and then focus on a traumatic image (e.g., finding oneself with heavy bleeding), an associated thought (e.g., 'My baby and I are going to die'), the emotion (e.g., extreme fear), and physical sensations, while receiving bilateral stimulation, most commonly in the form of eye movements.[27]

Importance of the review

Although TFPT are both effective and acceptable as treatments for PTSD in general and clinical populations, postpartum women are typically excluded from research studies, so the clinical utility of these interventions is yet to be established.[2] There is currently no systematic review that synthesises evidence regarding the effectiveness of TFPT for women who have suffered a traumatic birth. A Cochrane review of psychosocial and psychological interventions (e.g. CBT) for postnatal depression does exist,[29 30] but PTSD and trauma

symptoms are not included as outcomes of interest. It is quite possible that PTSD following childbirth differs from PTSD that occurs in other contexts.[31] Unlike typical stressors that contribute to PTSD, such as abuse, assault, torture, or war, childbirth is by and large deemed to be a positive event, while also concurrently seeming traumatic for some women. The implication is that women's needs may be misunderstood.[32] Behaviours indicative of PTSD, such as social withdrawal and avoidance, may be misattributed to needing to care for a baby, when in fact this is as a consequence of PTSD. It is also evident that for some women caring for a baby continues to be a reminder of traumatic experiences, which may in turn mediate the propensity for developing strong bonds and secure attachments between mother and child. Overall, it is likely to be clinically important to take account of the postnatal context when planning and delivering TFPT.

OBJECTIVES

The primary objective of this systematic review is to assess the effectiveness of TFPT, compared with usual postpartum care for PTSD or post-traumatic stress symptoms in women following traumatic birth.

Secondary objectives are to examine the effectiveness of these psychological interventions for common co-morbid symptoms including depression, anxiety or distress, as well as any adverse effects including an increase in PTSD symptoms or death.

METHOD AND ANALYSIS

Inclusion/exclusion criteria

Population

Women experiencing post-traumatic stress symptoms and/or the impact of these following traumatic birth, who meet PTSD diagnostic threshold, or who have sub-threshold symptoms. Diagnostic assessment could be made according to self-report, such as via a questionnaire (e.g. PTSD Symptom Scale – Self Report version [PSS-SR][33]), or via a clinician administered assessment (e.g. Structured Clinical Interview for DSM-IV [SCID][34 35]); Clinician-administered PTSD scale [CAPS][36]). There is no restriction on age, nationality or birth mode.

Intervention

Trauma-focused psychological therapies (TFPT) added to usual (standard) postnatal care to reduce symptoms of PTSD. Psychological interventions that will be included in this review are as follows:

1. Exposure therapy: Any individual therapy which involves guiding the individual to relive and process the trauma memory through creating a narrative using formats such as writing or audio-recording. During therapy, the patient will revisit the narrative repeatedly in order to habituate or develop tolerance of trauma symptoms.

2. *Trauma-focused cognitive behavioural therapy (TFCBT):* Any psychological therapy that predominantly employs trauma-focused cognitive, behavioural or cognitive-behavioural techniques, and that aim to support individuals to identify unhelpful thoughts or thinking styles, and behaviours, and develop new ways of thinking about or coping with trauma.

Examples of therapies within this category are cognitive therapy,[37] cognitive processing therapy[38] and prolonged exposure.[39]

3. EMDR: A structured protocol-driven trauma-focused therapy, which relies on an adaptive information process model of PTSD.[40] EMDR comprises eight elements, including recall of images, thoughts, emotions and bodily sensations associated with traumatic events, while receiving bilateral stimulation.

4. Any other psychological intervention that does not fit the above categories, but clearly describes the theoretical underpinning and is intended to target trauma symptoms and related distress in postpartum females.

Comparators

1. Standard postnatal care (which denotes the usual postnatal care provided within the first six weeks post-birth in settings which do not routinely offer TFPT).
2. Standard postnatal care, plus any non-specific supportive counselling or 'attention control' (e.g. befriending) provided by primary care/postnatal follow-up.

Types of outcome measures

1. Primary outcome

Recovery (dichotomous outcomes) from, or reduction (continuous outcomes) in PTSD or trauma symptoms as measured by validated scales e.g. PSS-SR[33], CAPS[36], Impact of Events Scale (IES).[41] Scores of continuous outcome measures reported, such as PSS-SR and CAPS, will be converted to indicate recovery or not from PTSD according to well-established cut-off

scores (e.g. cut-off scores for the PSS-SR, the CAPS and the IES are 14, 40 and 19) or as described by the study authors.

