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Psychotherapy versus treatment as usual and other control interventions in children with overweight. A protocol for systematic review with meta-analysis and Trial Sequential Analysis

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Psychotherapy versus treatment as usual and other control interventions in

 children with overweight. A protocol for systematic review with meta-analysis and Trial Sequential Analysis Rashid R¹, Condon L², Gluud C³, Jakobsen JC^{3,4,5}, Lindschou JC³, and Lissau I⁶ Affiliations ¹ Paediatric Unit, Department of Child Health, St John's Hospital, Livingston, United Kingdom, ² School of Medicine, University of Nottingham, Medical School, Nottingham, United Kingdom ³ Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark ⁴ Department of Cardiology, Holbæk Hospital, Denmark ⁵ Department of Regional Health Research, The Faculty of Health Sciences, University of Southern Denmark ⁶ Clinical Research Centre, University Hospital Copenhagen, Hvidovre, Denmark **Correspondence to** Dr Rajeeb Rashid Postal Address: Paediatric Unit, Department of Child Health, St John's Hospital, Livingston, United Kingdom, EH54 6PP Telephone Number: 0044 – 7984405808 Email: rajeeb.rashid@nhs.net Word Count 2663

ABSTRACT

Introduction The prevalence of overweight and obesity in children is increasing worldwide. Multi-component interventions incorporating diet, physical activity, and behavioural change have been shown to improve body mass index (BMI). However, the impact of psychotherapy is poorly explored. This systematic review aims to assess the benefits and harms of psychotherapeutic approaches for children with overweight.

Methods and analysis We will include randomised clinical trials involving children with overweight irrespective of publication type, year, status, or language. Psychotherapy will be compared with no intervention; wait list control; treatment as usual; sham psychotherapy; or pharmaceutical placebo. Children between 0-18 years with overweight will be included. The following databases will be searched: Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, MEDLINE, Excerpta Medica database (Embase), PsycINFO, PubMed, and Web of Science (SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC), CINAHL and LILACS. Primary outcomes will be body weight, quality of life, and proportion of patients with serious adverse events. Secondary outcomes will be BMI z-score, self-efficacy, anxiety, depression, and proportion of patients with non-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 through eight domains. We will 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 (GRADE). The systematic review will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidance.

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

Keywords: Obesity, overweight, children, adolescents, psychotherapy, intervention,

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2 3 4	53	treatment, systematic review.							
4 5 6	54								
7 8	55	Article summary							
9 10 11	56	Strength and limitations of the study							
11 12 13	57	• This review will be the first systematic review to investigate the benefits and harms							
14 15	58	of psychotherapy in children with overweight following Cochrane methodology.							
16 17	59	• A comprehensive search strategy will be used with a large number of databases							
18 19 20	60	searched.							
20 21 22	61	Only Randomised Controlled Trials in children with overweight will be included.							
23 24	62	• The review will perform Meta-analysis, Trial Sequential Analysis and use the Grading							
25 26	63	of Recommendations Assessment, Development and Evaluation Tool.							
27 28 20	64	• We expect high heterogeneity across studies which may lead to challenges in							
29 30 31	65	performing a Meta-analysis.							
32 33	66	It is anticipated that many papers will not provide sufficient details on all variables of							
34 35	67	interest and will lead to reliance on communication with corresponding authors for							
36 37	68	additional information							
38 39 40	69								
40 41 42	70								
43 44	71	INTRODUCTION							
45 46	72	The prevalence of overweight is increasing worldwide both among children and adults							
47 48 49	73	irrespective of income (1-3). The rate of paediatric overweight has risen worldwide over the							
50 51	74	last few decades (4) despite significant resources being spent on reversing these trends.							
52 53	75	This widens health inequality, as the prevalence of children with overweight is higher in							
54 55	76	areas of social deprivation (5). Recent data from the World Health Organisation continues to							
56 57	77	show an increasing prevalence of obesity in children in Europe (6, 7). The International Task							
58 59									

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obesity in children (8). Throughout this paper, we will use the term overweight for all children
with overweight including all levels of obesity.

These developments have both short-term and long-term consequences on cardio-vascular 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 increase 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 (12-15)(16).

As such, psychological variables such as quality of life, self-efficacy, 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).

95 Psychotherapeutic interventions

Psychotherapy is widely used in the management of overweight children. It may support the child to change and maintain more weight-friendly habits whilst also potentially improving body image, self-esteem, and social adaptation (20). Several types of psychotherapy are used in the treatment of children with overweight. 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 child overweight often as part of multi-component programs (28-34). Cognitive-behavioural

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therapy is a very widely used form of psychotherapy that has been used to treat overweight in children (35-37). Group psychotherapy is an alternative to individual programs 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 overweight teenage girls (39-41). Finally, psychodynamic therapy emphasises the systematic study of the psychological drivers that underlie human behaviour, feelings, and emotions associated with weight qain (42). Psychotherapeutic approaches thus seek to support the child and their parents towards a healthier weight in the child.

³ 114

115 Systematic reviews on interventions

The effects of interventions for children with overweight have been analysed recently in Cochrane systematic reviews Cochrane reviews (43-45). Quality of life was included in only two of these reviews, showing no effects in children after 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 pre-school children, multi-component interventions showed reductions in BMI (P<0.00001) and improvements in some markers of quality of life (43). Whilst 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 GRADE (46-55). In this systematic review, 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 control interventions, and GRADE assessments into consideration.

59 130 **Objectives** Page 7 of 27

The objective of this review will be to assess the benefits and harms of psychotherapy
versus no intervention; wait list control; treatment as usual; sham psychotherapy in children
with overweight (including all levels of obesity).

0 134

135 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 (56)
(Additional File 1).

