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Psychotherapy versus treatment as usual and other control interventions in children and adolescents with overweight and obesity: a protocol for systematic review with meta-analysis and Trial Sequential Analysis

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ABSTRACT

Introduction The prevalence of children with overweight and obesity is increasing worldwide. Multicomponent interventions incorporating diet, physical activity and behavioural change have shown limited improvement to body mass index (BMI). However, the impact of psychotherapy is poorly explored. This systematic review aims to assess the effects of psychotherapeutic approaches for children with all degrees of overweight.

Methods and analysis We will include randomised clinical trials involving children and adolescents between 0 and 18 years with overweight and obesity, irrespective of publication type, year, status or language up to April 2020. Psychotherapy will be compared with no intervention; wait list control; treatment as usual; sham psychotherapy or pharmaceutical placebo. The following databases will be searched: Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, MEDLINE, Embase, PsycINFO, PubMed, Web of Science, CINAHL and LILACS. Primary outcomes will be BMI z-score, quality of life measured by a validated scale and proportion of patients with serious adverse events. Secondary outcomes will be body weight, self-esteem, anxiety, depression and proportion of patients with non-serious adverse events. Exploratory outcomes will be body fat, muscle mass and serious adverse events. Study inclusion, data extraction and bias risk assessments will be conducted independently by at least two authors. We will assess risk of bias according to Cochrane guidelines and the Cochrane Effective Practice and Organisation of Care guidance. We will use meta-analysis and control risks of random errors with Trial Sequential Analysis. The quality of the evidence will be assessed using Grading of Recommendations Assessment, Development and Evaluation Tool. The systematic review will be reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Cochrane guidelines.

Ethics and dissemination As individual patient data will not be included, we do not require ethics approval. This review will be published in a peer review journal.

PROSPERO registration number CRD42018086458.

Strengths and limitations of the study

- This review will be the first systematic review of randomised controlled trials to investigate the benefits and harms of psychotherapy in children with overweight following Cochrane methodology.
- The review will perform meta-analysis, Trial Sequential Analysis and use Grading of Recommendations Assessment, Development and Evaluation Tool.
- This protocol has been registered on PROSPERO and aims to demonstrate a rigorous, methodical approach to our systematic review and thus reduce the risk of bias.
- We expect high heterogeneity across studies which may lead to challenges in performing a meta-analysis.
- It is anticipated that many papers will not provide sufficient details on all variables of interest and will lead to reliance on communication with corresponding authors for additional information.

INTRODUCTION

The prevalence of overweight is increasing worldwide both among children and adults irrespective of income.[1–3] The rate of overweight in the paediatric population has risen worldwide over the last few decades[4] despite significant resources being spent on reversing these trends. This widens health inequality, as the prevalence of children with overweight is higher in areas of social deprivation.[5] Recent data from the WHO continues to show an increasing prevalence of children with obesity in Europe.[6 7] The International Task Force of Obesity produced age-specific and sex-specific cut-off for the definition of overweight and obesity in children.[8] Throughout

this paper, children and adolescents between 0 and 18 years will be referred to as children. Children with all degrees of overweight. including obese and morbidly obese, will be referred to as overweight in the remaining part of the paper.

Overweight has both short-term and long-term consequences on cardiovascular disease, type 2 diabetes, metabolic syndrome and cancer, resulting in a significant burden on health services across the world.[9] The severity of these comorbidities typically increases with the severity of overweight.[10 11] Mental health sequelae such as poor self-esteem, anxiety and depression may result in bullying, discrimination, long-term socioeconomic disadvantages and is often coupled with difficult family circumstances.[12–16]

As such, psychological variables such as quality of life, self-esteem, life events, parental attitudes, eating disorders and anxiety need to be addressed in the long-term treatment of overweight and obesity. Psycho-education, cognitive behavioural therapy, solution-based therapy, including systemic therapy, and psychodynamic counselling are used.[17–19]