2. Secondary outcomes

- Recovery (dichotomous outcomes) from, or reduction (continuous outcomes) in depressive symptoms as measured by validated scales, e.g. Edinburgh Postnatal Depression Scale (EPDS),[42] Beck Depression Inventory (BDI),[43] State of Anxiety and Depression (SAD)[44]
- Recovery (dichotomous outcomes) from, or reduction (continuous outcomes) in anxiety symptoms as measured by validated scales, e.g. Beck Anxiety Inventory (BAI: Beck et al. 1988), Hospital Anxiety and Depression Scale[45]
- Well-being or quality of life, e.g. Short Form-36 (SF-36)[46]
- Adverse events or effects, e.g. increased PTSD or trauma symptom severity, death.

Timing of outcome measurements

Timing of outcome measurements will be grouped into three periods of time:

Short term: up to six months post intervention;

Medium term: between six and 12 months post intervention

Long term: over 12 months post intervention.

Types of studies

We will include all randomised controlled trials (RCTs), cluster RCTs, quasi-randomised trials, (such as trials which allocate study participants according to day of the week), and RCTs that comprise a crossover methodology that compare TFPT for PTSD symptoms in

women following traumatic birth with usual postpartum care. Study populations which comprise non-postpartum individuals will be included if the subset of data specific to the women are published or obtainable from the paper/trialists. There will be no restriction based on the study sample size, language, study setting or publication status.

Data sources and search strategy

We will carry out systematic searches in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PsycINFO, and OpenGrey using a search strategy developed in consultation with an information specialist at the academic institution where the first reviewer (MF) is based (Table 1). To maximise search sensitivity, we will use both index terms (e.g. Medical Subject Heading: MeSH) and free-text terms referring to population (e.g. 'pregnancy', 'postnatal') and interventions (e.g. 'Cognitive Therapy', 'Eye Movement Desensitization Reprocessing') without terms referring to outcomes. No restrictions on date, language, or publication status will be applied to the searches. The electronic searches will be supplemented by a hand search of the reference lists of all included studies. The citations we retrieve from the searches will be imported into the reference management software package EndNote X7.

Table 1 Searching strategy (Medline)

Population	AND	Intervention	AND	Study design[i)]
exp Pregnancy/		exp Cognitive Therapy/		exp Clinical Trial/
OR		*OR*		*OR*
exp Pregnancy Outcome/		CBT.mp.		exp Clinical Trial, Phase I/
OR		*OR*		*OR*
exp Delivery, Obstetric/		exp Eye Movement Desensitization Reprocessing/		exp Clinical Trial, Phase II/
OR		*OR*		*OR*
exp Parturition/		EMDR		exp Clinical Trial, Phase III/
OR		*OR*		*OR*
birth.mp		exp Behavior Therapy/		exp Clinical Trial, Phase IV/
OR		*OR*		*OR*
childbirth.mp		Behaviour* therapy.mp		exp Controlled Clinical Trial/
OR		*OR*		*OR*
exp Postnatal Care/		exp Psychotherapy/		exp Randomized Controlled Trial/
OR		*OR*		*OR*
postnatal.mp.		psychological.mp		exp Random Allocation/
OR		*OR*		*OR*
exp Postpartum Period/		exp Psychological Techniques/		randomised.mp
OR		*OR*		*OR*
postpartum.mp		exp Psychology, Experimental/		trial.mp
OR		*OR*		*OR*
exp Maternal Health Services/		Trauma focused.mp		RCT.mp
OR				
exp Infant, Newborn/				
OR				
exp Cesarean Section/				
OR				
caesarean				
OR				
exp Stillbirth/				
exp Intensive Care, Neonatal/				
OR				
exp Intensive Care Units, Neonatal/				

i) Search will be performed initially with sets of terms referring to population and interventions The terms referring to study design may be added if necessary, to increase search specificity.

Data collection and analysis

Selection of studies

Two reviewers will independently screen titles and abstracts of all potential studies identified through the search strategy, and they will code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve.' The two reviewers will then independently read the full text of the studies retrieved to determine whether trials meet the inclusion criteria or to record reasons for excluding ineligible studies. A third author will undertake a random check of 10%

of results at each stage. Any disagreements will be resolved through discussion or, if required, through consultation with other review authors. The process of the study selection will be outlined in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram and 'characteristics of excluded studies' table.

