Systematic Reviews

PROTOCOL

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Protocol for a systematic review with meta-analysis and trial sequential analysis of preventive interventions versus any control intervention for parents with a mental disorder on offspring outcomes

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Abstract

Background Offspring of parents with a mental disorder are at high risk of a range of adverse outcomes, highlighting the need for preventive interventions. However, a comprehensive overview of the beneficial and harmful effects of preventive interventions for parents with mental disorders on offspring outcomes are uncertain. The main objective of this systematic review will be to assess the effects of preventive interventions versus any control intervention for parents with a mental disorder on offspring outcomes.

Methods/design We will conduct a systematic review with meta-analysis and report it as recommended by Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA), bias will be assessed with the Cochrane Risk of Bias tool-version 2 (ROB2), an eight-step procedure will be used to assess if the thresholds for clinical significance are crossed, trial sequential analysis will be conducted to control for random errors, and the certainty of the evidence will be assessed with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. To identify relevant trials, we will search for published trials in several electronic databases from their inception to the present. We will also search for unpublished trials and grey literature. Two review authors will independently screen the articles, extract data, and perform a risk of bias assessment. We will include any published or unpublished randomized clinical trial comparing a psychological preventive intervention versus any control intervention for parents with any mental disorder. The primary outcomes will be quality of life and incidence of a mental disorder. Secondary outcomes will include internalizing symptoms, externalizing symptoms, serious adverse events, out-of-home placement, and absence from school or daycare. Exploratory outcomes include trauma, socioemotional development, and language development. All outcomes will be assessed in offsping only.

Discussion There is an urgent need for a comprehensive, updated systematic review of the beneficial and harmful effects of preventive interventions for children of parents with a mental disorder. The findings of this systematic review are expected to provide evidence-based information for policymakers, clinicians, and researchers to help them

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make informed decisions about the most effective interventions and guide future research for this highly prevalent population.

Systematic review registration PROSPERO CRD42023463421.

Keywords Parents with a mental disorder, Intergenerational transmission, Child, Offspring, Parent, Preventive intervention, Mental disorder, Systematic review, Meta-analysis

Background

Parents with mental disorders

The World Health Organization (WHO) estimates that approximately 970 million people worldwide are affected by mental disorders [1], many of whom are parents and caregivers [2]. Mental disorders constitute the largest cause of disability worldwide [3] and encompass conditions such as substance use disorders, psychotic disorders, mood disorders, anxiety disorders, and personality disorders, which can vary in severity [4] and vary over time in diagnostic categories or be in remission. The lifetime prevalence of any mental disorder is estimated to be approximately 26% [5]. Cross-sectional studies indicate that between 15 and 55% of patients attending adult mental health services are parents [2]. The parent's capacity to provide consistent, adequate, and sensitive care required for healthy child development and well-being is often affected by psychiatric symptoms [6]. Moreover, the psychosocial context, including factors such as the parent's occupational status, presence or absence of the other parent, availability of social support, and financial resources, may significantly impacts parenting [7], and further exacerbate parenting challenges. It is important to note that while mental disorders in parents can have adverse effects on offspring and impact parenting abilities [8, 9], not all parents with mental disorders struggle to take care of their children, and the impact of psychiatric symptoms on parenting varies across individuals [6, 10].

Offspring of parents with mental disorders

Approximately 17–25% of all children worldwide have at least one parent with a mental disorder [2, 11–13]. Offspring of parents with mental disorders have an elevated risk of various adverse immediate and long-term outcomes, suggesting an intergenerational transmission of adversity from parent to offspring [14, 15]. Research consistently shows that offspring of parents with a mental disorder are 3–12 times more likely to develop a mental disorder themselves [14]. Epidemiological studies suggest that approximately 50% of offspring of parents with severe mental disorders have developed a mental disorder by age 30 [15]. Mental health problems often originate early in life and can develop through a complex interplay of biological factors (e.g., genetic heritability) and environmental factors (e.g., psychosocial disadvantages, maladaptive parenting) [11, 16, 17]. Offspring of parents with mental disorders show more suicidal behavior, participation in violence and crime [18], poor school performance [19], developmental delays [20], out-of-home placements [21], and exposure to maltreatment, such as abuse and neglect [22, 23]. Offspring of parents with mental disorders are five times more likely to utilize social, health, and mental health services compared to the general population [11]. Thus, the personal, social, and economic costs associated with parental mental disorders are significant and far-reaching.

