ABSTRACT

Introduction Complementary and alternative therapies (CATs) refer to a diverse range of approaches that can be used as add-on or an alternative to conventional therapies. While a number of individual studies and systematic reviews (SRs) or meta-analyses (MAs) have investigated the effectiveness of specific types of CATs to treat depressive symptoms at specific moments of the perinatal period, an overarching synthesis of the literature is currently lacking. We will conduct an umbrella review of SRs and MAs to assess to which extent CATs are associated with depressive symptoms reduction during pregnancy or after childbirth.

Methods and analysis We will search a broad set of electronic databases (MEDLINE via Ovid, Embase.com, CINAHL via EBSCOhost, PsycINFO via Ovid, AMED and Google Scholar). We will include SRs with or without MAs meeting the following criteria: (1) the review should focus mostly on individual studies reporting a randomised controlled design; (2) diagnosis should be made during pregnancy or during the postpartum using a clinical interview according to DSM or ICD criteria; (3) the reviewed intervention should start during pregnancy or in the first postpartum year and meet the criteria for being considered as CAT. The main outcome will be depressive symptoms reduction during pregnancy or after childbirth. Secondary outcomes will include the remission of depression according to DSM criteria and intervention acceptability. Overlap between reviews will be described, quantified and discussed. We will rate the quality of the included SRs or MAs using the AMSTAR-2 tool. MAs will be performed by using the data from the individual RCT studies included in the SRs or MAs. Sensitivity analyses restricted to studies with a low-moderate risk of bias will be realised. Publication bias will be examined visually by using a funnel plot, and formally using the Egger’s test and test of excess significance.

Ethics and dissemination We intend to publish the results of the umbrella review in an international peer-reviewed journal. Oral presentations in congresses and internal diffusion through the Rise up-PPD European COST Action network are also planned.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To our knowledge, this will be the first umbrella review of systematic reviews or meta-analyses examining the effectiveness of complementary and alternative therapies to treat peripartum depression.⇒ A biomedical information specialist from the Medical Library of Erasmus MC, University Medical Center Rotterdam, designed the search strategy.⇒ Under-reporting of negative or non-significant results due to publication bias in individual studies included in the systematic reviews or meta-analyses could limit the accuracy of the synthesis.⇒ Given the focus on the effectiveness of complementary and alternative therapies to treat peripartum depression, we will not be able to balance their effects against their potential harms or risks⇒ Since systematic reviews and meta-analyses are rarely or intermittently updated, they become rapidly outdated, which could also limit the accuracy of the synthesis.

INTRODUCTION

Peripartum depression (PPD) (ie, a non-psychotic depressive episode that may occur during pregnancy and the first year after childbirth) is often associated with poor maternal and child outcomes (eg, low maternal well-being and quality of life, suicide for mothers, impairments in cognitive and emotional development of the child). According to a recent systematic review, its prevalence is estimated at 11.9% of the mothers. PPD is a major public health
native therapies (CATs) refer to a diverse range of are effective to treat PPD. Complementary and alter-
non-pharmacological treatments. According to a recent umbrella review, cognitive–behavioural therapy (CBT) and interpersonal psychotherapy (IPT) are effective to treat PPD. Complementary and alternative therapies (CATs) refer to a diverse range of approaches that can be used as add-on or an alternative to conventional therapies. CATs are commonly used during the perinatal period around the world (>50% of the perinatal women from the general population) and have been identified as promising treatment options to treat PPD, especially when CBT and IPT are not available or feasible, for example, due to language problems, reduced mobility, financial issues.13

While there has been a number of individual studies and systematic reviews or meta-analyses on CATs’ effectiveness on PPD, there is a lack of consensus on which interventions could be considered as CAT (ie, heterogeneity across studies in the categorisation of the following interventions: food supplementation, acupuncture, massage, body-oriented therapies, yoga, light therapy, integrative collaborative care, mindfulness, relaxation, physical exercise). In addition, most of these systematic reviews/meta-analyses focus on one specific type of CAT (eg, physical exercise only in Davenport et al; food supplementation only in Mocking et al; peer-support intervention only in Huang et al) or one specific moment of the perinatal period (eg, during pregnancy for Van Ravesteyn et al and Smith et al, during the post partum for Carter et al, Tong et al and Wu et al). Finally, there is a lack of consensus on the duration of the perinatal period across studies (eg, from 12 weeks after childbirth in Li et al to 6 months after childbirth in Mocking et al and 1 year after childbirth in Nillni et al or Huang et al).

