Effectiveness of Weight Management Interventions in Children: A Targeted Systematic Review for the USPSTF

abstract

CONTEXT: Targeted systematic review to support the updated US Preventive Services Task Force (USPSTF) recommendation on screening for obesity in children and adolescents.

OBJECTIVES: To examine the benefits and harms of behavioral and pharmacologic weight-management interventions for overweight and obese children and adolescents.

METHODS: Our data sources were Ovid Medline, PsycINFO, the Education Resources Information Center, the Database of Abstracts of Reviews of Effects, the Cochrane databases, reference lists of other reviews and trials, and expert recommendations. After 2 investigators reviewed 2786 abstracts and 369 articles against inclusion/exclusion criteria, we included 15 fair- to good-quality trials in which the effects of treatment on weight, weight-related comorbidities, and harms were evaluated. Studies were quality rated by 2 investigators using established criteria. Investigators abstracted data into standard evidence tables.

RESULTS: In the available research, obese (or overweight) children and adolescents aged 4 to 18 years were enrolled, and no studies targeted those younger than 4 years. Comprehensive behavioral interventions of medium-to-high intensity were the most effective behavioral approach with 1.9 to 3.3 kg/m^2 difference favoring intervention groups at 12 months. More limited evidence suggests that these improvements can be maintained over the 12 months after the end of treatments and that there are few harms with behavioral interventions. Two medications combined with behavioral interventions resulted in small (0.85 kg/m^2 for orlistat) or moderate (2.6 kg/m^2 for sibutramine) BMI reduction in obese adolescents on active medication; however, no studies followed weight changes after medication use ended. Potential adverse effects were greater than for behavioral interventions alone and varied in severity. Only 1 medication (orlistat) has been approved by the US Food and Drug Administration for prescription use in those aged ≥12 years.

CONCLUSIONS: Over the past several years, research into weight management in obese children and adolescents has improved in quality and quantity. Despite important gaps, available research supports at least short-term benefits of comprehensive medium- to high-intensity behavioral interventions in obese children and adolescents. *Pediatrics* 2010;125:e396–e418

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In 2005, the US Preventive Services Task Force (USPSTF) found insufficient evidence to recommend for or against routine primary care screening for overweight in children and adolescents as a means of preventing adverse health outcomes (an "I" recommendation).[1,2] The USPSTF concluded that, although there was fair evidence that overweight adolescents and children aged ≥8 years are at increased risk for becoming obese adults, the efficacy of behavioral counseling or other primary care–relevant interventions for treating overweight children and adolescents was uncertain.

Given the findings in a recently published systematic review on weight-management programs for children and adolescents,[3] the USPSTF decided to update its recommendation, focusing on the critical evidence gap concerning treatment efficacy at the time of the last review. Thus, for this targeted systematic review, we examined evidence on primary care–relevant behavioral and pharmacologic weight-management interventions for overweight and/or obese children and adolescents (defined as those between 2 and 18 years of age who meet criteria for increased BMI appropriate to their age and gender).*

Behaviorally based interventions are considered the first line of treatment for overweight and obesity in children and adolescents. These interventions promote weight loss through modifications in diet and activity level and often involve parents or entire families,

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*The USPSTF has updated its terminology to be consistent with revised recommendations by the Expert Committee on child and youth obesity.[4] Although cutoffs remain the same, the Expert Committee now recommends using the term "overweight" to refer to children aged 2 to 18 years with a BMI in the 85th to 94th percentiles for their age and gender (previously referred to as "at risk for overweight") and "obese" to refer to children with a BMI at ≥95th percentile for their age and gender (previously "overweight"). Children or adolescents who have a BMI at ≥30 (the adult criterion) are also considered to be "obese."

particularly for younger children. Behavioral interventions often include cognitive and behavioral management techniques to help participants initiate and sustain needed lifestyle changes; such elements may address problem-solving, goal-setting, limiting exposure to unhealthy food, healthy thinking about food and the body, and relapse prevention.[5,6]

Pharmacologic agents are potential adjuncts to behavioral interventions for severely obese adolescents. The US Food and Drug Administration (FDA) approved the lipase inhibitor orlistat for prescription use in obese adolescents aged ≥12 years[7] and sibutramine, a centrally acting appetite suppressant, for adolescents aged ≥16 years.[8] Both drugs have potential negative adverse effects.[9] Bariatric surgery as a possible treatment for severely obese older adolescents was judged by the USPSTF to be out of scope for this review.

METHODS

Using the methods of the USPSTF,[10] we developed 3 key questions (KQs) (with 6 sub-KQs) and an analytic framework (Fig 1) to evaluate the effectiveness and safety of primary care–relevant behavioral and pharmacologic treatments for overweight and/or obese children.