Preventive interventions for parents with a mental disorder

Preventive interventions for parents with a mental disorder have significant potential to address the intergenerational transmission of mental health problems and promoting the well-being of both parents and offspring. Childhood and adolescence is a critical developmental period and presents a significant "window of opportunity" in terms of preventing long-term adverse problems and promoting healthy development and well-being in offspring [11, 24, 25]. Preventive interventions are aimed at identifying and addressing mental health antecedents at an early stage, promoting resilience, implementing protective factors, and supporting healthy child development. By intervening early in life, there is a greater possibility of preventing or minimizing the onset and severity of mental health problems, leading to improved long-term outcomes for both parents and offspring, thereby reducing the burden on healthcare systems, schools, and other support services can be reduced. By addressing the needs of this population, preventive interventions have the potential to create a positive, long-lasting impact on individuals, families, and society as a whole.

A number of psychological preventive interventions for parents with mental disorder exist. These interventions are typically underpinned by psychotherapeutic theories, with the most common ones being cognitive behavioral therapy (CBT), psychoeducation, and attachment/psychodynamic informed interventions [26–28]. While many of the existing interventions that have been evaluated in randomized clinical trials are structured, manualized, and based on a clear theoretical model

of causality, some are less explicit in their theoretical and clinical underpinnings and approach. Most of the interventions are disorder specific, that is, developed specifically for parents with a particular mental disorder, typically depression or substance abuse, with only a few transdiagnostic interventions targeting parents with mental illness irrespective of the specific diagnosis [26–28]. Preventive interventions for this population are developed to be delivered from the postpartum period until the offspring reach adolescence. The intervention can involve the offspring, parent affected by a mental disorder, offspring-parent dyad, couples, or the whole family and can be delivered in an individual (i.e., parent only) or group format (i.e., groups for parents) or a combination of both modalities. Usually, interventions for parents of infants or small children involve the parent only or parent–child dyad, while interventions for parents with older children and adolescents typically involve the whole family or separate groups for adolescents. The interventions are designed for delivery in different settings, such as at home, at a specialized clinic, or online, and may vary greatly in terms of length and number of sessions—from "brief" (<12 sessions) to "long-term" (>20 sessions). For an overview of examples of existing preventive interventions for parents with mental disorders previously evaluated in randomized controlled trials, see Supplementary Table 1.

How the interventions might work

Preventive interventions for parents with mental disorders are underpinned by theories of change with regard to the ways in which psychiatric symptoms may affect parenting, family, and offspring and thus the prevention of adversity and promotion of resilience [24]. Different mechanisms of change are postulated in accordance with the theoretical models underpinning interventions for parents with mental disorders. Broadly speaking, psychodynamic- and attachment-informed interventions aim to help parents understand and reflect upon their own and their child's mental states and connect their own past experiences with current difficulties related to parenting to promote sensitive caregiving and a secure attachment relationship between parent and child. Specifically, this may involve interventions such as video feedback intervention to promote positive parenting (VIPP) [29] or interpersonal therapy (IPT) [30]. CBT-informed interventions are usually based on cognitive restructuring and behavioral challenges. In working with older children and adolescents, the aim may be to increase their understanding of the parent's mental disorder and identify and challenge negative thoughts and beliefs and to learn behavioral skills [31]. For parents, the aim is to improve parenting skills using behavioral training and support parent–child interactions using reinforcement of positive relationships [32]. Psychoeducational interventions are often delivered to the whole family, sometimes combined with behavioral parenting skill strategies. They typically aim at improving communication and understanding of the parent's mental disorder and its impact on the family. This includes interventions such as Family Talk [33] and Focus on Families [34].

