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Treatment of pediatric obesity. A systematic review and meta-analysis of randomized trials

Brief title: Meta-analysis of treatments for pediatric obesity

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Abstract

Context: The efficacy of treatments for pediatric obesity remains unclear.

Objective: We performed a systematic review of randomized trials to estimate the efficacy of nonsurgical interventions for pediatric obesity.

Data Sources: Librarian-designed search strategies of nine electronic databases from inception until February 2006, review of reference lists from published reviews, and content expert advice provided potentially eligible studies.

Study Selection: Eligible studies were randomized trials of overweight children and adolescents assessing the effect of nonsurgical interventions on obesity outcomes.

Data Extraction: Independently and in duplicate, reviewers assessed the quality of each trial and collected data on interventions and outcomes.

Data Synthesis: Of 76 eligible trials, 61 had complete data for meta-analysis. Short-term medications were effective, including sibutramine (random-effects pooled estimate of body mass index (BMI) loss of 2.4 kg/m^2 (95% confidence interval (CI) 1.8, 3.1, proportion of between-study inconsistency not due to chance (I^2) = 30%) and orlistat (BMI loss 0.7 kg/m^2 (CI 0.3, 1.2), I^2 = 0%). Trials that measured the effect of physical activity on adiposity (i.e. percent body fat, fat free mass) found a moderate treatment effect (effect size -0.52, CI -0.73, -0.30, I^2 = 0%) while trials measuring the effect on BMI found no significant effect (effect size -0.02, CI -0.21, 0.18, I^2= 0%), but reporting bias may explain this finding. Combined lifestyle interventions (24 trials) led to small changes in BMI.

Conclusions: Limited evidence supports the short-term efficacy of medications and lifestyle interventions. The long-term efficacy and safety of pediatric obesity treatments remains unclear.

There is an epidemic of childhood obesity that is associated with an increased incidence of cardiovascular risk factors, adult obesity, and obesity-related comorbidities (1). The American Academy of Pediatrics and the Center for Disease Control use the term overweight to denote excessive body weight and obesity to describe excessive body fat. In 1998, an expert committee established general pediatric treatment guidelines based on body mass index (BMI), a measure of body weight (2). These guidelines suggested clinicians to advise weight loss in children aged 2-7 years with BMI> 95th percentile and complications (mild hypertension, dyslipidemia, and insulin resistance) and weight maintenance to children without any of these complications (2). These guidelines also suggested clinicians to advise weight loss to children 7 years or older with BMI > 95th percentile and or BMI 85-94th percentile and complications (2). A recently published consensus statement offered similar advice, indicating lifestyle counseling for children with BMI ≥ 85th percentile and specialist care for children with BMI ≥ 95th percentile (3). Authors of these and other efforts to guide clinical practice benefited only marginally, if at all, from rigorous summaries of the best available evidence from clinical care research.

The Endocrine Society decided to formulate clinical practice guidelines for the management of pediatric obesity. In doing so, it formed a Task Force to develop these recommendations. This Task Force asked the Mayo Knowledge and Encounter Research Unit, under contract to perform evidence syntheses with the Endocrine Society, to conduct a systematic review of the literature on the treatment of pediatric obesity. This report briefly summarizes the findings of a systematic review and meta-analyses of randomized trials published in the literature up to February 2006 and reports on the effect of evaluated treatments on obesity outcomes.

Methods

The Endocrine Society Pediatric Obesity Task Force commissioned this review, approved the review protocol, offered references, and provided insight into the interpretation of the results. We have produced this report in adherence with the Quality of Reporting of Meta-analyses (QUOROM) standards for reporting systematic reviews of randomized trials (4).

Clinical Question: What is the efficacy of weight loss interventions (diet, physical activity, pharmacological agents) for overweight children and adolescents?

Eligibility Criteria

Eligible studies were fully published randomized trials (in any language) with majority of participants being overweight (as defined in each study) children and adolescents (ages 2-18) and assessing the effect of lifestyle and pharmacologic interventions on obesity outcomes. Prevention trials were included in the accompanying prevention review (Kamath et al, 2007); that prevention review shares common search and selection processes with this treatment review, but no common analyses. While trials of children and adolescents with insulin resistance and type 2 diabetes were included, we excluded trials of patients with type 1 diabetes, eating disorders (bulimia or anorexia nervosa), Prader-Willi patients, and other patients in which obesity is part of a clinical syndrome and follows different natural and clinical histories.