Psychotherapeutic interventions

Psychotherapy is widely used in the management of children with overweight. It may support the child to change and maintain more weight-friendly habits while also potentially improving body image, self-esteem and social adaptation.[20] Several types of psychotherapy are used in the treatment of children with overweight. Solution-focused brief therapy might be an effective modality for weight management in children through helping them to use their inner resources.[21 22] Motivational interviewing appears to be a beneficial communication tool for initiating and maintaining healthy habits and weight reduction through self-help or self-determination.[23–27] Family therapy is a form of systemic therapy, widely used to treat children with overweight, often as part of multicomponent programmes.[28–34] Cognitive-behavioural therapy is a very widely used form of psychotherapy that has been used to treat children with overweight.[35–37] Group psychotherapy is an alternative to individual programmes for supporting weight loss in teenagers.[36 38] Interpersonal therapy is most commonly used to treat low mood, depression and disordered eating with studies showing indications of its efficacy in decreasing the weight gain in teenage girls with overweight.[39–41] Finally, psycho-dynamic therapy emphasises the systematic study of the psychological drivers that underlie human behaviour, feelings and emotions associated with weight gain.[42] Psychotherapeutic approaches thus seek to support the child and their parents towards a healthier weight in the child.

Systematic reviews on interventions

The effects of interventions for children with overweight have been analysed recently in Cochrane reviews.[43–45] Quality of life was included in only two of these reviews, showing no effects in children after the end of intervention.[44 45] A moderate improvement of health-related quality of life in the intervention groups was seen in older children (p=0.01), but the evidence was uncertain.[44 45] In preschool children, multicomponent interventions showed reductions in body mass index (BMI) (p<0.00001) and improvements in some markers of quality of life.[43]

Overall, systematic reviews have not shown that structured interventions in children with overweight are associated with an increased risk of depression or anxiety and may result in a mild reduction in symptoms.[46] Similarly, a very recent systematic review demonstrated that paediatric obesity treatment improves self-esteem and body image in the short and medium term. These findings may underpin improvements in other psychological outcomes.[47] However, a 5-year follow-up study in adolescents with morbid obesity who underwent bariatric surgery demonstrated no significant improvement in self-esteem.[48] Potentially, a small proportion of participants may be at risk of developing worsening pathology, which clinicians should monitor, while treatment of weight concerns should be considered within treatment plans for young people with depression and obesity.[46] Identification of these young people and provision of additional support may improve treatment outcomes while benefits to psychological well-being following treatment should be considered when assessing treatment success.

While previous reviews have commented upon the significant risk of bias in many studies, none of the earlier reviews have consistently assessed the risk of bias, the risk of random errors, or assessed the overall evidence certainty with Grading of Recommendations Assessment, Development and Evaluation (GRADE).[49–58]

Objective

The objective of this systematic review will be to assess the benefits and harms of psychotherapy versus no intervention in children with all degrees of overweight (including all levels of obesity); wait list control; treatment as usual; sham psychotherapy or pharmaceutical placebo. Benefits will include a reduction of BMI z-score or body weight and quality of life while harms will include developing eating disorders.

METHODS AND ANALYSIS

This systematic review protocol has been developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines[59] (online supplemental additional file 1). We will assess the beneficial and harmful effects of psychotherapy for in children with overweight taking risks of bias (systematic errors), risks of play of chance (random errors), type of psychotherapy and control interventions and GRADE assessments into consideration.

Criteria for considering studies for this review

Types of studies

Randomised clinical trials irrespective of language, publication status, publication type or publication year will be searched for and include benefits and harms. We will follow Population, Intervention, Control and Outcomes (PICO) criteria as per the Cochrane Handbook for Systematic Reviews of Interventions for inclusion and exclusion criteria.[60] Eligible studies which are not published in English will be translated using Google translate. Authors will be contacted if necessary, for an English translation or for any clarification of their data. Data on harms from quasi-randomised studies, controlled clinical studies and other observational studies if retrieved from our searches for randomised clinical trials will be included. Such data will be described narratively as adverse events are rarely reported in randomised clinical trials while such observational studies may provide information on rare or late occurring adverse events.[61]

Types of participants

All children who are overweight (including all levels of obesity) up to 18 years of age. We will also include randomised clinical trials which include children and young adults below the age of 21 years. Children with associated co-morbidities, either physical or psychological secondary to overweight and obesity will be included.