Why is it important to do this review?

To date, three systematic reviews with meta-analyses have been conducted to assess the effects of preventive interventions for offspring of parents with mental disorders on offspring psychopathology, all of which have some limitations. Thus far, no systematic reviews have assessed the effects of preventive interventions for parents with mental disorders on other important offspring outcomes than psychopathology, such as quality of life, out-of-home placement, and childhood trauma. The characteristics and results of these previous reviews are summarized in Supplementary Table 2.

The earliest of the previous reviews conducted by Siegenthaler and colleagues assessed the effects of preventive interventions in reducing the risk of mental disorders in the offspring of parents with a mental disorder, including affective disorders, substance or drug abuse, and anxiety disorders [27]. This review compared preventive interventions versus treatment as usual, which was not otherwise specified, and found that preventive interventions reduced the risk of offspring developing the same mental disorder as the affected parent by 40% and reduced internalizing symptoms but not externalizing symptoms in offspring. This review is limited however by not assessing the incidence of offspring developing a different diagnosis from the affected parent and by not assessing other adverse effects on offspring. Furthermore, the review authors did not publish a protocol before conducting the review, and they did not assess the risk of bias (other than publication bias) or certainty of the evidence. Finally, this review is limited by not performing trial sequential analyses to assess the risk of random errors. Therefore, there is a risk that the meta-analysis was underpowered to confirm or reject realistic intervention effects. Together, these methodological limitations decrease the validity of the review results.

A more recent review by Thanhäuser and colleagues assessed the effects of preventive interventions on mental disorders and internalizing and externalizing symptoms in offspring of parents with a mental disorder, including depression, substance use disorders, anxiety disorder, and mixed disorders (not otherwise specified) [28]. This review compared preventive interventions versus no intervention, treatment as usual, or an alternative,

less intensive and less specific intervention. This review showed that preventive interventions reduced mental disorders in offspring and reduced internalizing symptoms but not externalizing symptoms. However, this review has several limitations. The review authors did not publish a protocol before conducting the review, nor did they assess other adverse effects on offspring, risk of bias (other than publication bias) or certainty of the evidence. Finally, this review is limited by not performing trial sequential analyses to assess the risk of random errors. Therefore, there is a risk that the meta-analysis was underpowered to confirm or reject realistic intervention effects. In sum, these methodological limitations decrease the validity of the review results.

The final and most recent previous review conducted by Lannes and colleagues assessed the effects of psychological interventions in preventing negative mental health outcomes in the offspring of parents with a mental disorder, including mood disorders, anxiety disorders, psychotic disorders or substance use disorders [26]. This review showed that preventive interventions reduced the incidence of mental disorders in offspring by almost 50% and reduced internalizing symptoms but not externalizing symptoms in offspring. This review is limited by not assessing other adverse effects on offspring and by not specifying in the preregistered protocol which timepoint they used for their primary outcome. Furthermore, this review is also limited by not assessing the risk of bias and by not performing trial sequential analyses to assess the risk of random errors. Therefore, there is a risk that the meta-analysis was underpowered to confirm or reject realistic intervention effects. Taken together, these methodological limitations decrease certainty in the validity of the review results.

Common to all the previous systematic reviews outlined above is that they are limited by only assessing one primary outcome, despite the recommendation provided by the Cochrane collaboration that the conclusions of systematic reviews always should be based on two to three patient (i.e., offspring) important outcomes [35]. As previously mentioned, it is well documented that offspring of parents with mental disorders are at high risk of experiencing a range of adverse outcomes other than developing a mental disorder, such as low quality of life, child maltreatment, and out-of-home placement, compared to other children [36]. Neither of the previous reviews have assessed the effects of preventive interventions for parents with mental disorders beyond offspring psychopathology. By assessing a broader range of potential beneficial and harmful effects on offspring, we gain a more nuanced understanding of the overall impact of preventive interventions for parents with mental disorders on offspring can be produced. A systematic evaluation of other important outcomes is essential to better inform future research, policy, and clinical decision-making. In addition, since the last systematic review was conducted and published, a number of potentially eligible randomized clinical trials have been conducted [37–40], emphasizing the importance of a new comprehensive systematic review of preventive interventions for this population.