Eligible lifestyle interventions included any treatment strategy aimed at changing the diet and/or activity level of overweight children. These interventions could target the participant directly or through their family, school, or community. Eligible trials could enroll

community agents, school personnel, family members, or health care personnel to deliver the interventions.

Eligible pharmacological interventions were medications used with the objective of reducing obesity measures in overweight children. We excluded trials of agents administered with the intent to reduce cardiovascular risk factors in obese children, such as antihypertensive and antihyperlipidemic agents.

Eligible studies assessed an objective mass-based obesity measurement at end of the study period (regardless of whether authors reported the results of the intervention on this measure). Mass-based outcomes included body mass index (BMI; preferred outcome), percent overweight, percent fat free mass and visceral adiposity measurements (5). We excluded trials measuring percent weight loss irrespective of height. Outcome effects measured within 6 months of onset of intervention were deemed 'short-term'.

Identification and retrieval

An expert reference librarian (P.J.E.) designed and conducted the electronic search strategy with input from a team of pediatric physicians and researchers. To identify eligible studies, our systematic search included the electronic databases MEDLINE, EMBASE, ERIC, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), PSYCInfo, Dissertation Abstracts International, Science Citation Index, and Social Science Citation Index, in all cases from their inception until February 2006 (detailed search strategies available from the authors). We also reviewed the reference sections of identified reviews and published guidelines. Finally, we received suggestions for inclusion of articles from

pediatric obesity experts that comprised the Endocrine Society Pediatric Obesity Task Force.

One team of two reviewers (L.M., C.C.K.) independently identified for full text retrieval all eligible records from the abstracts and titles; records in which the reviewers disagreed were also retrieved in full text. Teams of two reviewers (L.M., R.P., A.H.) working independently and in duplicate again reviewed the full text articles for eligibility; an endocrinologist with expertise in research methodology (V.M.M.) not involved in the initial assessment resolved disagreements.

Data Collection

Working in duplicate, six trained reviewers extracted the following data from each eligible article: year and journal of publication, type of study (e.g., pilot), level of randomization (e.g., community, school, or clinical), participants (age and gender), measure of obesity (BMI, percent overweight, percent fat-free mass, or visceral adiposity), experimental and control interventions (type of intervention, deliverer of intervention, level and duration of intervention) and results. When authors reported both end-of-study results and change-from-baseline results we collected end-of-study results assuming that imbalances at baseline between groups were random and would "even out" as we pooled across trials. When possible we calculated mean or variance data from related information (e.g., reported t scores and P values, standard errors and confidence intervals) using standard procedures recommended in the Cochrane Reviewers' Handbook version 4.2.5 (www. Cochrane.org/resources/handbook/).

Quality Assessment

To ascertain the validity of eligible randomized trials, pairs of reviewers working independently and with substantial reliability (corresponding kappa where appropriate) determined the extent to which trials reported concealment of allocation (k=0.94), blinding of patients (k=0.94) provider of intervention (k=0.94) and data collectors (k=1), blinding to the hypothesis (k=1), level of randomization (k=0.83), and extent of loss to follow-up (i.e. the percent of patients in whom the investigators were not able to ascertain outcomes).

Author contact

Using up to two electronic mail contacts to the corresponding and/or first author of each eligible article, we sought to confirm our data extraction and quality assessment and to request missing information about trial design and quality, study characteristics or outcome data. The response rate to our requests was approximately 22%.

Statistical Analysis

Meta-analysis

For each analysis, we determined the effect size (standardized mean difference) and 95% confidence interval (CI) for the difference between treatment arm and control arm. The standardized mean difference resulted from dividing the mean difference between arms by the pooled variance between arms with adjustment for small samples (Hedges *g*) as implemented in Revman 4.2 (Cochrane Collaboration). We considered standardized mean differences of about 0.2 or less as small, about 0.5 as moderate, and of about 0.8 or greater as large effect sizes. We used random effects meta-analysis to compare the effects on obesity outcomes of diet alone vs. control, exercise alone vs. control, pharmacological

therapy vs. placebo control and combined lifestyle modifications vs. control. We quantified the extent to which the between-study variability observed were due to true between-study differences (rather than to chance) using the I^2 statistic (6). Inconsistency was small when $I^2 < 25\%$, moderate 25-50% and large > 50%.