To our knowledge, there is no umbrella review (ie, a systematic review of systematic reviews and meta-analyses) on the effectiveness of CATs in the treatment of PPD. Thus, an overarching synthesis of the literature on CAT effectiveness in PPD is timely and currently needed. Here, we propose the study protocol for an umbrella review aimed to answer the question whether CATs are associated with improvement of perinatal depressive symptoms, providing a robust synthesis of current published evidence on this topic, that can inform further research and routine clinical practice in understanding and considering different treatment options for PPD, next to CBT and IPT.

METHODS AND ANALYSIS

This study is an umbrella review, that is, a review of previously published systematic reviews or meta-analyses. The methods have been developed, based on recent guidance for the conduct of umbrella reviews (ie, 10 key points including the following: ensure that the umbrella review is really needed, prespecify the protocol, clearly define the variables of interest, estimate a common effect size, report the heterogeneity and potential biases, perform a stratification of the evidence, conduct sensitivity analyses, report transparent results, use appropriate software and acknowledge the limitations). The protocol has been developed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses protocols guidelines.

Searches

The search strategy has been designed by a biomedical information specialist (WMB) from the Medical Library of Erasmus MC, University Medical Center Rotterdam following the method as described by Bramer et al. We will search MEDLINE via Ovid, Embase.com, CINAHL via EBSCOhost, PsycINFO via Ovid, AMED and Google Scholar for published and peer-reviewed systematic reviews or meta-analyses. The search strategies for Embase and Medline used relevant thesaurus terms from Emtree and Medical Subject Headings, respectively. Next to that, in all databases terms will be searched in titles and abstracts of articles. The search combined terms for (1) postpartum depression or depression during pregnancy and (2) different forms of complementary medicine such as mindfulness and plant extracts, as well as terms for e-health. No time restriction and language restriction will be set, but conference abstracts are excluded from the search in Embase.com. We will also handsearch the reference list of the included reviews/meta-analyses for additional relevant systematic reviews or meta-analyses not retrieved in the electronic database searching. The full search strategy, search terms and syntax are presented in online supplemental table 1. The search will be updated prior to publication, so that there is no more than 6 months between the last search date and the date of publication. The umbrella review will begin on 1 September 2021 with an estimated completion date is 1 July 2022.

Types of studies to be included

We will include systematic reviews with or without meta-analyses. To define which articles can be considered as a systematic review, we will use the criteria proposed by Krnic Martinic et al: (1) specific research question;
We will not exclude low-one that meets the inclusion criteria detailed below. A pre-
mental health conditions.

To be included, systematic reviews or meta-analyses will need to focus mostly on individual studies reporting a randomised controlled design (i.e., >50% of RCT in the individual studies). Because a sufficient number of randomised controlled studies have been conducted since 2018,14 we will exclude systematic reviews or meta-analyses focusing predominantly on non-randomised observational studies, retrospective studies, case–control studies or case studies. We will exclude systematic reviews or meta-analyses aiming at the prevention of PPD. In case of overlapping reviews, we will include the largest (i.e., including the largest underlying dataset), the most recent and those of highest quality. In case the overlap is less distinctive, we will include both reviews. Overlap between reviews will be described and quantified.26 We will describe the consistency or inconsistency between overlapping reviews in the narrative synthesis of the qualitative findings. Meta-analysis will be performed by using the data from the individual RCT studies included in the systematic reviews or meta-analyses. Duplicate studies will be excluded. We will check if any individual study included in smaller meta-analyses was not included in the largest meta-analysis. In that case, we will rerun the meta-analysis including studies from the largest meta-analysis and any additional study from the smaller one that meets the inclusion criteria detailed below. We will not exclude low-quality systematic reviews or meta-analyses according to AMSTAR-2 scores.27 We will deal with the review quality in the post hoc analyses. We do not plan to include ongoing systematic reviews or individual RCTs in the present umbrella review.

**Interventions**

To be included in the present umbrella review, systematic reviews or meta-analyses should meet the following criteria: (1) the reviewed intervention or the majority of reviewed interventions should start during pregnancy or in the first year post partum and (2) the reviewed intervention should meet the criteria for being considered as CAT (i.e., all the interventions that are not pharmacological treatment, CBT or IPT or interventions using medical devices, for example, bright light therapy, rTMS or tDCS). CAT include nutritional (e.g., special diets, dietary supplements, herbs, prebiotics and probiotics), psychological and physical approaches (e.g., meditation, mindfulness, massage, yoga, Tai Chi, physical activity, chiropractic and osteopathic manipulation, relaxation techniques, music therapy, art therapy, dance, acupuncture, manual therapies, practices of traditional healers11). We will exclude reviews exclusively focusing on CBT, IPT and e-Health or online interventions derived from CBT or IPT. We will also exclude the interventions where it is not possible to disentangle the effects of CAT from those of a validated psychological or psychosocial treatment (e.g., CBT or IPT). We will not exclude systematic reviews or meta-analyses for co-occurring use of pharmacological treatment.