Randomized clinical trials and systematic reviews of such trials are considered the gold standard when evaluating intervention effects [35]. Despite the significant personal, social, and economic costs associated with parental mental disorders, no existing systematic review has systematically assessed a wide range of both beneficial and harmful effects of preventive interventions for parents with mental disorders on offspring. The present systematic review of randomized clinical trials aims to fill this evidence gap and thus provide the basis for developing evidence-based guideline recommendations for the use of preventive interventions for offspring of parents with a mental disorder, taking into consideration the risk of bias (systematic errors), play of chance (random errors), and confidence in the findings. The findings are thus expected to provide valuable information for policymakers, clinicians, and researchers, helping them to make informed decisions about the most effective interventions for this population.

Methods

The present protocol for a systematic review has been registered in the PROSPERO database (CRD42023463421) and is being reported in accordance with the guidelines provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement [41] (see checklist in Additional file).

Criteria for considering trials for this systematic review

Types of trials

We will include randomized clinical trials irrespective of trial design, setting, publication status, publication year, country, and reporting of outcomes. We will not include quasirandomized trials or observational studies.

Types of participants

Participants will be offspring of parents with any of the following mental disorders: substance/drug use disorders, psychotic disorders, mood disorders, anxiety and trauma disorders, personality disorders, attention deficit disorders, and developmental disorders, as defined in either ICD-10 [42] or DSM-5 [4] or earlier versions (ICD-10 codes: F10-19, F20-29, F30-39, F40-49, F50-59, F60-69, F80-89, F90-98), or assessed with standardized validated

questionnaires or clinical interviews. Participants will be included irrespective of sex and comorbidities.

Types of interventions

Experimental group: We will accept any type of psychological intervention (as defined by the trialists).
Control group: We will accept any type of control intervention, e.g., treatment as usual (or similar terminology), sham interventions, wait-list, or no intervention.

Outcome measures

All outcomes in this systematic review will be assessed as offspring outcomes.

Primary outcomes:

- Quality of life in offspring (continuous data)
- Proportion of offspring with one or more mental disorders (dichotomous data)

Secondary outcomes:

1. Internalizing symptoms in offspring (continuous data)
2. Externalizing symptoms in offspring (continuous data)
3. Proportion of offspring with one or more serious adverse events (dichotomous data).
4. Proportion of offspringin out-of-home placement (dichotomous data)
5. Proportion of offspring with one or more days absent from school or daycare the past month (dichotomous data)

Exploratory outcomes:

1. Frequency of trauma in offspring (continuous data)
2. Socioemotional development in offspring (continuous data)
3. Language development in offspring (continuous data)

For a detailed description of outcome measurement methods to assess the primary, secondary, and exploratory outcomes, see Supplementary Material 2.

Assessment time points

The primary assessment time point will be the maximum follow-up for all outcomes.

Search methods for the identification of studies

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), Latin American and Caribbean Health Sciences Literature (LILACS), PsycINFO, Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index—Science (CPCI-S), and Conference Proceedings Citation Index—Social Science & Humanities (CPCI-SSH) to identify relevant trials. We will search all databases from their inception to the present. For a detailed search strategy for all electronic databases, see Additional File 2.