Subgroup analysis

We performed four subgroup analyses. Several narrative reviews reported that delivering combined lifestyle interventions involving parents or the family was a promising approach to treating obesity; hence, we performed a subgroup analysis comparing the effect of this intervention when delivered to the child or the adolescent and compared its effects when it was delivered with some degree of parental participation. We analyzed combined lifestyle interventions delivered to various age-group specific targets. Also, we hypothesized that physical activity interventions could have a greater effect on percent body fat than on BMI; hence, we performed a sub-group analysis of these trials by outcome. In addition, we sought to determine whether reduced sedentary behavior and increased physical activity had distinct impact on obesity outcomes. Finally, we tested for a subgroup interaction between the choice of outcome measure (change-from-baseline vs. end-of-study) and the treatment effect, but these tests were not contributory.

Results

Search Results

Figure 1 describes the flow of candidate and eligible articles. After searching the electronic databases, we identified 1162 abstracts, of which 263 were deemed relevant by title and

abstract alone. Also we found an additional 65 articles from review of references from relevant reviews and guidelines and from input from the obesity task force members. After review of 328 full text articles for treatment and prevention of pediatric obesity, 75 articles were eligible for the review on treatment of pediatric obesity. One additional trial we detected in the FDA website and considered unpublished was indeed published at the time of final draft of this report and was included (7); in all, 61 had complete data to include in meta-analyses.

Overall methodological quality

Table 1 shows the reported methodological quality of the eligible trials for each of the review questions. Almost all trials across these reviews lacked reporting or conduct of allocation concealment, and blinding (except for placebo-controlled drug trials); nearly half of the trials lost 10% or more participants to follow-up (i.e., had not outcome data at the end of trial for these randomized participants).

Meta-analyses

Figure 2 summarizes the results of each of the meta-analyses listed below. The **Appendix** includes detailed tables of study characteristics and meta-analytic plots for each of the questions below.

Pharmacological treatments

This review includes 17 trials of pharmacological interventions (**Appendix Table 1**); none explicitly required patients to have attempted lifestyle interventions prior to enrollment. Three trials assessed the effect of sibutramine on adolescents with obesity. The pooled effect

size was large (-1.01, CI -1.28, -0.73, I^2=30%); this effect is consistent with a loss in BMI of 2.4 kg/m^2 (CI 1.8, 3.1 kg/ m^2) after 6 months of use (**Appendix Figure 1**). Patients taking sibutramine had higher rates of elevated blood pressure and pulse rate than patients taking placebo.

Three randomized trials of orlistat found a small to moderate effect on obesity outcomes (-0.29, CI -0.46, -0.12, I^2 =0%); this effect is consistent with a loss in BMI of 0.7 kg/m^2 (CI 0.3, 1.2 kg/m^2) (**Appendix Figure 1**) More patients taking orlistat reported gastrointestinal side effects including abdominal discomfort, pain, and steatorrhea than patients on placebo.

Three randomized trials of metformin monotherapy on hyperinsulinemic non-diabetic obese adolescents, showed a small nonsignificant change in obesity outcome at 6 months (-0.17, CI -0.62, 0.28) (**Appendix Figure 1**).

Other trials measured the effect of sympathomimetics (ephedrine and caffeine, dexfenfluoramine), DHEA, and fiber supplements. We found no trials of rimonabant in children or adolescents.

Lifestyle intervention - Dietary interventions only

There were six eligible trials of dietary interventions alone (**Appendix Table 2**). These trials evaluated different diets against control: reduced-glycemic-load diet, protein-sparing modified diet, low-carbohydrate diet, high-protein diet and hypocaloric diet. The pooled effect across all these diets was -0.22 (CI -0.56, 0.11) with small between study

inconsistency (I^2 = 22.5%). Two trials that assessed interventions focused on reducing carbohydrates in the diet estimated nonsignificant large reductions in obesity outcome (8, 9).