Types of interventions

As the experimental intervention, we will include any type of solution-focused brief therapy, family therapy, cognitive behavioural therapy, interpersonal therapy or psycho-dynamic therapy as described in our introduction with the intention to treat children with overweight. The therapy can be delivered, face-to-face, either individually, delivered to parents only or in groups, in any setting. The control intervention can be no intervention; wait list control; treatment as usual; sham psychotherapy or pharmaceutical placebo.

There is no restriction as to who delivers the treatment or treatment duration. We will accept any co-intervention providing that they are planned to be delivered in similar fashion in both the experimental group and the control group.

Types of outcomes

We will assess all outcomes at baseline and then at two time points:

- End of intervention, as defined by trialist (our primary time point of interest).
- Maximum follow up.

Primary outcomes

1. BMI z-score (kg/m^2).
2. Quality of life: as measured by a scale that has been validated for use in the target population.[62]
3. Proportion of participants with one or more serious adverse events; that is, any untoward medical occurrence that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity.[63 64]

Secondary outcomes

1. Body weight measured in kg.
2. Self-esteem.
3. Anxiety.
4. Depression.
5. Proportion of participants with at least one non-serious adverse event.[63 64]

Exploratory outcomes

1. Body fat (%) measured by bioimpedance or dual energy X-ray absorptiometry.[65 66]
2. Muscle mass (kg) via bioimpedance or dual energy X-ray absorptiometry .[65 66]
3. Individual serious adverse events and individual adverse events not considered serious.

Search methods for identification of studies

Electronic searches

Searches will include literature up to April 2020. We will search the following databases: The Cochrane Library, MEDLINE, Excerpta Medica database (Embase), PsycINFO, Web of Science (SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC), CINAHL and LILACS. Examples of keywords used in the search strategy will include: obesity, overweight, psychotherapy, BMI, weight gain, weight loss, hyperphagia and systematic review. Controlled descriptors will be included using MeSH. A preliminary search strategy for MEDLINE is enclosed as online supplemental additional file 2.

Searching other resources

We will search for trials or ongoing studies on the following resources:

- ClinicalTrials.gov (http://www.clinicaltrials.gov).
- Google Scholar (https://scholar.google.com/).
- European Medicine Agency (http://www.ema.europa.eu/ema/).
- United States Food and Drug Administration (http://ww.fda.gov).
- Medicines and Healthcare Products Regulatory Agency (https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency).
- The WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (http://www.who.int/).
- Global Obesity Forum (previously International Association for the Study of Obesity) (http://www.iaso.org).
- European Association for the Study of Obesity (http://easo.org).

Keywords used in the search strategy

- Obesity.
- Overweight.
- Psychotherapy.

- BMI.
- Weight gain.
- Weight loss.
- Hyperphagia.
- Randomised clinical trial .

A preliminary search strategy for MEDLINE is enclosed as online supplemental additional file 2.

Data collection and analysis

Selection of studies

We will perform the review following the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions*.[60] The meta-analyses will be performed using Review Manager and Trial Sequential Analysis programme.[67 68]

At least two authors will independently screen titles and abstracts using software Covidence,[69]. They will retrieve all identified and relevant full-text publications after which two authors will independently screen the full text and identify and record reasons for exclusion of the ineligible studies. Disagreement will be resolved through discussion or by consulting a with a third author. Trial selection will be displayed in an adapted flow diagram as per the PRISMA statement. At least two authors will extract data. Disagreement will be resolved by discussing with a third author. We will assess duplicate publications and companion papers of a trial together.