Searching other resources

The reference lists of relevant publications will be checked for any unidentified randomized trials. We will contact the authors of the included studies by email asking for unpublished randomized trials. Furthermore, we will search for ongoing trials on the following websites:

- ClinicalTrials.gov (www.clinicaltrials.gov)
- Google Scholar (https://scholar.google.dk/)
- The Turning Research into Practice (TRIP) Database (https://www.tripdatabase.com/)
- European Medicines Agency (EMA) (http://www.ema.europa.eu/ema/)
- Medicines and Healthcare Products Regulatory Agency (https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatoryagency)
- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/)
- Cochrane Database of Systematic Reviews
- http://www.evidencebasedpsychotherapies.org/index.php?id=25

Additionally, we will hand search conference abstracts from psychiatry and preventive intervention conferences for relevant trials. We will also consider unpublished and grey literature trials if we identify these.

Data collection and analysis

We will conduct the systematic review following the recommendations of the Cochrane Collaboration [35]. The analyses will be performed using Trial Sequential Analysis [43] and the latest version of Stata [44].

Selection of studies

Two authors will independently screen titles and abstracts (EH, JK). We will retrieve all relevant full-text trial publications, and two review authors will independently screen the full text and identify and record reasons for the exclusion of the ineligible trials (EH, JK). Any disagreement will be resolved through discussion or, if needed, we will consult a third author (SJ). Trial selection will be displayed in an adapted flow diagram as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [45].

Data extraction and management

Two authors will independently extract data from the included trials in a designated data extraction template developed for this review (EH, JK). Disagreements will be resolved through discussion until consensus or, if needed, consultation with a third author (SJ). We will assess duplicate publications and companion papers of a trial together to evaluate all available data simultaneously (maximize data extraction, correct bias assessment). We will contact the trial authors by email to provide any additional data that may not have been reported sufficiently or at all in the publication. We will note in the "Characteristics of included studies" table if outcome data were not reported in a usable way.

General characteristics

We will extract the following data: year published, country, publication status, clinical trial registry, profit bias, protocol, and funding. In addition, notable conflicts of interest of trial authors will be extracted, if available.

Trial characteristics

We will extract the following data: bias risk components (as defined below), trial design, number of intervention arms, data collection time points and primary endpoint, inclusion and exclusion criteria, compliance with interventions, and study attrition rates.

Participant characteristics

We will extract the following data for the offspring: number of randomized participants, number of analyzed participants, number of participants lost to follow-up/withdrawals/crossover, compliance with interventions, age range (mean or median), sex ratio, age at baseline assessment and maximum follow-up for all outcomes. We will extract the following data for parents: age range (mean or median), sex ratio, and type of mental disorder(s): number of randomized participants, number of analyzed participants, number of participants lost to follow-up/withdrawals/crossover.

Intervention characteristics

We will extract the following data for both the experimental and control interventions: type of intervention, treatment duration, number of sessions (dose), session lengths (minutes), number of sessions per week, treatment format, type of participants involved (offspring, parent, parent–offspring dyad, family), delivery setting, service providers' educational background, and duration of training of therapists.

Outcomes

All outcomes listed above will be extracted from each randomized clinical trial.

Assessment of risk of bias in included studies

Risk of bias assessment will be based on the Cochrane Risk of Bias tool–version 2 (RoB 2) as recommended in the Cochrane Handbook for Systematic Reviews of Interventions [35] for both individual- and cluster-randomized clinical trials. We will evaluate the methodology with respect to the following bias domains:

- Risk of bias arising from the randomization process
- Risk of bias due to deviating from the intended interventions (effect of assignment to intervention)
- Risk of bias due to missing outcome data
- Risk of bias in measurement of the outcome
- Risk of bias in the selection of the reported results

The overall assessment of risk of bias will be judged as "low risk" if all of the domains are assessed as "low risk." If one or more domains are assessed as "some concerns" or "high risk," the overall assessment will be judged as "high risk."

We will assess the domains "risk of bias due to missing outcome data," "risk of bias in measurement of the outcome," and "risk of bias in selection of the reported result" for each outcome in addition to each trial. Our primary conclusions will be based on the results of our primary outcome results with an overall low risk of bias. Both our primary and secondary conclusions will be presented in the "Summary of findings" tables.