We based our updated literature searches on the previous USPSTF review[2] and intervening systematic reviews from the National Institute for Health and Clinical Excellence (NICE) and the Agency for Healthcare Quality and Research (AHRQ).[9,11] We searched Ovid Medline, PsycINFO, the Database of Abstracts of Reviews of Effects, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and the Education Resources Information Center from 2005 (2003 for pharmacologic treatments) to June 10, 2008, to identify lit-

erature that was published after the search dates of these reports (see Appendices 1 and 2). Besides examining trials from key previous systematic reviews,[2,3,11] we hand-searched the reference lists of other good-quality reviews of childhood obesity treatment,[5,12–14] of all included trials, and further supplemented with expert-identified studies. We did not examine non–peer-reviewed sources (gray literature) or non–English-language literature.

Two investigators independently reviewed 2786 abstracts and 369 articles (Fig 2) against inclusion and exclusion criteria prespecified for each KQ (Appendix 3). Discrepancies were resolved by consensus. One investigator abstracted prespecified study information (Appendix 4) into evidence tables, and a second investigator verified the accuracy. Two investigators independently quality rated the studies by using design-specific criteria (Appendix 5). Discrepancies were resolved by consensus or consultation with a third investigator. Poor-quality studies were excluded.

Among behavioral trials, hours of contact was calculated as a proxy for treatment intensity and categorized as very low (<10 hours), low (10–25 hours), moderate (26–75 hours), or high (>75 hours). Weight outcomes were categorized as short-term (6–12 months since beginning treatment) or maintenance (between 1 and 4 years after beginning treatment and at least 12 months after ending active treatment). Interventions were considered comprehensive if they included (1) weight-loss or healthy diet counseling, (2) physical activity counseling or physical activity program participation, and (3) behavioral management techniques to help make and sustain changes in diet and physical activity.
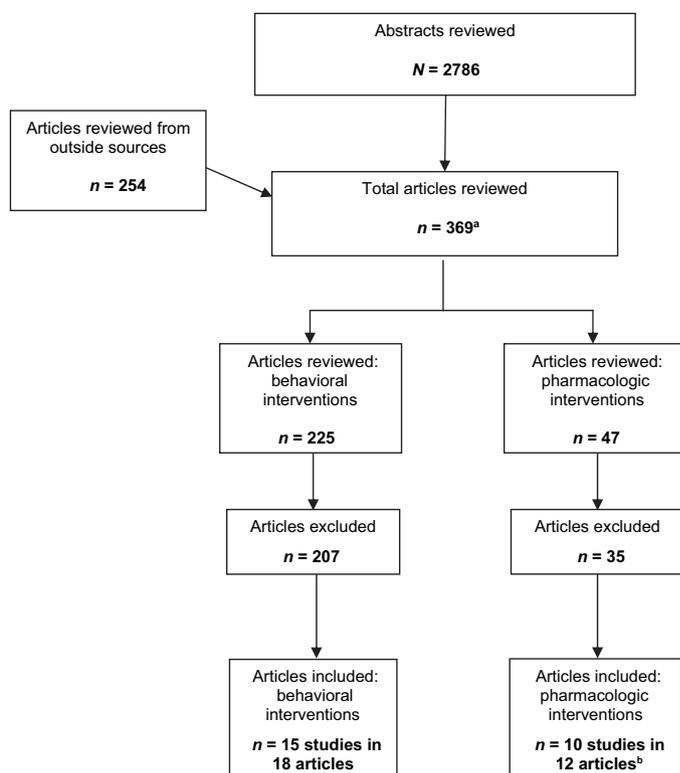
When possible, data were synthesized by using quantitative methods. For many questions, however, we relied on

FIGURE 1
Analytic framework and KQs.
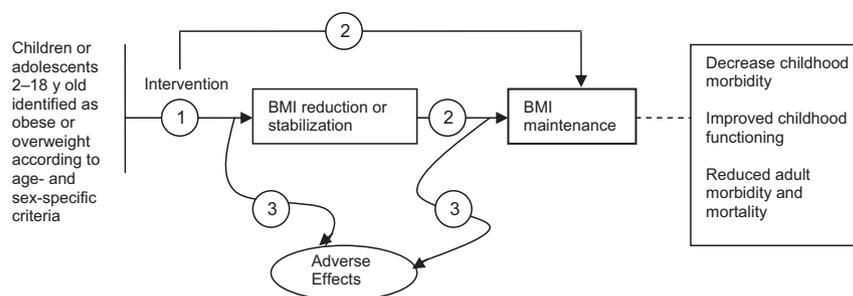
KQs
KQ1. Do weight-management programs (behavioral, pharmacologic) lead to BMI, weight, or adiposity stabilization or reduction in children and adolescents who are obese (≥95th BMI percentile) or overweight (85–94th percentile)?
  KQ1a. Do these programs lead to other positive outcomes (eg, improved behavioral or physiologic measures, decreased childhood morbidity, improved childhood functioning, or reduced adult morbidity and mortality)?
  KQ1b. Do specific components of the programs influence the effectiveness of the programs?
  KQ1c. Are there population or environmental factors that influence the effectiveness of the programs?