1 139

140 Criteria for Considering Studies for this Review

141 Types of studies

Randomised clinical trials irrespective of language, publication status, publication type, or publication year will be searched for and included regarding benefits and harms. Eligible studies which are not published in English will be translated using Google translate. 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 whilst such observational studies may provide information on rare or late occurring adverse events (57).

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7 150

151 Types of participants

All children whom are overweight, (including all levels of obesity) up to 18 years of age. We will also include RCTs which include and 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.

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157 Types of interventions

As the experimental intervention, we will include any type of brief therapy, family therapy, cognitive behavioural therapy, interpersonal therapy, or psycho-dynamic therapy as described in the Introduction with the intention to treat overweight children. 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.

165 There is no restriction as to who delivers the treatment or treatment duration. We will 166 accept any co-intervention providing that they are planned to be delivered in similar fashion 167 in both the experimental group and the control group.

169 Types of outcomes

170 We will assess all outcomes at two time points:

171 - End of intervention, as defined by trialist (primary time point of interest)

172 - Maximum follow up.

1 174 Primary outcomes

175 1. Body weight measured in kg.

- 2. Quality of life: as measured by a scale that has been validated for use in the target population (58).
- 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 (59, 60).

60 182 *Secondary outcomes* BMJ Open

1		C C
2 3 4	183	1. BMI z-score (kg/m2)
5 6	184	2. Self-efficacy.
7 8	185	3. Anxiety.
9 10 11	186	4. Depression.
12 13	187	5. Proportion of participants with at least one non-serious adverse event (59, 60).
14 15 16	188	Exploratory outcomes
17 18	189	1. Body fat (%) measured by bioimpedance or Dual Energy X-ray Absorptiometry (61,
19 20	190	62)
21 22 23	191	2. Muscle mass (kg) via bioimpedance or Dual Energy X-ray Absorptiometry (61, 62).
23 24 25	192	3. Individual serious adverse events and individual adverse events not considered
26 27	193	serious.
28 29	194	
30 31	195	Search methods for identification of studies
32 33 34	196	Electronic searches
35 36	197	We will search the following databases: The Cochrane Library, MEDLINE, Excerpta Medica
37 38	198	database (Embase), PsycINFO, Web of Science (SCI-EXPANDED, SSCI, A&HCI, CPCI-S,
39 40	199	CPCI-SSH, ESCI, CCR-EXPANDED, IC), CINAHL, and LILACS. Examples of keywords used in
41 42 43	200	search strategy include: obesity, overweight, psychotherapy, body mass index, weight gain,
44 45	201	weight loss, hyperphagia and systematic review. A preliminary search strategy for MEDLINE
46 47	202	is enclosed as appendix 2.
48 49	203	
50 51 52	204	Searching other resources
52 53 54	205	We will search for trials or ongoing studies on the following resources:
55 56	206	ClinicalTrials.gov (www.clinicaltrials.gov)
57 58	207	Google Scholar (<u>https://scholar.google.com/</u>)
59 60	208	European Medicine Agency (http:// www.ema.europa.eu/ema/)

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9

2 3	200	United Chates Food and Duris Administration (usualda appr)			
4 5	209	 United States Food and Drug Administration (ww.fda.gov) 			
6	210	Medicines and Healthcare Products Regulatory Agency			
7 8	211	(https://www.gov.uk/government/organisations/medicines-and-			
9 10 11	212	healthcare-products-regulatory- agency)			
12 13	213	The World Health Organization (<u>www.who.int/</u>) ICTRP Search Portal			
14 15 16 17	214	Global Obesity Forum (previously International Association for the Study of Obesity)			
	215	(www.iaso.org)			
18 19	216	European Association for the Study of Obesity (EASO) (easo.org).			
20 21 22	217				
23 24	218	Keywords used in the search strategy			
25 26	219	Obesity			
27 28	220	Overweight			
29 30 31 32 33 34 35	221	Psychotherapy			
	222	Body mass index			
	223	Weight gain			
36 37	224	Weight loss			
38 39 40	225	Hyperphagia			
40 41 42	226	Systematic review			
43 44	227	A preliminary search strategy for MEDLINE is enclosed as appendix 2.			
45 46	228				
47 48 49 50	229	Data collection and analysis			
	230	Selection of studies			
51 52 53 54 55	231	We will perform the review following the recommendations in the Cochrane Handbook for			
	232	Systematic Reviews of Interventions (63). The meta-analyses will be performed using			
56 57	233	Review Manager and Trial Sequential Analysis program (64, 65).			
58 59 60	234				

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Two authors will independently screen titles and abstracts. 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 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. 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.

³ 244 Data extraction and management

Data extraction will be performed by two authors independently, who will both compare the extracted data. Disagreements will be resolved by a third author. We will use Review Manager software to extract data. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. Two review authors will independently transfer data into the Review Manager file. Disagreements will be resolved through discussion or by consulting a third author.

1 252 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 (EPOC) Group's guidance (66, 67). We will evaluate the methodology in respect of:

- Random sequence generation
- Allocation concealment
- Blinding of participants and treatment providers

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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 Attached File 3. **Meta-analysis** Data will be meta-analysed using RevMan 5 statistical software (68). We will use STATA statistical software (STATA 2015) in case of zero event trials, where RevMan 5 zero event handling is insufficient (69, 70). We will assess our intervention effects with random-effects model meta-analyses and fixed-effect model meta-analyses (71-73), using the more conservative point estimate of the two (74). Three primary outcomes will be examined with $P \leq 0.025$ being statistically significant (74). An eight-step procedure will be used to assess if the thresholds for significance are crossed (74). Five secondary outcomes will be examined with P≤0.017 being statistically significant (74). The results of the exploratory outcomes will be considered hypothesis generating only. Analysis of all included studies will be compared to a subgroup analysis comparing trials at low risk of bias compared to trials at high risk of bias. If the results do not differ, primary conclusions will be based at the overall analysis. If the results differ, primary conclusions will be based on studies at low risk of bias. A table describing the types of serious adverse events in each trial will be provided. **Trial Sequential Analysis**