Lifestyle interventions - Physical activity interventions only

Of the 20 eligible physical activity trials (**Appendix Table 3)** the 17 trials with complete data yielded inconsistent results (I^2 = 32%; **Appendix Figure 2**). We explored the extent to which differences in obesity outcome measures could explain the observed inconsistency (i.e., measures of adiposity (i.e. percent body fat, fat free mass) could be more sensitive to change associated with physical activity than BMI)(5). Indeed, we found an outcome-treatment interaction (*P*=.0007); trials that measured the effect of physical activity on adiposity found a moderate treatment effect (-0.52, CI -0.73, -0.30, I^2 = 0%) and trials measuring the effect on BMI found no significant effect (-0.02, CI -0.21, 0.18, I^2= 0%). When we limited the subgroup analysis to the 6 trials that reported the effect of lifestyle interventions on both outcomes, the interaction was no longer significant (*P*=.28), suggesting the initial observation resulted from reporting bias. Four trials evaluated reduced sedentary behavior as the key activity intervention (10, 11). Three of these trials (n=116) reported sufficient data to analyze; the point estimate was consistent with no benefit but the results were imprecise (0.02, CI -0.35, 0.39) (10, 12, 13) (**Appendix Figure 3)**.

Combination lifestyle interventions (physical activity, dietary modification)

The pooled estimate across 23 trials assessing the efficacy of combination of lifestyle interventions with complete data out of the 30 eligible trials (**Appendix Table 4**) was consistent with a small to moderate treatment effect (**Appendix Figure 4**). The largest

effects were associated with parental involvement in delivering the intervention, when the parents were either targeted individually or with the child. We did not find a significant interaction between age of participants and the effect of lifestyle interventions with parental involvement, but there was a trend towards a larger treatment effect in children aged 8 years or less (-0.70, CI -1.00, -0.40) (**Appendix Figure 5**).

Discussion

In this systematic review and meta-analyses of available randomized trials of treatments for childhood obesity, we found evidence of: (a) short-term efficacy of pharmacological interventions (sibutramine and orlistat in adolescents) on BMI; (b) moderate treatment effect of physical activity on adiposity, but not on BMI; and (c) small to moderate treatment effect of combined lifestyle interventions on BMI. Nonsignificant trends favored delivering combined lifestyle interventions with parental involvement, particularly to children 8 year-old or younger. Our review provides no data to directly compare the relative efficacy of pharmacological agents with each other, with lifestyle interventions, or with bariatric surgery.

Limitations and strengths

Our systematic review has some limitations. Of the 76 final articles which met inclusion criteria, 61 had complete data and were included in the analysis. This likely represents a high probability of reporting bias. Despite our best efforts, we may have missed eligible studies that could contribute to publication bias, i.e. overestimating the treatment effect. Overall, included trials have limited methodological features that protect their results from bias and therefore can only yield weak inferences. Pooling across trials with high degree of

clinical or statistical inconsistency increases the risk of spuriously precise estimates with limited clinical sense; the limited duration of the included trials weakens inferences about the long-term effect of the studied interventions.

Transparent reporting of the included trials, efforts to limit selection bias and reporting bias (including extensive author contact), attention to quality of methods, and focused and parsimonious analyses (including selected subgroup analyses) strengthen the inferences from this review. Our report should help readers discern the extent to which the design and methods of the eligible trials are consistent with the pooled estimates. We put forth pooled estimates as we think they are helpful in summarizing the available evidence.

Comparison with other reviews

While our review includes 42 more trials and is current as of February 2006, our inferences are not very different from those drawn from a Cochrane review in 2003. In it, Summerbell and colleagues concluded that most studies were too small to detect treatment effects and outcomes measured were inconsistent across studies (1) . We have extended the latter inference to note that perhaps measures of fat distribution are more sensitive to change than BMI. Our results are also consistent with another review that found short-term pharmacological therapy beneficial in obese adolescents (19).

The effects of parental involvement in treatment of childhood obesity remain unclear, but widely advocated (20) particularly for younger patients (21, 22). Our review weakly suggests that parental involvement amongst children and adolescent had a small treatment effect with a trend towards a larger effect among patients 8 years-old or younger.