Data extraction and management

Data extraction will be performed by at least two authors independently using software Covidence,[69] who will both compare the extracted data for primary, secondary and exploratory outcomes. Disagreements will be resolved by a third author. We will use Review Manager software to extract data.[64] For outcome data not reported in a usable manner, we will present this in a table outlining the characteristics of these studies using the following headings: Methods, Participants, Interventions, Outcomes and Notes described in chapter 4 (section 4.6.1) of the *Cochrane Handbook for Systematic Reviews of Interventions*.[60] Two review authors will independently transfer data into the Covidence. Disagreements will be resolved through discussion or by consulting a third author.

Assessment of risk of bias in included studies

The risk of bias of every included trial will be evaluated independently by at least two authors. In case of any disagreement, discrepancies will be discussed with a third author and resolved by consensus. Risk of bias will be assessed using Cochrane's 'Risk of bias' assessment tool and the Cochrane Effective Practice and Organisation of Care Group's guidance.[70 71] We will evaluate the methodology in respect of:

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and treatment providers.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other risks of bias.
- Overall risk of bias.

Classification of the trials will follow criteria defined in online supplemental additional file 3.

Meta-analysis

Data will be meta-analysed using RevMan V.5 statistical software.[72] We will use STATA statistical software (STATA 2015) in case of zero event trials, where RevMan V.5 zero event handling is insufficient.[73 74]

We will assess our intervention effects with random-effects model meta-analyses and fixed-effect model meta-analyses,[75–77] using the more conservative point estimate of the two.[78] Three primary outcomes will be examined with $p \leq 0.025$ being statistically significant.[78] An eight-step procedure will be used to assess if the thresholds for significance are crossed.[78] Five secondary outcomes will be examined with $p \leq 0.017$ being statistically significant.[78] Analysis of the exploratory outcomes will be considered hypothesis generating only. We will measure effect size using standardised mean differences using CIs of 95%. Analysis of all included studies will be compared with a subgroup analysis comparing trials at low risk of bias to trials at high risk of bias. If the results do not differ, primary conclusions will be based on the overall analysis. If the results differ, primary conclusions will be based on trials at low risk of bias. A table describing the types of serious adverse events in each trial will be provided.

Trial Sequential Analysis

Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. In order to control the risks of type I errors and type II errors,[57 58 79] Trial Sequential Analysis will be conducted on the outcomes. In order to do so, we will calculate the required information size (that is the number of participants needed in a meta-analysis to detect or reject a certain intervention effect).[79]

For continuous outcomes, we will in the Trial Sequential Analysis use the observed SD, a mean difference of the observed SD/2, an alpha of 2.5% for our three primary outcomes and an alpha of 1.67% for our five secondary outcomes, and a beta of 10%.[80] For dichotomous outcomes, we will use the proportion of participants with an outcome in the control group, a relative risk reduction of 20%, and an alpha of 2.5% for our primary outcomes and an alpha of 1.67% for secondary outcomes, and a beta of 10%.[80] We will calculate risk ratios with 95% CI for dichotomous outcomes.

Subgroup analysis

In order to investigate and compare different trials and interventions subgroup analysis will be performed on the following:

- Trials at high risk of bias trials compared to trials at low risk of bias trials.

- Trial stratified according to experimental interventions.
- Trials stratified according to weight status: overweight, obese or morbidly obese at the point of entry into the trial.[8]
- Trials stratified according to the duration of intervention, the number of in person sessions and length of sessions in hours.[81]
- Trials stratified if treatment fidelity was assessed or not.[82]
- Trials stratified according to the control interventions.
- Complexity: trials with participants with no co-morbidities compared to trials with participants pre-existing co-morbidities.
- Trials in which the experimental intervention was evaluated by either the parents or the child after the treatment sessions had been delivered compared to trials in which the experimental intervention was not evaluated by either the parents or the child after the treatment sessions had been delivered.