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1 2

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2 3 4	286	Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive						
5 6	287	testing of accumulating data when updating reviews. In order to minimise the risks of type I						
7 8	288	errors and type II errors (55, 75, 76), Trial Sequential Analysis will be conducted on the						
9 10 11	289	outcomes. In order to do so we will calculate the required information size (that is the						
12 13 14 15 16 17	290	number of participants needed in a meta-analysis to detect or reject a certain intervention						
	291	effect) (75).						
	292							
18 19 20	293	For continuous outcomes, we will in the Trial Sequential Analysis use the observed SD, a						
20 21 22	294	mean difference of the observed SD/2, an alpha of 2.5% for our three primary outcomes						
22 23 24	295	and an alpha of 1.67% for our five secondary outcomes, and a beta of 10% (77). For						
25 26	296	dichotomous outcomes, we will use the proportion of participants with an outcome in						
27 28 20	297	the control group, a relative risk reduction of 20%, and an alpha of 2.5% for our						
29 30 31	298	primary outcomes and an alpha of 1.67% for secondary outcomes, and a beta of 10%						
32 33	299	(77). We will calculate risk ratios with 95% confidence interval (CI) for dichotomous						
34 35	300	outcomes.						
36 37	301							
38 39 40 41 42	302	Subgroup analysis						
	303	Subgroup analysis will be performed						
43 44	304	• Trials at high risk of bias trials compared to trials at low risk of bias trials.						
45 46	305	Trial stratified according to experimental interventions.						
47 48	306	Trials stratified according to the control interventions.						
49 50 51	307	• Complexity: trials with participants with no co-morbidities compared to trials with						
52 53	308	participants pre-existing co-morbidities.						
53 54 55 56 57 58 59 60	309	• Trials in which the experimental intervention was evaluated by either the parents or the						
	310	child after the treatment sessions had been delivered compared to trials in which the						

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1 2		
2 3 4	311	experimental intervention was not evaluated by either the parents or the child after the
5 6	312	treatment sessions had been delivered.
7 8 9	313	
10 11	314	We will use the formal test for subgroup interactions in Review Manager (68).
12 13	315	
14 15	316	Sensitivity analysis
16 17	317	To assess the potential impact of bias, we will perform a sensitivity analysis to exclude trials
18 19 20	318	at overall 'high risk of bias'.
20 21 22	319	To assess the potential impact of the missing data for dichotomous outcomes, we will
23 24	320	perform the following sensitivity analyses.
25 26	321	• 'Best-worst-case' scenario: we will assume that all participants lost to follow-up in
27 28 29 30 31	322	the experimental group had no serious adverse events, including not developing any
	323	psychiatric disease such as an eating disorder.
32 33	324	• 'Worst-best-case' scenario: we will assume that all participants lost to follow-up in
34 35	325	the experimental group, had a serious adverse event, for instance, developing a
36 37	326	psychiatric disease such as an eating disorder.
38 39	327	
40 41 42	328	Statistical heterogeneity will be assessed by visual inspection of the forest plots and I ²
42 43 44	329	statistic values (74). Underlying reasons behind statistical heterogeneity in meta-analyses
45 46	330	will be investigated by assessing trial characteristics.
47 48	331	
49 50	332	Summary of findings table
51 52 53	333	A summary of findings table using each of the prespecified primary outcomes will be
54 55	334	presented using GRADE considerations for studies contributing data to the meta-analyses for
56 57 58 59 60	335	the prespecified outcomes (74, 78-91). Methods and recommendations described in Chapter

8 (Section 8.5) and Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions (63) using GRADEpro software will be used.

DISCUSSION

This review will aim to provide evidence on the potential effects of psychotherapy as an intervention for overweight children. Currently, there is no comprehensive systematic review of psychotherapeutic interventions in the treatment of overweight children 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. 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

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> Author contributions IL, RR, LC, CG, JCJ, and JL wrote the first draft of the protocol. RR, IL, JCJ, CG, LC, and JL have revised the protocol. All authors critically reviewed and approved the manuscript. IL is the guarantor of the review.

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3 4	362	
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6	363	Competing interests None known.
7		
8	364	
9		
10	365	Patient consent Not required.
11		
12 13	366	
14		
15	367	Provenance and peer review Not commissioned; externally peer reviewed.
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5 6	609	Appendices
7 8 9	610	Additional File 1: Prisma-P+ checklist.
10	611	Additional File 2: Preliminary search strategy for MEDLINE (Ovid).
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Update	1b	If the protocol is for an update of a previous systematic review, identify as such				X	1
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number		;		x	51
Authors		, , , , , , , , , , , , , , , , , , ,	<u></u>			·	
Contact	За	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; provide participation and e-mail address of all protocol authors; protocol author and e-mail address of all protocol authors; protocol author are participation and e-mail address of all protocol author are participation and e-mail address of all protocol author are participation and e-mail address of all protocol author are participation and e-mail address of are participation are		3l	Х		5-23
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Sources	5a	Indicate sources of financial or other support for the review			Х		361
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Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protoc	2			X	
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	_				2
Section/topic	#	Checklist item	Information Yes	n reported No	Line number(s)
		participants, interventions, comparators, and outcomes (PICO)	105		
METHODS		es se s			
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and reporting the characteristics (e.g., years considered, language, publication status) to be used as criteria eligibility for the review	x		140-167
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study artifiers, trial registers, or other grey literature sources) with planned dates of coverage	x		195-216
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including Biar hed 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 BORE	X		229-233
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) a hrough each phase of the review (i.e., screening, eligibility, and inclusion in meta-analyss)	x		235-242
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done indep additly, in duplicate), any processes for obtaining and confirming data from investigators	x		244-250
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 give additional outcomes, with rationale	x		169-193
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 deta synthesis	x		Additional File 3; 252-266
DATA					-
	15a	Describe criteria under which study data will be quantitatively synthesized	X		268-283
Synthesis	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methads of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., <i>I</i> ² , Kendall's tau)	x		285-300, 328- 330
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		302-326
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned		<u> </u>	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	Х		Additional file 3

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Section/topic	#	Checklist item	right, includ	infoi		n reported	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	ding t		'es X	No	number(s) 332-337
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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)

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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, onsite 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.