Data extraction and management

Two review authors will independently extract data using a data extraction form designed for this review which include details about study eligibility; sample frame and size; participant characteristics; diagnosis and diagnostic criteria used; nature, timing, and duration of intervention; number and frequency of sessions; professional background of trial therapists; outcomes (primary and secondary measures); statistical analyses; duration of follow-up; and attrition. Attempts will be made to obtain missing and/or unpublished details, by contacting study authors. This process will involve contacting trialists for independent datasets of postnatal women, if they are included in trials that also include other trauma victims.

Risk of bias assessment

Two review authors will independently assess the risk of bias of all included studies, using the approach recommended in the *Cochrane Handbook for Systematic Review of Interventions*.[47] The Cochrane's risk-of-bias tool addresses six specific domains: (1) sequence allocation for randomisation; (2) allocation concealment; (3) blinding of personnel and assessors; (4) incomplete outcome data; (5) selective reporting; and (6) any other notable risks of bias. For each item, one of the following three judgements will be made: 'low risk' of bias (plausible bias – unlikely to seriously alter the results), 'high risk' of bias (plausible bias that seriously weakens confidence in the results), or 'unclear risk' of bias (plausible bias that raises some doubt about the results) when insufficient information was reported to permit

judgment. The process for reaching judgments will be described in the risk-of-bias tables to ensure transparency.

Summary Assessments of Risk of Bias

The overall quality of the evidence for each outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[47 48] The overall quality of evidence for each outcome will be assigned to one of four levels – high, moderate, low, or very low – according to factors including within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias.[47 48]

Measures of treatment effect

For dichotomous outcomes, such as the presence of PTSD, depression or anxiety, the Mantel-Haenszel method for computing the pooled risk ratio (RR) with 95% confidence intervals (CI) will be used. For continuous data, and where different scales have been used, the standardised mean difference (SMD) and 95% CI will be calculated to indicate the direction and consistency of effect. The weighted mean difference (WMD) and 95% CI will be calculated where all outcomes were measured using the same scale in the same way.

Multiplicity and unit of analysis issues

If a study reports data for more than one outcome or time-point, analyses will be conducted separately for each outcome/time point (short, medium, long term). For trials with multiple arms of treatment in a study, the appropriateness of combining data to create a single pair-wise comparison will be considered if therapies are sufficiently similar. Alternatively, data from the arms of the trial which fit closest to the review objectives will be used. Where

studies have adopted a cross-over design, only outcome data from the first randomisation period will be included. If cluster-randomised trials are identified, sample sizes will be adjusted using an estimate of the intra-cluster correlation co-efficient (ICC) from the trial or from a study of a similar population, based on statistical advice.

Dealing with missing data

Dealing with missing data may include imputing outcomes for the missing participants to facilitate an intention-to-treat (ITT) analysis.[47] This may involve a sensitivity analysis by imputing outcomes for the missing participants with the most optimistic and the most pessimistic scenarios and then comparing the results of these two analyses. The sensitivity analysis may also be conducted to facilitate comparisons of the ITT with imputations from 'available case analysis' (i.e. analyse data with participants whose outcomes are known).[47] If these analyses yield similar results in the same direction of the effects of the treatment (indicating participants with missing outcomes are safely excluded), the results of available case analysis will be used for meta-analysis. The impact of including these studies in the overall assessment of treatment effect (summary effect) will be further assessed with additional sensitivity analysis comparing the results of meta-analyses with and without trials which are rated as high risk bias due to missing data (see Sensitivity analysis).

Assessment of reporting biases

When sufficient studies are available (n=10 or more), we will construct funnel plots and scrutinised them for signs of asymmetry [47].

Data synthesis

Random effects meta-analyses will be performed which will produce the average effect size of the intervention across studies, allowing for differences in the treatment effect from study to study. Random effects meta-analyses is a conservative option and more appropriate for this study than a fixed-effect model (which assumes that there is one true effect) because the populations and settings are likely to be slightly different, therefore the effects are likely to be slightly different. However, if there are only few studies (2-4 studies), it may be inadequate to accurately estimate of the width of the distribution of intervention effects.[47 49] In this case a fixed-effect analysis will be performed. Then, the results obtained from these two methods random effects and fixed-effect models will be compared to seek potential bias and heterogeneity. Analyses will be conducted by a statistician (ESWN) using a statistical software, STATA 14.

Heterogeneity

Heterogeneity will be assessed within each comparison. In the instance of clinical heterogeneity (e.g. variation in study settings, intervention modality), we will conduct subgroup analyses. Alternatively, if there is methodological heterogeneity (e.g. variation in study designs, outcome measures or risk of bias), we will perform sensitivity-analyses, where data are available. If there is significant heterogeneity between studies, extracted data will be synthesised into a narrative summary.