We will use the formal test for subgroup interactions in Review Manager.[72]

Sensitivity analysis

To assess the potential impact of the missing data for dichotomous outcomes, we will perform the following sensitivity analyses.

- 'Best–worst case' scenario: we will assume that all participants lost to follow-up in the experimental group had no serious adverse events, including not developing any psychiatric disease such as an eating disorder.
- 'Worst–best case' scenario: we will assume that all participants lost to follow-up in the experimental group, had a serious adverse event, for instance, developing a psychiatric disease such as an eating disorder.[46]

Statistical heterogeneity will be assessed by visual inspection of the forest plots and I^2 statistic values.[78] Underlying reasons behind statistical heterogeneity in meta-analyses will be investigated by assessing trial characteristics.

Summary of findings table

A summary of findings table using each of the prespecified primary outcomes will be presented using GRADE considerations for studies contributing data to the meta-analyses for the prespecified outcomes.[78 83–96] Methods and recommendations described in chapter 8 (section 8.5) and chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions*[60] using GRADEpro software will be used.

DISCUSSION

This protocol intends to outline a rigorous, methodical approach to developing a systematic review to provide evidence on the potential effects of psychotherapy as an intervention for children with overweight. The protocol has been registered on PROSPERO and through peer review and publication aims to reduce the risk of bias in the future systematic review.

Currently, there is no comprehensive systematic review of psychotherapeutic interventions in the treatment of children with overweight to inform clinical practice. Previous systematic reviews in this population have considered behavioural interventions for lifestyle behaviour change as a mediating factor for weight loss initiation and maintenance.[44 45] We will also be able to assess the different types of psychotherapeutic interventions as well as their individual comparison groups (no intervention; wait list control; treatment as usual; sham psychotherapy; or pharmaceutical placebo). This review will also highlight any gaps in the evidence base of such interventions which will help to shape the development and optimisation of future interventions.

ETHICS AND DISSEMINATION

No ethical approval required. Dissemination of results will be published in peer reviewed journals.

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PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X	☐	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	X	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐	x	52
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X	☐	5-24
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X	☐	390-392
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	☐	X	
Support					
Sources	5a	Indicate sources of financial or other support for the review	X	☐	394
Sponsor	5b	Provide name for the review funder and/or sponsor	X	☐	394
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	X	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X	☐	72-142

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X	☐	144-157
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X	☐	159-188
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X	☐	216-249
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	X	☐	Additional File 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X	☐	252-255
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analyss)	X	☐	257-264
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X	☐	266-275
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X	☐	Additional File 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X	☐	190-214
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	X	☐	Additional File 3; 277-291
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X	☐	293-324
	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 (e.g., I^2, Kendall's tau)	X	☐	293-324
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-	X	☐	326-357

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		regression)			
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned		X	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X	☐	Additional file 3
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X	☐	359-364

Additional File 2

NOTES: unless stated otherwise, search terms are free text terms; MeSH: Medical subject heading (Medline medical index term); an asterisk (*) stands for 'any character(s)', a question mark stands for 'one or no character'.

1. exp Obesity/
2. exp Hyperphagia/
3. exp body mass index/
4. exp Weight Gain/
5. exp Weight Loss/
6. exp Anti-Obesity Agents/
7. (Pickwick* syndrom* or Prader willi syndrom* or obes* or adipos* or overweight* or 'over weight*' or overeat* or 'over eat*' or 'over feed*' or overfeed* or binge eating disorder* or 'fat overload' syndrom*).mp. or (weight and (gain or cycling or reduc* or loss or losing or maint* or decreas* or watch* or diet* or control*)).ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp PSYCHOTHERAPY/
10. (psycho* or counsel* or depression or depressiv* or balint or crisis intervention* or assert* near training or ((person or client) and cent*) or psychodrama* or psycho drama* or paradoxic* techni* or rational emoti* or role play* or relax* near train* or socioenvironment* or socio environment* or sociotherap* or transactional).mp. or behavio?r modific*.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
11. ((interpersonal or art or aversion or behavio?r or colo?r or cognitiv* or dance or gestalt or music or milieu or nondirectiv* or non directiv* or problem solving or problemsolving or self control or selfcontrol or play or reality or socio or supportiv*) and therap*).ti,ab.
12. 9 or 10 or 11
13. 8 and 12
14. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
15. 13 and 14
16. limit 15 to (("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)" or "young adult (19 to 24 years)") and humans)