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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 metaanalysis and Trial Sequential Analysis

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Keywords:	PAEDIATRICS, Paediatric endocrinology < DIABETES & ENDOCRINOLOGY, PUBLIC HEALTH, Child & adolescent psychiatry < PSYCHIATRY	

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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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28 ABSTRACT

Introduction The prevalence of overweight and obesity in children is increasing worldwide. Multi-component 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.

4 Methods and analysis We will include randomised clinical trials involving children and 5 adolescents between 0-18 years with overweight and obesity, irrespective of publication type, year, status, or language up to April 2020. Psychotherapy will be compared with no 6 intervention; wait list control; treatment as usual; sham psychotherapy; or pharmaceutical 7 placebo. The following databases will be searched: Cochrane Central Register of Controlled 8 Trials, Cochrane Database of Systematic Reviews, MEDLINE, Embase, PsycINFO, PubMed, and 9 0 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. 1 2 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 3 4 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 5 6 Cochrane guidelines and the Cochrane EPOC guidance. We will use meta-analysis and control 7 risks of random errors with Trial Sequential Analysis. The quality of the evidence will be assessed using GRADE. The systematic review will be reported according to PRISMA and 8 Cochrane guidelines. 9

50 **Ethics and Dissemination** As individual patient data will not be included, we do not require 51 ethics approval. This review will be published in a peer review journal.

52 **PROSPERO registration number**: CRD42018086458

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53	Keywords:	Obesity,	overweight,	children,	adolescents,	psychotherapy,	intervention,
54	treatment, systematic review.						

56 Article summary

57 Strength 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 (GRADE).
- 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.
- 72 INTRODUCTION

The prevalence of overweight is increasing worldwide both among children and adults irrespective of income (1-3). The rate of paediatric overweight 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 World Health Organization continues to show an increasing prevalence of obesity in children in Europe (6, 7). The International Task Force of

Obesity produced age and sex specific cut-off for the definition of overweight and obesity in children (8). Throughout this paper, children and adolescents between 0-18 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 cardio-vascular 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).

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- **Psychotherapeutic interventions**

Psychotherapy is widely used in the management of overweight children. It may support the child to change and maintain more weight-friendly habits whilst 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 selfdetermination (23-27). Family therapy is a form of systemic therapy, widely used to treat child

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overweight often as part of multi-component programs (28-34). Cognitive-behavioural therapy is a very widely used form of psychotherapy that has been used to treat overweight in children (35-37). Group psychotherapy is an alternative to individual programs 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 overweight teenage girls (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.

3 114

115 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 end of intervention (44, 45). A moderate improvement of healthrelated quality of life in the intervention groups was seen in older children (P=0.01), but the evidence was uncertain (44, 45). In pre-school children, multi-component interventions showed reductions in BMI (P<0.00001) and improvements in some markers of quality of life (43).

3 123

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 morbidly obese adolescents with bariatric surgery demonstrated no significant improvement of self-esteem (48). Potentially, a small proportion

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of participants may be at risk of developing worsening pathology, which clinicians should monitor, whilst 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 whilst benefits to psychological well-being following treatment should be considered when assessing treatment success. Whilst 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 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. 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) quidelines (59) (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**

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157 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 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 whilst such observational studies may provide information on rare or late occurring adverse events (61).

169 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.

175 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 overweight children. 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.

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2								
3 4	183	There is no restriction as to who delivers the treatment or treatment duration. We will accept						
5 6	184	any co-intervention providing that they are planned to be delivered in similar fashion in both						
7 8	185	he experimental group and the control group.						
9 10 11	186							
12 13	187	Types of outcomes						
14 15	188	We will assess all outcomes at baseline and then at two time points:						
16 17	189	- End of intervention, as defined by trialist (our primary time point of interest)						
18 19 20	190	- Maximum follow up.						
20 21 22	191							
22 23 24	192	Primary outcomes						
25 26	193	1. BMI z-score (kg/m ²).						
27 28	194	2. Quality of life: as measured by a scale that has been validated for use in the target						
29 30 31	195	population (62).						
32 33	196	3. Proportion of participants with one or more serious adverse events; that is, any						
34 35	197	untoward medical occurrence that results in death, is life-threatening, requires						
36 37	198	hospitalisation or prolongation of existing hospitalisation, results in persistent or						
38 39 40 41	199	significant disability or incapacity (63, 64).						
41 42 43	200	Secondary outcomes 1. Body weight measured in kg.						
44 45	201	1. Body weight measured in kg.						
46 47	202	2. Self-esteem.						
48 49 50	203	3. Anxiety.						
50 51 52	204	4. Depression.						
53 54	205	5. Proportion of participants with at least one non-serious adverse event (63, 64).						
55 56 57 58 59 60	Exploratory outcomes							

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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 search strategy include: obesity, overweight, psychotherapy, body mass index, weight gain, weight loss, hyperphagia and systematic review. Controlled descriptors will be included using MeSH. A preliminary search strategy for MEDLINE is enclosed as Additional File 2. Searching other resources We will search for trials or ongoing studies on the following resources: ClinicalTrials.gov (www.clinicaltrials.gov) Google Scholar (https://scholar.google.com/) European Medicine Agency (http://www.ema.europa.eu/ema/) United States Food and Drug Administration (ww.fda.gov) Medicines and Healthcare Products Regulatory Agency (https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory- agency)