Implications for practice, research, and policy

The available evidence should inform the practice of evidence-based obesity treatment in children. This systematic evidence summary helped guideline developers with the Task Force on Pediatric Obesity of the Endocrine Society to consider the quality of evidence and grade of recommendation for each of the treatment guidelines. Those guidelines reflect the clinical implications of our findings.

There are some research implications of this review. While in adults, adverse health outcomes linked to obesity appear related to excessive body fat and distribution, there is no simple, reproducible, accurate, and cost-effective method to measure fat mass in children. BMI is currently the standard of following obesity status in children as recommended by the American Academy of Pediatrics (11). However, BMI does not completely inform health risks in children (3), requires accuracy and reproducibility in the measure of both height and weight, misinterprets risk in muscular and short children, and may be less responsive to change. While potentially more responsive to health interventions, the strength and shape of the association (e.g., J-curve, threshold) between measures of body fat and metabolic and cardiovascular outcomes related to obesity remain largely unknown. Hence, trialists should consider choosing to assess the effect of interventions on responsive outcomes either by choosing those outcomes (such as fat free mass or percent body fat) or by testing the effect on less responsive outcomes (like BMI) of more powerful interventions over a longer period of time.

Numerous factors contribute to obesity, including but not limited to genetics, environment,

metabolic, biochemical, psychological and physiological (11). These complex causal links make it unlikely that a single "silver bullet" intervention will be successful for all obese patients. This would suggest a careful multidisciplinary and multimodality approach. The accompanying Endocrine Society practice guidelines offer such an approach: an evaluation and treatment algorithm for pediatric obesity. Long-term randomized trials of this and other comprehensive multimodality algorithms offer the opportunity to ascertain the extent to which a comprehensive approach is effective, safe, and feasible in reducing the burden of obesity and its complications among children and adolescents at greatest risk of weight-related morbidity. Promising interventions for high risk individuals, such as bariatric surgery and novel pharmacological agents also require rigorous assessment with attention to long-term patient important outcomes.

In conclusion, limited evidence supports the short-term efficacy of selected pharmacological monotherapy, increased physical activity and combined lifestyle interventions. The long-term impact of obesity treatments on the health of children and adolescents remains unclear.

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Figure Legends

Figure 1: QUOROM flow chart of study selection

Figure 2. Overall summary of meta-analyses results. Overall summary of random effects meta-analyses of randomized trials of treatments for pediatric obesity. Plot shows meta-analytic point estimates (closed circles) and 95% confidence intervals (horizontal lines). BMI, body mass index; CI, confidence interval; SMD, standardized mean differences.

Table 1. Summary table of methodological features to prevent bias in eligible trials, by review question

Review question (No. trials)	Allocation concealment			Blinding	Loss to follow-up		
	Yes	Not reported	No		<10%	10-20%	≥20%
Pharmacological interventions (n=17)	1 (6%)	5	11	16 (94%)*	6	5	6 (35%)
Diet interventions (n=6)	0 (0%)	5	1	0 (0%)	2	3	1 (16.7%)
Physical activity interventions (n=20)	0 (0%)	2	18	0 (0%)	10	2	5 (25%)
Combined lifestyle (n=30)	0 (0%)	1	29	0 (0%)	16	7	5 (17%)

* Presumed blind for participants and caregivers (unclear for data collectors) because of use of a placebo control