**Control condition**

We will include systematic reviews/meta-analyses using one or more control conditions (i.e., placebo, TAU or active comparators). We will not exclude systematic reviews/meta-analyses with poorly specified control conditions. To avoid artificial inflation of the intervention effect sizes, we will deal with this issue in post hoc analyses (e.g., sensitivity analysis restricted to systematic reviews/meta-analyses with well specified control conditions).

**Main outcome**

The main outcome will be depressive symptoms reduction during pregnancy or after childbirth. For the meta-analysis part of this umbrella review, we will include only studies using a validated self-report or observer-report instrument to assess depressive symptoms, for example, one or more of the following instruments: EPDS (10 items28); Beck Depression Inventory-II (21 items31); Hamilton Depression Scale (24 items30) and Montgomery-Asberg Depression Rating Scale (10 items31).

**Additional outcomes**

We will consider the remission of depression according to DSM criteria (i.e., symptom remission) and intervention acceptability as additional outcomes.

**Selection (screening) and coding**

Systematic reviews/meta-analyses identified with electronic and manual searches will be imported in EndNote and deduplicated according to the method described by Bramer et al.24 We will follow the procedure for reviewing retrieved references for inclusion in systematic reviews using EndNote described by Bramer et al.24
The screening process will be conducted in two separate stages:

1. Two authors (FP and AG-A) will independently screen the title and abstracts of all non-duplicated papers and exclude those not pertinent. Potential discrepancies will be resolved by consensus between the two authors. When consensus is not reached, a third senior author (ML-vdB) will act as an arbitrator.

2. Two authors (FP and AG-A) will independently apply eligibility criteria and screen the full-text papers to select the included reviews. Disputed items will be solved discussing together and reading further the paper to reach a final decision. When needed, a third senior author (ML-vdB) will act as an arbitrator. When relevant, we will contact the corresponding author for further information about the study. We will report excluded reviews at these stages with the reasons for exclusion.

In addition, the inter-rater reliability will be calculated.

Data extraction

Two authors (NA-M and AG-A) will perform independently the data extraction. For each systematic review or meta-analysis extract the following information: (1) general information (author, year of publication, country, type of review, objective of the review, overlap with other reviews); (2) inclusion and exclusion criteria relating to the type of studies included (ie, study design), the study population (diagnostic criteria) or the intervention (CAT definition criteria, type, format and length of the intervention), context of the study (inpatient/outpatient care, countries/continents of the unique studies, etc); (3) electronic databases searched by the authors; (4) number and types of studies included; (5) participants characteristics (total and per arm number of participant, mean age); (6) information about the person who delivered the intervention (midwife, nurse, community health worker, clinical psychologist, etc), intensity and frequency of the intervention; (7) outcome measure (instrument used to measure effectiveness, reliability); (8) variables relating to quality assessment, including method used to assess the quality of the included studies; (9) gestational period (eg, pregnancy, post partum or both); (10) follow-up period; (11) method of synthesis, main findings, type of effect size and numerical variables for each effect size with 95% CI, (12) measures of heterogeneity between studies (eg, Cochrane’s $χ^2$ test, $I^2$ test); (13) measures of publication bias (eg, Egger’s test) and (14) presence and description of subgroup or sensitivity analyses (eg, reviews with low to moderate risk of bias, samples, depression severity, gestational period, type of outcome measure; year of publication, individual vs group-based interventions).

Quality assessment

The risk of bias will be assessed using the AMSTAR-2, a validated instrument to assess the methodological quality of systematic reviews or meta-analyses. This 16-item instrument is not intended to generate an overall score, users being rather instructed to consider the potential impact of an inadequate rating for each item (in particular those considered as critical, ie, protocol registration before starting the review, adequacy of the literature search, justification for excluding individual studies, risk of bias from individual studies, appropriateness of meta-analytical methods, consideration of risk of bias when interpreting the results of the review, assessment of presence and likely impact of publication/selective reporting bias). Two independent researchers (FP and AG-A) will extract AMSTAR-2 scores for each review and discrepancies will be resolved through consensus with the participation of a third senior researcher (ML-vdB). The AMSTAR scores will be used in sensitivity and meta-regression analyses to control the impact of study quality on the overall estimates.

Strategy for data synthesis

We will summarise the umbrella review process, the overall quality of the included systematic reviews and meta-analyses and the consistency or inconsistency between overlapping reviews in the narrative synthesis of the qualitative findings.