The World Health Organization (www.who.int/) ICTRP Search Portal

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2 3 4	233	Global Obesity Forum (previously International Association for the Study of Obesity)
5 6	234	(www.iaso.org)
7 8 9	235	• European Association for the Study of Obesity (EASO) (easo.org).
9 10 11	236	
12 13	237	Keywords used in the search strategy
14 15	238	Obesity
16 17 18	239	• Overweight
19 20	240	Psychotherapy
21 22	241	Body mass index
23 24	242	Weight gain
25 26	243	Weight loss
27 28 29	244	Hyperphagia
30 31	245	Systematic review
32 33	246	A preliminary search strategy for MEDLINE is enclosed as Additional File 2.
34 35	247	
36 37	248	Data collection and analysis
38 39 40	249	Selection of studies
40 41 42	250	We will perform the review following the recommendations in the Cochrane Handbook for
43 44	251	Systematic Reviews of Interventions (60). The meta-analyses will be performed using Review
45 46	252	Manager and Trial Sequential Analysis program (67, 68).
47 48	253	
49 50 51	254	At least two authors will independently screen titles and abstracts. They will retrieve all
51 52 53	255	identified and relevant full text publications after which two authors will independently screen
55 54 55	256	the full text and identify and record reasons for exclusion of the ineligible studies.
56 57	257	Disagreement will be resolved through discussion or by consulting a with a third author. Trial
58 59 60	258	selection will be displayed in an adapted flow diagram as per the Preferred Reporting Items

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for Systematic Reviews and Meta-Analyses (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 (EPOC) 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

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3 4	285	Selective outcome reporting
5 6	286	Other risks of bias
7 8	287	Overall risk of bias
9 10	288	Classification of the trials will follow criteria defined in Additional File 3.
11 12 13	289	
13 14 15	290	Meta-analysis
16 17	291	Data will be meta-analysed using RevMan 5 statistical software (72). We will use STATA
18 19	292	statistical software (STATA 2015) in case of zero event trials, where RevMan 5 zero event
20 21	293	handling is insufficient (73, 74).
22 23	294	
24 25 26	295	We will assess our intervention effects with random-effects model meta-analyses and fixed-
20 27 28	296	effect model meta-analyses (75-77), using the more conservative point estimate of the two
29 30	297	(78). Three primary outcomes will be examined with $P \leq 0.025$ being statistically significant
31 32	298	(78). An eight-step procedure will be used to assess if the thresholds for significance are
33 34	299	crossed (78). Five secondary outcomes will be examined with $P \leq 0.017$ being statistically
35 36	300	significant (78). The results of the exploratory outcomes will be considered hypothesis
37 38	301	generating only. We will measure effect size using standardised mean differences using
39 40 41	302	confidence intervals of 95%. Analysis of all included studies will be compared to a subgroup
41 42 43		analysis comparing trials at low risk of bias to trials at high risk of bias. If the results do not
44 45	303	
46 47	304	differ, primary conclusions will be based at the overall analysis. If the results differ, primary
48 49	305	conclusions will be based on trials at low risk of bias. A table describing the types of serious
50 51	306	adverse events in each trial will be provided.
52 53	307	
54 55	308	Trial Sequential Analysis
56	309	Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive

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

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errors and type II errors (58, 79, 80), 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% (81). 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% (81). We will calculate risk ratios with 95% confidence interval (CI) for dichotomous outcomes.

/ 8 322

323 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 duration of intervention, the number of in person sessions, and length of sessions in hours (82).
 - Trials stratified if treatment fidelity was assessed or not (83).
- Trials stratified according to the control interventions.
- Complexity: trials with participants with no co-morbidities compared to trials with participants pre-existing co-morbidities.

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1 2		
- 3 4	336	• Trials in which the experimental intervention was evaluated by either the parents or the
5 6	337	child after the treatment sessions had been delivered compared to trials in which the
7 8	338	experimental intervention was not evaluated by either the parents or the child after the
9 10 11	339	treatment sessions had been delivered.
11 12 13	340	
14 15	341	We will use the formal test for subgroup interactions in Review Manager (72).
16 17	342	
18 19	343	Sensitivity analysis
20 21	344	To assess the potential impact of the missing data for dichotomous outcomes, we will perform
22 23 24	345	the following sensitivity analyses.
25 26	346	'Best-worst-case' scenario: we will assume that all participants lost to follow-up in the
27 28	347	experimental group had no serious adverse events, including not developing any
29 30	348	psychiatric disease such as an eating disorder.
31 32	349	'Worst-best-case' scenario: we will assume that all participants lost to follow-up in the
33 34 35	350	experimental group, had a serious adverse event, for instance, developing a psychiatric
36 37	351	disease such as an eating disorder (46).
38 39	352	Statistical heterogeneity will be assessed by visual inspection of the forest plots and I ² statistic
40 41	353	values (78). Underlying reasons behind statistical heterogeneity in meta-analyses will be
42 43 44	354	investigated by assessing trial characteristics.
45 46	355	
47 48	356	Summary of findings table
49 50	357	A summary of findings table using each of the prespecified primary outcomes will be presented
51 52	358	using GRADE considerations for studies contributing data to the meta-analyses for the
53 54 55	359	prespecified outcomes (78, 84-97). Methods and recommendations described in Chapter 8
56 57	360	(Section 8.5) and Chapter 12 of the Cochrane Handbook for Systematic Reviews of
58 59	361	Interventions (60) using GRADEpro software will be used.
60		

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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 overweight children. 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 overweight children 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. Acknowledgements We would like to thank Sarah Louise Klingenberg, Information Specialist at the Copenhagen Trial Unit, Centre for Clinical Intervention Research for her guidance and assistance on developing search methods and keywords for search strategies.