Figure 1

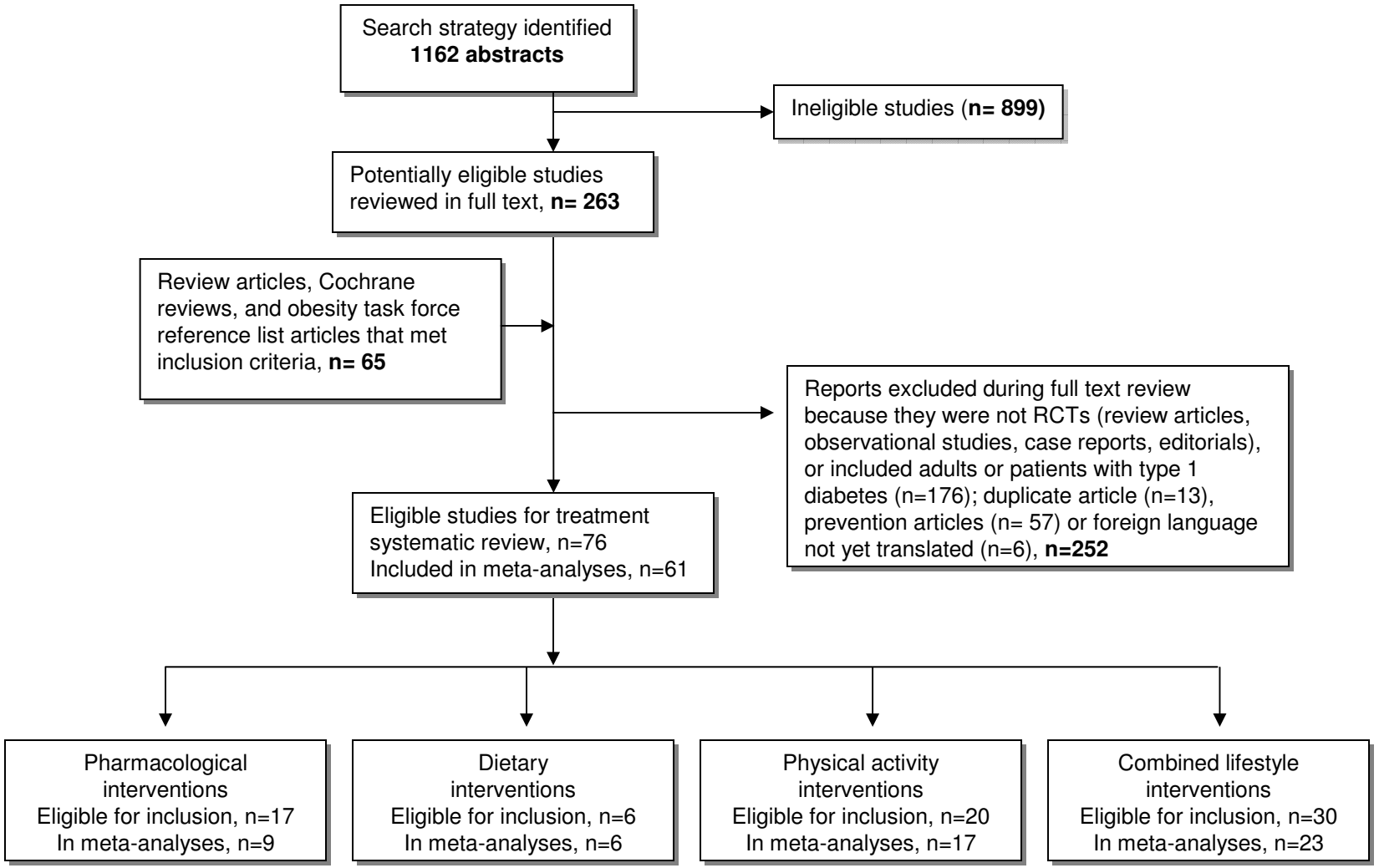
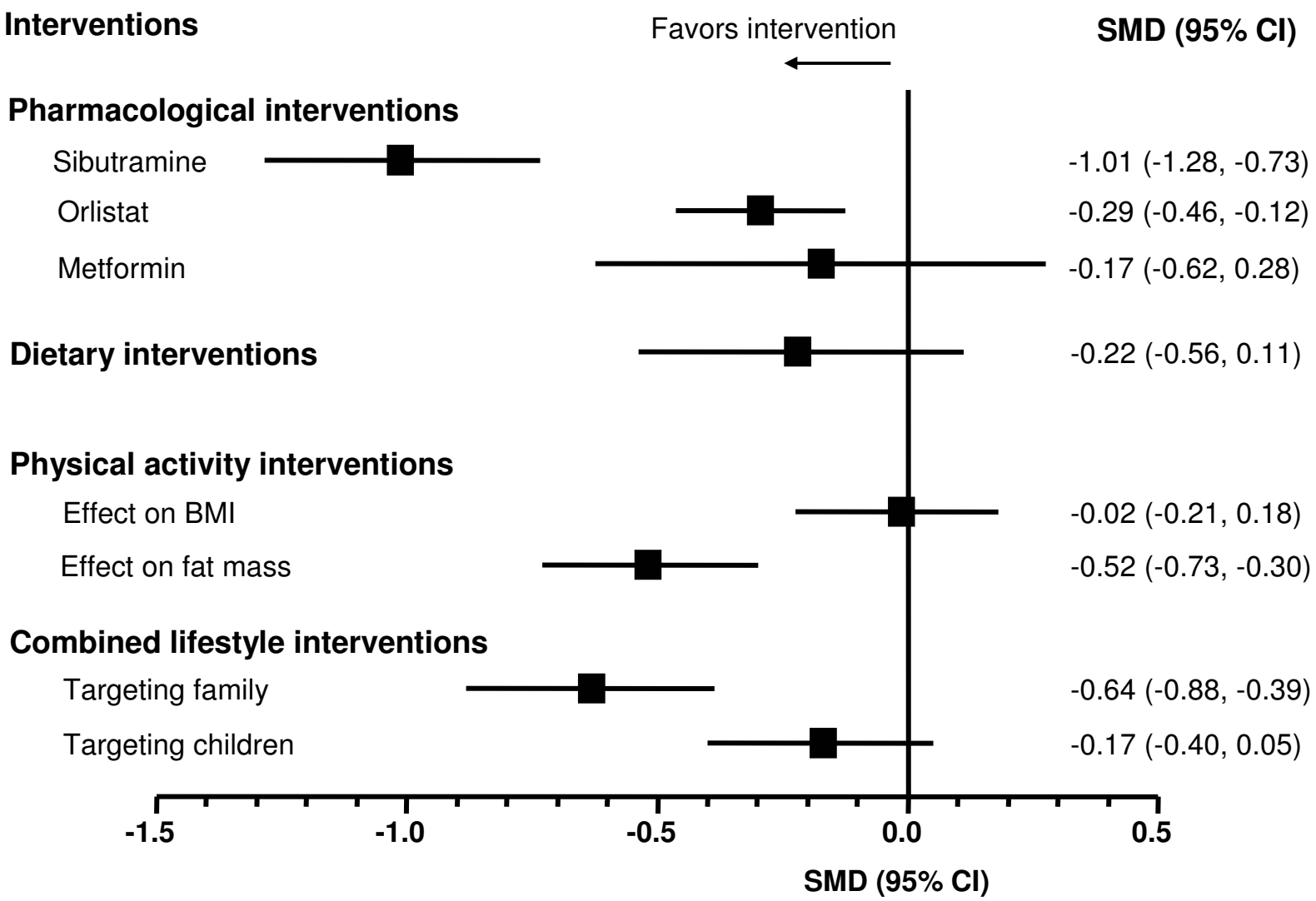