Differences between the protocol and the review

The systematic review will be conducted according to this published protocol, and any deviations from it will be reported in the " Differences between the protocol and the review" section of the systematic review.

Measures of treatment effect

Dichotomous outcomes

We will calculate risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes.

Continuous outcomes

We will calculate the mean differences (MDs) and consider calculating the standardized mean difference (SMD) with 95% CI for continuous outcomes.

Dealing with missing data

We will use intention-to-treat data if provided by the trialists. We will, as the first option, contact all trial authors to obtain any relevant missing data (i.e., for data extraction and for assessment of risk of bias, as specified above).

Dichotomous outcomes

We will not impute missing values for any outcomes in our primary analysis. We will impute data in the sensitivity analyses (see below).

Continuous outcomes

We will primarily analyze scores assessed at single time points. We will analyze changes from baseline scores using an MD if the same scale is used across trials. For different measurement scales in the same analysis model, we will use the SMD effect size. In case some studies do not report change scores but provide follow-up values, we will combine them together in a single model using MD [35]. If standard deviations (SDs) are not reported, we will calculate the SDs using relevant trial data (e.g., *P* values), if available. We will not use intention-to-treat data if the original report does not contain such data; per protocol data will then be used. In our best–worst and worst–best scenarios (see paragraph below) for continuous outcomes, we will impute data.

Assessment of heterogeneity

We will primarily investigate forest plots to visually assess any sign of heterogeneity. We will also assess the presence of statistical heterogeneity using the I^2 statistic. We will also investigate possible sources of heterogeneity through subgroup analyses. In the event of high heterogeneity assessed via visual inspection of the forest plot, we may decide not to combine the data in a meta-analysis and will then report the results narratively [35].

Assessment or reporting biases

If ten or more trials are included, we will assess reporting bias using a funnel plot, which will be visually inspected. We are aware of the limitations of a funnel plot (i.e., a funnel plot assesses bias due to small sample size). For dichotomous outcomes, we will test asymmetry with the Harbord test if τ^2 is less than 0.1 and with the Rücker test if τ^2 is more than 0.1. For continuous outcomes, we will use the regression asymmetry test [46] and the adjusted rank correlation [47].

Unit of analysis issues

We will only include randomized clinical trials. We will only include the relevant trial arms if multiple arms are reported in a single trial. For trials using a crossover design, only data from the first period will be included [35, 48]. If a trial has multiple relevant experimental groups, we will divide the number of events and sample size for the control group by the number of experimental groups for dichotomous data and keep the main score for continuous data [35]. We will include cluster-randomized trials after adjusting the original sample size of the trial to the effective sample size using the intracluster correlation coefficient from the "design effect" [35]. Therefore, we will not have any unit of analysis issues.

Data synthesis

Meta-analysis

We will undertake the meta-analysis in accordance with the recommendations stated in the *Cochrane Handbook for Systematic Reviews of Interventions* [35] and the eight-step assessment suggested by Jakobsen et al. [49]. We will use the statistical software Stata version 18 [44] to analyze the data. We will assess the intervention effects with both random-effects model meta-analyses (Hartung–Knapp–Sidik–Jonkman) [50] and fixed-effect model meta-analyses (Mantel–Haenszel for dichotomous outcomes and inverse variance for continuous outcomes) and report both results [35, 51]. We will use the more conservative result of the two as the primary result. The more conservative point estimate is the estimate closest to zero effect. If the two estimates were similar, we used the estimate with the widest CI. We will report the less conservative result as a sensitivity analysis [49]. We will assess a total of two primary outcomes, and we will therefore consider a *P* value of 0.033 or less as the threshold for statistical significance. We will investigate possible heterogeneity through subgroup analyses. If quantitative synthesis is not appropriate due to considerable heterogeneity or a

small number of included trials, we will report the results in a narrative way.