Meta-analysis

If the underlying data allows, we will conduct a number of random effects meta-analyses with weighted effect sizes to estimate the effectiveness of CATs on perinatal depressive symptoms stratified by type of therapy. Random-effects analyses will be used to estimate an overall treatment effect since it produces a more reliable estimate than fixed effect analysis in case of substantial heterogeneity. In each stratum, we will calculate aggregated effect sizes using bias-corrected standardised mean estimates, that is, Hedges’ $g$, with 95% CIs and prediction intervals between the intervention group and the control group at the end of the trial. Hedges’ $g$ corrects for differences in variances resulting from the inclusion of trials with varying sample sizes. The magnitude of Hedges’ $g$ can be interpreted as small (0.20), moderate (0.50) or large (0.80). $P$ values <0.05 will be considered significant. Results will be presented using forest plots. Cochran’s Q-test, $I^2$ and $T^2$ statistics will be used to quantify heterogeneity across trials. Heterogeneity will be explored further using subgroup analysis (see Subgroup/sensitivity analyses). To examine the impact of the modelling method, we will calculate the pooled treatment effect using both fixed and random-effects modelling. All statistical analyses will be performed by using STATA. Meta-regression procedures will be conducted when relevant.

Subgroup/sensitivity analyses

If the underlying data allows, we will conduct sensitivity analyses restricted only to studies with a low-moderate risk of bias (particularly in terms of allocation concealment, blinding and outcome selective reporting). Other sensitivity analyses (eg, samples, depression severity, type of measure of outcome, year of publication, gestational period, individual vs group-based interventions, open access
supervised vs unsupervised intervention, type of provider delivering the intervention) will be conducted when relevant. Publication/selective reporting bias will be examined visually by using a funnel plot, and formally using the Egger’s test and test of excess significance.

We will grade the meta-analyses evidence using the approach proposed by Fusar-Poli and Radua:\(^2\)

- Convincing (class I) when number of cases is >1000, \(p<10^{-6}\), \(I^2<50\%\), 95% prediction interval excluding the null, no small-study effects and no excess significance bias.
- Highly suggestive (class II) when number of cases is >1000, \(p<10^{-6}\), largest study with a statistically significant effect and class I criteria not met.
- Suggestive (class III) when number of cases is >1000, \(p<10^{-3}\) and class I–II criteria not met.
- Weak (class IV) when \(p<0.05\) and class I–III criteria not met.
- Non-significant when \(p>0.05\).

**Patient and public involvement**

Patients were not involved in the design or realisation of the present umbrella review. However, CATs figure among the most popular treatment approaches in women with peripartum psychiatric disorders.

**DISCUSSION**

To our knowledge, this will be the first umbrella review of systematic reviews or meta-analyses examining the effectiveness of CATs to treat PPD. From a clinical perspective, gaining insight into which CATs are effective as adjunctive or alternative therapies to treat peripartum depression and into potential moderators of treatment effectiveness may inform a comprehensive, collaborative and personalised medicine approach of PPD.\(^8\) It may also inform the development of international clinical recommendations and guidelines for the use of CATs to treat PPD, which is one of the actions planned within the Rise-up-PPD European COST Action ‘Research Innovation and Sustainable Pan-European Network in Peripartum Depression Disorder’ network (CA18138).\(^1\) From a research perspective, our umbrella review will highlight knowledge gaps in the existing body of evidence to guide future research. Overall, this umbrella review will contribute to the current knowledge on treatment options for PPD with implications for both clinical practice and research.\(^8\)

However, there will also be some limitations. First, under-reporting of negative or non-significant results due to publication bias in individual studies included in the systematic reviews or meta-analyses could limit the accuracy of the synthesis. Second, we will focus on the effectiveness of CATs to treat PPD and will therefore not be able to balance their effects against their potential harms or risks. Third, since systematic reviews and meta-analyses are rarely or intermittently updated, they become rapidly outdated, which could also limit the accuracy of the synthesis.\(^35\) Fourth, another limitation could be related to the small number of individual studies on some emerging interventions that may have prevented the realisation of a systematic review or a meta-analysis.

**ETHICS AND DISSEMINATION**

We intend to publish the results of the umbrella review in an international peer-reviewed journal. Oral presentations in congresses and internal diffusion through the Rise up-PPD European COST Action network are also planned.

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**Contributors**

JD drafted the article. WMB made the search strategy and will conduct the database searching. AG-A, FP and ML-vdB will make the first screening based on titles and abstracts and the second screening based on the full text papers against the eligibility criteria to select the included studies. NA-M, AG-A and AMK will extract the data and create the extraction form. AG-A, FP and ML-vdB will make the quality assessment. AMK will conduct the statistical analysis. All authors will contribute to the interpretation of the data and critically revise the article.

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**Competing interests**

None declared.

**Patient and public involvement**

Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication**

Not applicable.

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**Supplemental material**

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