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3 4	387	Author contributions IL, RR, LC, CG, JCJ, and JL wrote the first draft of the protocol. RR,
5 6 7	388	IL, JCJ, CG, LC, and JL have revised the protocol. All authors critically reviewed and approved
7 8 9	389	the manuscript. IL is the guarantor of the review.
) 10 11	390	
12 13	391	Funding This research received no specific grants from any funding agency.
14 15 16	392	
10 17 18	393	Competing interests None known.
19 20	394	
21 22	395	Patient consent Not required.
23 24	396	
25 26 27	397	Patient and Public Involvement No patient involvement
28 29	398	
30 31	399	Provenance and peer review Not commissioned, externally peer reviewed.
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23 of 28 BMJ Open 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 - Money D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Informati Yes	on reported No	Line number(s)
ADMINISTRATIVE IN	IFORMAT	TION da			
Title					
Identification	1a	Identify the report as a protocol of a systematic review	Х		2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		Х	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract		x	52
Authors		ing, ing			
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide perside mailing address of corresponding author	X		5-24
Contributions	Зb	Describe contributions of protocol authors and identify the guarantor of the review	Х		387-389
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, deruify 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	Х		391
Sponsor	5b	Provide name for the review funder and/or sponsor	Х		391
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	Х		72-140
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			2019-03			2
Section/topic	#	Checklist item		Information Yes	n reported No	Line number(s)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	n 5 Novem	X		142-156,
METHODS			ber			
Eligibility criteria	8	characteristics (e.g., years considered, language, publication status) to be used as chienta-	2020. Dov	X		158-185
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study and trial registers, or other grey literature sources) with planned dates of coverage	noac Seloac	Х		213-245
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including at limits, such that it could be repeated		X		Additional File 2
STUDY RECORDS		limits, such that it could be repeated	13 27			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the ev		Х		249-252
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) the each phase of the review (i.e., screening, eligibility, and inclusion in meta-analyss)	o <mark>g</mark> gh	X		254-261
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independent in duplicate), any processes for obtaining and confirming data from investigators	lently,	Х		263-272
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources) pre-planned data assumptions and simplifications	Ð,	Х		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	on Jur	X		187-211
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including wheth will be done at the outcome or study level, or both; state how this information will be used in synthesis		X		Additional File 3; 274-288
DATA			at			
	15a	Describe criteria under which study data will be quantitatively synthesized	Agen	X		290-321
Synthesis	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methe handling data, and methods of combining data from studies, including any planned exploration consistency (e.g., <i>I</i> ² , Kendall's tau)	or go f iii	X		290-321
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-	graphique	X		323-354

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Section/topic	#	Checklist item	ht, including for	-036058 o		n reported No	Line number(s)
		regression)	ng fo	5 P			
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	ог и us п			X	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, s reporting within studies)	esurela Srela	cter 2	X		Additional file 3
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	ement ted to t	020. Do	X		356-361
		regression) If quantitative synthesis is not appropriate, describe the type of summary planned Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, reporting within studies) Describe how the strength of the body of evidence will be assessed (e.g., GRADE)		ed from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l	Ç		Tect Central Access Publisher

Additional File 2

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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, onsite 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.

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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'.

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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.

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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 metaanalysis and Trial Sequential Analysis

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3	review with meta-analysis and Trial Sequential Analysis
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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

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28 ABSTRACT

Introduction The prevalence of children with overweight and obesity is increasing worldwide. Multi-component 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.

34 Methods and analysis We will include randomised clinical trials involving children and adolescents between 0-18 years with overweight and obesity, irrespective of publication type, 35 year, status, or language up to April 2020. Psychotherapy will be compared with no 36 intervention; wait list control; treatment as usual; sham psychotherapy; or pharmaceutical 37 placebo. The following databases will be searched: Cochrane Central Register of Controlled 38 Trials, Cochrane Database of Systematic Reviews, MEDLINE, Embase, PsycINFO, PubMed, and 39 40 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. 41 42 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 43 and serious adverse events. Study inclusion, data extraction and bias risk assessments will be 44 conducted independently by at least two authors. We will assess risk of bias according to 45 Cochrane guidelines and the Cochrane EPOC guidance. We will use meta-analysis and control 46 risks of random errors with Trial Sequential Analysis. The quality of the evidence will be 47 assessed using GRADE. The systematic review will be reported according to PRISMA and 48 Cochrane guidelines. 49

50 **Ethics and Dissemination** As individual patient data will not be included, we do not require 51 ethics approval. This review will be published in a peer review journal.

52 **PROSPERO registration number**: CRD42018086458

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Keywords: Obesity, overweight, children, adolescents, psychotherapy, intervention,
treatment, systematic review.

56 Article summary

57 Strength 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 (GRADE).
- 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.
- 72 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 World Health Organization continues to show an increasing prevalence of children with obesity in Europe (6, 7). The Page 5 of 28

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International Task Force of Obesity produced age and sex specific cut-off for the definition of overweight and obesity in children (8). Throughout this paper, children and adolescents between 0-18 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 cardio-vascular 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).

92 As such, psychological variables such as quality of life, self-esteem, life events, parental 93 attitudes, eating disorders and anxiety need to be addressed in the long-term treatment 94 of overweight and obesity. Psycho-education, cognitive behavioural therapy, solution-based 95 therapy, including systemic therapy, and psychodynamic counselling are used (17-19). Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

97 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 whilst 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-

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> determination (23-27). Family therapy is a form of systemic therapy, widely used to treat children with overweight, often as part of multi-component programs (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 programs 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.

- 3 116
- 117 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 end of intervention (44, 45). A moderate improvement of healthrelated quality of life in the intervention groups was seen in older children (P=0.01), but the evidence was uncertain (44, 45). In pre-school children, multi-component interventions showed reductions in BMI (P<0.00001) and improvements in some markers of quality of life (43).