Search strategy identified
1162 abstracts
Ineligible studies (**n= 899)**
Potentially eligible studies reviewed in full text, **n= 263**
Review articles, Cochrane reviews, and obesity task force reference list articles that met inclusion criteria, **n= 65**
Reports excluded during full text review because they were not RCTs (review articles, observational studies, case reports, editorials), or included adults or patients with type 1 diabetes (n=176); duplicate article (n=13), prevention articles (n= 57) or foreign language not yet translated (n=6), **n=252**
Eligible studies for treatment systematic review, n=76
Included in meta-analyses, n=61
Pharmacological interventions
Eligible for inclusion, n=17
In meta-analyses, n=9
Dietary interventions
Eligible for inclusion, n=6
In meta-analyses, n=6
Physical activity interventions
Eligible for inclusion, n=20
In meta-analyses, n=17
Combined lifestyle interventions
Eligible for inclusion, n=30
In meta-analyses, n=23

Figure 2


Interventions
Favors intervention
SMD (95% CI)
Pharmacological interventions
Sibutramine
-1.01 (-1.28, -0.73)
Orlistat
-0.29 (-0.46, -0.12)
Metformin
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Combined lifestyle interventions
Targeting family
-0.64 (-0.88, -0.39)
Targeting children
-0.17 (-0.40, 0.05)
-1.5
-1.0
-0.5
0.0
0.5
SMD (95% CI)