Trial sequential analysis

Trial sequential analysis estimates the diversity-adjusted required information size (DARIS), which is the number of participants needed in a meta-analysis to detect or reject a certain intervention effect [43]. Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. To control for the risks of type I errors and type II errors, we will perform trial sequential analysis [52] on the primary and secondary outcomes to calculate the required information size, that is, the cumulative *Z*-curve's breach of relevant trial sequential monitoring boundaries [43, 52, 52–58]. For dichotomous outcomes, we will estimate the required information size based on the observed proportion of participants with an event in the control group (the cumulative proportion of participants with an event in the control groups relative to all participants in the control groups), a relative risk reduction of 20%, an alpha of 3.3% for our primary outcomes, a beta of 10%, and the observed diversity as suggested by the trials in the meta-analysis. For continuous outcomes, we will in the trial sequential analysis use the observed SD in the control group, a mean difference of the observed SD/2, an alpha of 3.3% for our primary outcomes, a beta of 10%, and the observed diversity as suggested by the trials in the meta-analysis [49, 52]. A more detailed description of trial sequential analysis can be found in the trial sequential analysis manual [52] and at http://www.ctu.dk/tsa/.

Subgroup analysis

We will perform the following subgroup analyses when analyzing the primary outcomes: quality of life and incidence of mental disorders in offspring of parents with a mental disorder.

1. High risk of bias trials compared to low risk of bias trials
2. Type of experimental intervention
3. Type of comparator (e.g., treatment as usual, or similar terminology, sham intervention, wait-list, no intervention)
4. Unpublished trials versus published trials
5. Types of parental mental disorder (as defined by trialists)
6. Short-term vs long-term interventions (as defined by trialists)
7. Types of individuals involved (parent, offspring, family, parent–child).
8. Types of respondent of offspring mental disorder (clinician/national registers, offspring, i.e., self-report, teacher, parent)

We will use the formal test for subgroup interactions in Stata [44].

Sensitivity analysis

To assess the potential impact of missing data for dichotomous outcomes, we will perform the two following sensitivity analyses on both the primary and secondary dichotomous outcomes:

- "*Best–worst-case*" *scenario*: Based on the assumption that all offspring lost to follow-up in the experimental group had no mental disorder, no serious adverse events, and no out-of-home placements and that all offspring lost to follow-up in the control intervention group had a serious adverse event, a mental disorder or were placed out of home.
- "*Worst–best–case*" *scenario*: Based on the assumption that all offspring lost to follow-up in the experimental group had a mental disorder, had a serious adverse event, and were placed out of home and that all offspring lost to follow-up in the control group had no serious adverse event, had no mental disorder, and were not placed out of home.

To assess the potential impact of missing SDs for continuous outcomes, we will perform the following sensitivity analyses: When analyzing quality of life, internalizing symptoms, and externalizing symptoms, a "beneficial outcome" will be the group mean plus two SDs (we will second, use one SD in another sensitivity analysis) of the group mean, and a "harmful outcome" will be the group mean minus two SDs (we will second, use one SD in another sensitivity analysis) of the group mean.

Where SDs are missing and it is not possible to calculate them, we will impute SDs from trials with similar populations and at low risk of bias. If we identify no such trials, we will impute SDs from trials with a similar population. As the final option, we will impute the mean SD from all included trials.

We will present the results of these scenarios in our review. Other post hoc sensitivity analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results.

"Summary of findings" table

We will create a summary of findings table for the primary outcomes (quality of life and incidence of mental disorders in offspring of parents with a mental disorder) and secondary outcomes (internalizing symptoms,

externalizing symptoms, serious adverse events, out-of-home placement, and absence from school or daycare). We will use the five Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) [59] considerations: bias risk of the trials, consistency of effect, imprecision, indirectness, and publication bias, to assess the certainty of evidence in the trials. We will downgrade imprecision in GRADE by 2 levels if the accrued number of participants is below 50% of the DARIS and one level if between 50 and 100% of DARIS. We will not downgrade if benefit, harm, futility, or DARIS is reached. We will primarily present our results in the table based on the results from the trials with a low risk of bias, and secondarily, we will present the results based on all trials. When interpreting our results, we will consider the impact of the certainty of evidence upon the analysis and outcomes.