, 125

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). Page 7 of 28

 However, a 5 year follow-up study in adolescents with morbid obesity who underwent bariatric surgery demonstrated no significant improvement of self-esteem (48). Potentially, a small proportion of participants may be at risk of developing worsening pathology, which clinicians should monitor, whilst 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 whilst benefits to psychological well-being following treatment should be considered when assessing treatment success.

Whilst 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 GRADE (49-58).

¹ 143

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 whilst harms will include developing eating disorders.

7 150

9 151 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) (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 **BMJ** Open

(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 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 whilst 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.

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2 3	182	The therapy can be delivered, face-to-face either individually, delivered to parents only or in
4 5	102	
6	183	groups, in any setting. The control intervention can be no intervention; wait list control;
7 8	184	treatment as usual; sham psychotherapy; or pharmaceutical placebo.
9 10 11	185	
11 12 13 14 15 16 17	186	There is no restriction as to who delivers the treatment or treatment duration. We will accept
	187	any co-intervention providing that they are planned to be delivered in similar fashion in both
	188	the experimental group and the control group.
18 19	189	
20 21 22	190	Types of outcomes
22 23 24	191	We will assess all outcomes at baseline and then at two time points:
25 26	192	- End of intervention, as defined by trialist (our primary time point of interest)
27 28	193	- Maximum follow up.
29 30 31	194	
31 32 33 34 35 36 37 38 39 40 41 42	195	Primary outcomes
	196	1. BMI z-score (kg/m ²).
	197	2. Quality of life: as measured by a scale that has been validated for use in the target
	198	population (62).
	199	3. Proportion of participants with one or more serious adverse events; that is, any
42 43 44	200	untoward medical occurrence that results in death, is life-threatening, requires
45 46	201	hospitalisation or prolongation of existing hospitalisation, results in persistent or
47 48	202	significant disability or incapacity (63, 64).
49 50		
51 52	203	Secondary outcomes
53 54	204	1. Body weight measured in kg.
55 56	205	2. Self-esteem.
57 58	206	3. Anxiety.
59 60	207	4. Depression.

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2 3 4 5	208	5. Proportion of participants with at least one non-serious adverse event (63, 64).			
6 7	209	Exploratory outcomes			
8 9	210	1. Body fat (%) measured by bioimpedance or Dual Energy X-ray Absorptiometry (65,			
10 11 12	211	66).			
12 13 14	212	2. Muscle mass (kg) via bioimpedance or Dual Energy X-ray Absorptiometry (65, 66).			
15 16	213	3. Individual serious adverse events and individual adverse events not considered			
17 18	214	serious.			
19 20 21	215				
21 22 23	216	Search methods for identification of studies			
23 24 25 26 27 28 29 30 31 32 33 34	217	Electronic searches			
	218	Searches will include literature up to April 2020. We will search the following databases: The			
	219	Cochrane Library, MEDLINE, Excerpta Medica database (Embase), PsycINFO, Web of Science			
	220	(SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC), CINAHL and			
	221	LILACS. Examples of keywords used in the search strategy will include: obesity, overweight,			
35 36	222	psychotherapy, body mass index, weight gain, weight loss, hyperphagia and systematic			
37 38	223	review. Controlled descriptors will be included using MeSH. A preliminary search strategy for			
39 40 41	224	MEDLINE is enclosed as Additional File 2.			
42 43	225				
44 45 46 47 48 49 50 51 52	226	Searching other resources			
	227	We will search for trials or ongoing studies on the following resources:			
	228	ClinicalTrials.gov (www.clinicaltrials.gov)			
	229	Google Scholar (<u>https://scholar.google.com/</u>)			
53 54	230	 European Medicine Agency (http:// www.ema.europa.eu/ema/) 			
55 56	231	 United States Food and Drug Administration (ww.fda.gov) 			
57 58 59	232	Medicines and Healthcare Products Regulatory Agency			
60	233	(https://www.gov.uk/government/organisations/medicines-and-			

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2 3 4	234	healthcare-products-regulatory- agency)		
4 5 6	235	The World Health Organization (<u>www.who.int/</u>) ICTRP Search Portal		
7 8	236	Global Obesity Forum (previously International Association for the Study of Obesity)		
9 10 11	237	(www.iaso.org)		
12 13	238	• European Association for the Study of Obesity (EASO) (easo.org).		
14 15	239			
16 17	240	Keywords used in the search strategy		
18 19 20	241	• Obesity		
20 21 22	242	Overweight		
23 24	243	Psychotherapy		
25 26	244	Body mass index		
27 28 20	245	Weight gain		
29 30 31 32 33	246	Weight loss		
	247	Hyperphagia		
34 35	248	Systematic review		
36 37	249	A preliminary search strategy for MEDLINE is enclosed as Additional File 2.		
38 39 40	250			
41 42	251	Data collection and analysis		
43 44	252	Selection of studies		
45 46 47 48	253	We will perform the review following the recommendations in the Cochrane Handbook for		
	254	Systematic Reviews of Interventions (60). The meta-analyses will be performed using Review		
49 50 51	255	Manager and Trial Sequential Analysis program (67, 68).		
52 53	256			
54 55	257	At least two authors will independently screen titles and abstracts. They will retrieve all		
56 57	258	identified and relevant full text publications after which two authors will independently screen		
58 59 60	259	the full text and identify and record reasons for exclusion of the ineligible studies.		

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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 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (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.