KQ2. Do weight-management programs (behavioral, pharmacologic) help children and adolescents who were initially obese or overweight maintain BMI, weight, or adiposity improvements after the completion of an active intervention?
  KQ2a. Do these programs lead to other positive outcomes (eg, improved behavioral or physiologic measures, decreased childhood morbidity, improved childhood functioning, or reduced adult morbidity and mortality)?
  KQ2b. Do specific components of the programs influence the effectiveness of the programs?
  KQ2c. Are there population or environmental factors that influence the effectiveness of the programs?

KQ3. What are the adverse effects of weight-management programs (behavioral, pharmacologic) attempting to stabilize, reduce, or maintain BMI?

FIGURE 2
Abstract disposition summary. [a]The number of articles reviewed is inclusive of bariatric-surgery articles. [b]Includes studies in high risk populations discussed in full report.[40]

tistical test of heterogeneity (I^2), which measures the percentage of variability in effect size attributable to between-study variation (as opposed to within-study sampling error).[15] We considered values of <30% to indicate little heterogeneity and those of >50% to indicate possible substantial heterogeneity incompatible with pooling. We did not conduct funnel plots to assess for publication bias, because our data were too heterogeneous to combine or, when pooled, included no more than 3 studies. We used change in BMI from baseline as the preferred measure of weight change when it was available. If BMI change was unavailable and could not be calculated or obtained from the author, we used change in BMI standard deviation score (SDS) as our second choice and change in percent overweight as the third choice. Because we combined different outcomes, we analyzed standardized effect sizes. As a sensitivity analysis, we also ran meta-analyses to examine only those that reported BMI change. All meta-analyses were conducted by using RevMan 4.2 (Copenhagen: The Nordic Cochrane Center, The

qualitative synthesis because of significant heterogeneity in setting, age range, intervention approach, weight or other outcome reported, and length of follow-up. For the behavioral interventions, we conducted meta-analyses of short-term and maintenance outcomes separately. We performed a sta-

Cochrane Collection). We report additional details, including assumptions for modeling BMI change at various ages, in Appendix 1.

The AHRQ funded this work, provided project oversight, and assisted with internal and external review of the draft evidence synthesis but had no role in the design, conduct, or reporting of the review. We worked with 4 USPSTF members to develop the analytic framework, set the review scope, and resolve methodologic issues during the conduct of the review. The draft evidence synthesis was reviewed by 8 external peer reviewers and was revised for the final version.

RESULTS

KQ1: Do Weight-Management Programs (Behavioral, Combined Behavioral and Pharmacologic) Reduce or Stabilize Measured BMI, Weight, or Adiposity in Children and Adolescents Who Are Obese (≥95th BMI Percentile) or Overweight (84th–94th Percentile)?

Behavioral Interventions

We identified 11 fair- or good-quality behavioral intervention trials in 14 publications in which short-term weight outcomes (6–12 months after entry) in 1099 obese or overweight children and adolescents aged 4 to 18 years (Table 1) were reported.[16–29] The majority of the studies were published in 2005 or later, with only 2[22,23] included in the previous USPSTF review.[30] At study entry, most participants in these trials exceeded the 95th percentile for BMI and, in some cases, met adult criteria for class I obesity. We rated 6 of the trials[16,19,20,22,25,26] as good quality and the remaining trials as fair quality. Most trials that used randomization failed to report whether treatment allocation was blinded, and most trials did not report whether those conducting follow-up assessments were blind to the treatment condition. Many of the

trials were also quite small; only 3 trials had treatment arms with >40 participants at follow-up. Although several trials reported retention of ≥90%, retention in 3 trials was <70%.[16,17,23]

All 11 behavioral intervention trial results were consistent with a beneficial effect on BMI, BMI SDS, or percentage overweight, although not all differences were statistically significant (Table 1; Fig 3). At 6 to 12 months' follow-up, intervention groups were 0.3 to 3.3 kg/m² lighter than controls as a result of weight loss as well as weight-gain prevention among treated participants. Intervention effectiveness tended to increase with more intensive interventions, with the largest effects (between-group BMI differences of 1.9–3.3 kg/m²) reported for 3 moderate- to high-intensity comprehensive weight-management programs.[16,18,24] Data for noncomprehensive weight-management programs were limited and showed mixed results.