Discussion

The aim of this systematic review will be to assess the beneficial and harmful effects of any psychological preventive intervention for children of parents with a mental disorder on offspring outcomes. The prespecified primary outcomes will be quality of life and the proportion of children with a mental disorder. The prespecified secondary outcomes will be internalizing symptoms, externalizing symptoms, serious adverse events, out-of-home placement, and absence from school or daycare. This protocol has several strengths. First, this systematic review will broaden our knowledge on various beneficial and harmful effects of preventive intervention for parents with mental disorders, transcending the scope of offspring psychopathology. Second, we predefined our methodology based on the PRISMA statement and checklist [41, 45] and on the Cochrane Handbook for Systematic Reviews of Interventions [35]. Third, we will follow the eight-step procedure as suggested by Jakobsen et al. [49] and perform trial sequential analysis (TSA) [43] and GRADE assessment [59], thereby addressing both the risk of random errors and systematic errors. However, our protocol also has some limitations. There are potentially many comparisons that may increase the risk of type 1 errors. We adjusted our threshold for significance according to two primary outcomes, but we did not adjust the threshold for significance for the secondary outcomes or the comparisons (subgroup analyses and sensitivity analyses). We expect inadequate reporting of serious adverse events in the included trials, which will increase the risk of underestimating harmful effects. Moreover, we also expect a high degree of missing data for the continuous outcomes and very short follow-up time points, which we will take into account when interpreting the results. Although the effects of preventive interventions for offspring of parents with mental disorders have been evaluated in previous systematic reviews, these were inadequate due to the lack of systematic assessment of both beneficial and harmful effects of various important offspring outcomes. Hence, there is a need for a systematic review assessing the beneficial and harmful effects of preventive interventions in offspring of parents with a mental mental disorder. This systematic review will ultimately inform best practices in preventive interventions for parents with mental disorders and their offspring.

Abbreviations

CBT	Cognitive behavioral therapy
CENTRAL	Cochrane central register of controlled trials
CI	Confidence interval
CPCI-S	Conference proceedings citation index – social science & humanities
CTQ	Childhood trauma questionnaire
DSM-5	Diagnostic and statistical manual of mental disorders, 5th edition
EMA	European medicines agency
EMBASE	Excerpta medica database
GRADE	Grading of recommendations assessment, development, and evaluation
ICD-10	International classification of diseases, 10th revision
ICTRP	International clinical trials registry platform
IPT	Interpersonal therapy
LILACS	Latin American and Caribbean health sciences literature
MD	Mean differences
MEDLINE	Medical literature analysis and retrieval system online
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRISMA-P	Preferred reporting items for systematic reviews and meta-analyses protocols
PROSPERO	International prospective register of systematic reviews

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-024-02697-9.

Additional file 1. renamed_562baR1.

Additional file 2. PRISMA-P+checklist PREVENTR1

Additional file 3. Search strategy PREVENT Hestbaek et alR1

Additional file 4. Supplementary 2R1

Acknowledgements

We would like to thank Sarah Louise Klingenberg (Information Specialist, The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Copenhagen, Denmark) for making the search strategy.

Authors' contributions

EH wrote the first draft of the protocol with supervision from SJ. SJ and EH wrote the methods section in collaboration with MSV, JK, MV, and SS read and commented on the final manuscript before it was submitted for publication. All the authors have read and approved the final manuscript.

Funding

This study is funded by the Independent Research Fund Denmark (award number: 3101-00179B). The funds are not involved in the design, collection, analysis, interpretation of data, or writing of the manuscript.

Data availability
Data sharing is not applicable to this protocol article. We will publish all data including code in the supplementary material of the systematic review.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 16 October 2023 Accepted: 28 October 2024
Published online: 27 November 2024

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