266 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.

g 276

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 (EPOC) Group's guidance (70, 71). We will evaluate the methodology in respect of: Random sequence generation

- Allocation concealment
- Blinding of participants and treatment providers

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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 Additional File 3. **Meta-analysis** Data will be meta-analysed using RevMan 5 statistical software (72). We will use STATA statistical software (STATA 2015) in case of zero event trials, where RevMan 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). The results of the exploratory outcomes will be considered hypothesis generating only. We will measure effect size using standardised mean differences using confidence intervals of 95%. Analysis of all included studies will be compared to 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 at 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**

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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 (58, 79, 80), 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% (81). 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% (81). We will calculate risk ratios with 95% confidence interval (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 duration of intervention, the number of in person sessions, and length of sessions in hours (82).
 - Trials stratified if treatment fidelity was assessed or not (83).
- Trials stratified according to the control interventions.

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2 3 4	337	• Complexity: trials with participants with no co-morbidities compared to trials with
5	338	participants pre-existing co-morbidities.
7 8	339	• Trials in which the experimental intervention was evaluated by either the parents or the
9 10	340	child after the treatment sessions had been delivered compared to trials in which the
11 12 13	341	experimental intervention was not evaluated by either the parents or the child after the
14 15	342	treatment sessions had been delivered.
16 17	343	
18 19	344	We will use the formal test for subgroup interactions in Review Manager (72).
20 21 22	345	
23 24	346	Sensitivity analysis
25 26	347	To assess the potential impact of the missing data for dichotomous outcomes, we will perform
27 28	348	the following sensitivity analyses.
29 30 31	349	• 'Best-worst-case' scenario: we will assume that all participants lost to follow-up in the
32 33	350	experimental group had no serious adverse events, including not developing any
34 35	351	psychiatric disease such as an eating disorder.
36 37	352	'Worst-best-case' scenario: we will assume that all participants lost to follow-up in the
38 39 40	353	experimental group, had a serious adverse event, for instance, developing a psychiatric
40 41 42	354	disease such as an eating disorder (46).
43 44	355	Statistical heterogeneity will be assessed by visual inspection of the forest plots and I ² statistic
45 46	356	values (78). Underlying reasons behind statistical heterogeneity in meta-analyses will be
47 48 49	357	investigated by assessing trial characteristics.
50 51	358	
52 53	359	Summary of findings table
54 55	360	A summary of findings table using each of the prespecified primary outcomes will be presented
56 57	361	using GRADE considerations for studies contributing data to the meta-analyses for the
58 59 60	362	prespecified outcomes (78, 84-97). Methods and recommendations described in Chapter 8

363 (Section 8.5) and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of*364 *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.

21 371

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.

43 381

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46382ETHICS AND DISSEMINATION

383 No ethical approval required. Dissemination of results will be published in peer reviewed384 journals.

52 385

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 Specialist at the Copenhagen Trial Unit, Centre for Clinical Intervention Research for her
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2 3 4	389	
5 6	390	Author contributions IL, RR, LC, CG, JCJ, and JL wrote the first draft of the protocol. RR,
7 8 9	391	IL, JCJ, CG, LC, and JL have revised the protocol. All authors critically reviewed and approved
9 10 11	392	the manuscript. IL is the guarantor of the review.
12 13	393	
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16 17	395	
18 19	396	Competing interests None known.
20	330	
21	397	
22		
23 24	398	Patient consent Not required.
25 26	399	
27 28 20	400	Patient and Public Involvement No patient involvement
29 30 31	401	
32 33	402	Provenance and peer review Not commissioned, externally peer reviewed.
34 35	403	
36 37 38	404	
39 40	405	REFERENCES
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44	656	Appendices
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46 47	657	Additional File 1: Prisma-P+ checklist.
47 48		
49	658	Additional File 2: Preliminary search strategy for MEDLINE (Ovid).
50	038	Additional the 2. Treinfindly search strategy for the Derive (Ovid).
51	650	Additional File 2. Classification of randomized trials at low and at high risk of high
52	659	Additional File 3: Classification of randomised trials at low and at high risk of bias.
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BMJ Open 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 statements Paviews 2015 4:1 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 - Money D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 5:15

Section/topic	ppic # Checklist item		Information reported Line		
	"		Yes	No	number(s)
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Title					
Identification	1a	Identify the report as a protocol of a systematic review	Х		2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		Х	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract		X	52
Authors		, pg			
Contact	За	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide paysical mailing address of corresponding author	X		5-24
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Х		390-392
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, deruify 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		Х	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	Х		72-142
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						2
Section/topic	#	말 이 이 이 이 이 이 이 이 이 이 이 이 이 이 이 이 이 이 이		Informatio Yes	n reported No	Line number(s)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)		Х		144-157
METHODS		s seiger reig				- -
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and reporting the characteristics (e.g., years considered, language, publication status) to be used as criteria for the review		Х		159-188
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study atters, trial registers, or other grey literature sources) with planned dates of coverage		Х		216-249
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including an an architecture limits, such that it could be repeated	d	Х		Additional File 2
STUDY RECORDS		limits, such that it could be repeated				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the eview		Х		252-255
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) to get each phase of the review (i.e., screening, eligibility, and inclusion in meta-analyss)	h	Х		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	y,	Х		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	y	Х		Additional File 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and sadditional outcomes, with rationale		Х		190-214
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whethe the will be done at the outcome or study level, or both; state how this information will be used and the synthesis		Х		Additional File 3; 277-291
DATA		at A				
	15a	Describe criteria under which study data will be quantitatively synthesized		Х		293-324
Synthesis	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., <i>I</i> ² , Kendall's tau)		Х		293-324
	15c	Consistency (e.g., 7 ⁻ , Kendali's tau) og Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta- og		Х		326-357

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ection/topic	#	Checklist item	
		regression)	n 5 N Ng fo
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	love E
leta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, reporting within studies)	nseign Srelat
onfidence in umulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	020. Do ement led to t
		regression) If quantitative synthesis is not appropriate, describe the type of summary planned Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, reporting within studies) Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	nce Bibliographique (

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е	Х		Additional file 3	
	Х		359-364	



Additional File 2

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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
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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, onsite 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.

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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'.

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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.