Assessment of risk of bias in included studies

Random sequence generation

Low risk: If sequence generation was achieved using computer random number generator or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were also considered adequate if performed by an independent adjudicator.

Unclear risk: If the method of randomisation was not specified, but the trial was still presented as being randomised.

High risk: If the allocation sequence is not randomised or only quasi-randomised. These trials will be excluded.

Allocation concealment

Low risk: If the allocation of patients was performed by a central independent unit, on-site locked computer or identical-looking numbered sealed envelopes.

Uncertain risk: If the trial was classified as randomised but the allocation concealment process was not described.

High risk: If the allocation sequence was familiar to the investigators who assigned participants.

Blinding of participants and treatment providers

Low risk: If the participants and the treatment providers were blinded to intervention allocation and this was described.

Uncertain risk: If the procedure of blinding was insufficiently described.

High risk: If blinding of participants and the treatment providers was not performed.

Blinding of outcome assessment

Low risk of bias: If it was mentioned that outcome assessors were blinded and this was described.

Uncertain risk of bias: If it was not mentioned if the outcome assessors in the trial were blinded or the extent of blinding was insufficiently described.

High risk of bias: If no blinding or incomplete blinding of outcome assessors was performed.

Incomplete outcome data

Low risk of bias: If missing data were unlikely to make treatment effects depart from plausible values. This could be either (1) there were no drop-outs or withdrawals for all outcomes, or (2) the numbers and reasons for the withdrawals and drop-outs for all outcomes were clearly stated and could be described as being similar to both groups. Generally, the trial is judged as at a low risk of bias due to incomplete outcome data if drop-outs are less than 5%. However, the 5% cut-off is not definitive.

Uncertain risk of bias: If there was insufficient information to assess whether missing data were likely to induce bias on the results.

High risk of bias: If the results were likely to be biased due to missing data either because the pattern of drop-outs could be described as being different in the two intervention groups or the trial used improper methods in dealing with the missing data (e.g. last observation carried forward).

Selective outcome reporting

Low risk of bias: If a protocol was published before or at the time the trial was begun and the outcomes specified in the protocol were reported on. If there is no protocol

or the protocol was published after the trial has begun, reporting of serious adverse events will grant the trial a grade of low risk of bias.

Uncertain risk of bias: If no protocol was published and the outcome of serious adverse events were not reported on.

High risk of bias: If the outcomes in the protocol were not reported on.

Other risks of bias

Low risk of bias: If the trial appears to be free of other components (for example, academic bias or for-profit bias) that could put it at risk of bias.

Unclear risk of bias: If the trial may or may not be free of other components that could put it at risk of bias.

High risk of bias: If there are other factors in the trial that could put it at risk of bias (for example, authors conducted trials on the same topic, for- profit bias, etc.).

Overall risk of bias

Low risk of bias: The trial will be classified as overall 'low risk of bias' only if all of the bias domains described in the above paragraphs are classified as 'low risk of bias'.

High risk of bias: The trial will be classified as 'high risk of bias' if any of the bias risk domains described in the above are classified as 'unclear' or 'high risk of bias'.

We will assess the domains 'blinding of outcome assessment', 'incomplete outcome data', and 'selective out- come reporting' for each outcome result. Thus, we can assess the bias risk for each outcome assessed in addition to each trial. Our primary conclusions will be based on the results of our primary outcome results with overall low risk of bias. Both our primary and secondary conclusions will be presented in the summary of findings tables.