Where meta-analyses are performed, tests of statistical heterogeneity will be carried out using I^2 and Chi² statistics,[47] as well as visual inspection of the forest plots. If heterogeneity is identified (e.g. the I² is greater than 30%, and the *p* value is less than 0.10 in the Chi² test for heterogeneity or different direction of the effects), pre-specified subgroup analysis and meta-

regression analyses will be conducted to identify important determinants of heterogeneity when sufficient data are available.

Subgroup analysis and meta-regression

If possible, subgroup analyses will be undertaken as follow:

1. Study setting (high-income versus middle income versus low income countries)
2. Delivery mode of the intervention which shares the same theoretical modality (e.g. face-to-face versus web-based TFCBT)

Meta-regression analysis:

1. Intervention frequency (e.g. number of sessions)
2. Methodological heterogeneity of trial (e.g. ways of dealing with missing data, whether effect estimates from 'per-protocol' analyses differ compared with 'ITT' analyses)

Sensitivity analysis

Sensitivity analyses will be conducted to assess the effects of quality of trial methodology by comparing the results of meta-analyses with and without trials that are judged to have a high risk of bias for one or more of the domains of random sequence generation, allocation concealment, blinding of outcome assessment or incomplete outcome.

A sensitivity analysis will also be conducted to examine potential bias caused by missing data, by comparing results from different methods of dealing with missing data (e.g. available case analysis, ITT analysis using imputation of outcomes, assuming that all missing participants had positive outcome or that all missing participant had negative outcomes). Results of sensitivity will be reported in a Summary of Findings table.

Ethics and dissemination

Ethical approval is not required to conduct systematic reviews. The protocol was registered in PROSPERO (CRD42016043897). The findings of the review will be presented at relevant national and international conferences, and submitted to a peer-reviewed journal.

DISCUSSION

There is a lack of acknowledgement that women postpartum may be at risk of developing symptoms of trauma or PTSD. This means that their mental health needs likely remain undetected and unmet and, importantly, symptoms may impact on childcare and rearing. Women are not routinely included in studies investigating the effectiveness of psychological interventions for PTSD, and therefore we know little about whether these interventions are effective and acceptable to this population. We believe that this systematic review will be a valuable contribution to improving women's mental health and well-being following childbirth.

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AUTHORS' CONTRIBUTIONS

- MF: Proposing and designing the review, protocol development. Will contribute to: abstract screening, paper screening, data extraction, quality appraisal of papers, writing to authors of papers for additional information, analysis and interpretation of data, and writing the review.
- DS: Design of the review and protocol development. Will contribute to: abstract screening, paper screening, data extraction, quality appraisal of papers, interpretation of data, and writing the review.
- DB: Design of the review and protocol development. Will contribute to: quality appraisal of papers, interpretation of data, and writing the review.
- ESWN: Design of the review and protocol development. Will contribute to: checking accuracy of data extraction and conducting statistical analysis and reviewing the final report.
- JS: Proposing and designing the review, protocol development. Will contribute to: abstract screening, paper screening, data extraction, quality appraisal of papers, analysis and interpretation of data, and writing the review.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page #
ADMINISTRATIVE INFORMATION			
Title:			p. 1
Identification	1a	Identify the report as a protocol of a systematic review	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	The protocol was registered in PROSPERO (CRD42016043897) p.18
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Contact: p. 1 Email: submission system
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Contribution: p. 22
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			p. 22
Sources	5a	Indicate sources of financial or other support for the review	
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	p. 4-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	p. 7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Inclusion/exclusion criteria: p. 8-11
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	p. 11 'Data sources and search strategy'

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	p. 11-12 'Data sources and search strategy'
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	p. 11 (11a). To manage record, we will use the reference management software package EndNote X7 as described in 'Data sources and search strategy'.
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	p. 12 (11b) 'Selection of study'
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	p. 13 (11c, 12) 'Data extraction and management'
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	p.9-10 'Types of outcome measures'
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	p. 13 'Risk of bias assessment'
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	p. 16 (15a, 15b) 'Data synthesis' and 'Heterogeneity'
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	p. 17 (15c) 'Subgroup analysis and meta-regression' and 'Sensitivity analysis'
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	p. 16 (15d). Under the section of 'Heterogeneity', we described that "If comparable studies are not available with great clinical heterogeneity, extracted data will be synthesised into a narrative summary."
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	p. 14 'Summary Assessments of Risk of Bias' p. 15 'Assessment of reporting biases'
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	p. 14. We will use the GRADE approach as described in 'Summary Assessments of Risk of Bias'.

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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