Meta-analysis confirmed that among comprehensive weight-management programs, moderate- to high-intensity interventions had a homogeneous ($I^2 = 0\%$), significantly larger effect on weight outcomes (standardized mean difference [SMD]: −1.01 [95% confidence interval (CI): −1.24 to −0.78]) than very low-intensity interventions (SMD: −0.39 [95% CI: −0.66 to −0.11]) (Fig 3). Parallel analyses on the subset of trials that reported BMI change, calculating weighted mean differences, resulted in a similar pattern of results but with greater statistical heterogeneity ($I^2 = 64\%$) (figure not shown). In the single comprehensive medium- to high-intensity trial with 12 additional months of follow-up, benefits were maintained.

It should be noted that the standardized effect based on pooling the 3 comprehensive, very low-intensity (<10-hour) intervention trials showed a homogeneous ($I^2 = 0\%$), statistically significant, short-term benefit ($P = .006$). In the single trial with 6 additional months of

follow-up, benefits were not maintained.[20] Two of these trials were conducted in primary care settings and recruited participants through primary care. Although the data are sparse and must be interpreted cautiously, they suggest that primary care–based interventions of relatively low intensity could potentially improve BMI a modest amount, at least in the short-term.

Combined Behavioral and Pharmacologic Interventions

We identified 7 trials (all fair- or good-quality randomized, controlled trial [RCTs])[31–37] for which short-term weight effects of either sibutramine ($N = 715$) or orlistat ($N = 579$) plus behavioral counseling in adolescents aged 12 to 19 years (Table 2) were reported. All of the trials compared active medication plus behavioral counseling to placebo plus the same behavioral counseling. All participants met a BMI-based criteria for obesity (either above the age- and gender-specific 95th–97th percentile or at a BMI of >30 kg/m²), with the mean BMI typically 35 to 38 kg/m² at baseline. Of the 6 trials for which funding sources were reported, all but 1 was funded completely or partially by the pharmaceutical industry.

Two of the trials were large, multicenter RCTs conducted in North America: 1 trial of sibutramine[32] and 1 of orlistat.[33] Both evaluated 12 months of treatment and revealed it to be superior to placebo. In the large sibutramine trial ($N = 498$), mean BMI reduction in the sibutramine-treated group was 2.9 kg/m² compared with 0.3 kg/m² in the control group ($P < .001$).[32] In the large orlistat trial ($N = 539$), BMI reduction in the orlistat-treated group was 0.55 kg/m² compared with a gain of 0.3 kg/m² in the control group ($P < .001$).[33] Results from trials in which 6 months of sibutramine or orlistat were evaluated also favored the intervention groups

TABLE 1 Characteristics and Results of Behavioral Interventions Trials

Study Reference, Setting, and Design	Participants			Baseline BMI, Mean ± SD	Intervention Components	Net Intervention Hours (I-C)	Short-Term BMI Change, Mean Change (SD of Change)	Maintenance of BMI Change, Mean Change (SD of Change)
	N	Age, y	% Female					
Comprehensive programs								
Moderate- or high-intensity interventions								
Savoye et al[16] (2007), health care, RCT	174	8–16	61	I, 35.8 ± 7.6; C, 36.2 ± 6.2	I, D, PS, B, F, C, brief counseling	97.5	12 mo (after treatment)[a,b]: I, −1.7 ± 3.1 (c); C, 1.6 ± 3.2 (c)	NR
Reinehr et al[18] (2006) and Reinehr et al[28] (2007), health care, CCT	240	6–14	47	I, 27.0 ± 4.4 (c); C, 26.1 ± 4.0 (c)	I, D, PS, B, F, M; C, no treatment	76	12 mo (after treatment)[a,b]: I, 0.1 ± 1.9 (c); C, 2.0 ± 1.8 (c)	24 mo (12 mo after treatment)[a,b]: I, 1.2 ± 2.4 (c); C, 2.9 ± 1.9 (c)
Nemet et al[24] (2005), child health and sports center, RCT	54	6–16	44	I, 27.7 ± 3.6; C, 28.0 ± 5.2	I, D, PS, B, F, C, nutritional counseling	35.75	12 mo (9 mo after treatment)[a,b]: I, −1.5 ± 2.1 (c); C, 0.6 ± 2.5 (c)	NR
Low-intensity interventions								
Mellin et al[39] (1987), health care, RCT	66	12–18	79	% overweight[c]: I, 36.55% (NR); C, 29.5% (NR)	I, D, PS, B; C, no treatment	24	NR	15 mo (12 mo after treatment)[b] (% overweight[c]): I, −9.9 ± 15.0 ($P < .01$)[a]; C, −0.1 ± 13.2 (NS)[a]
Golley et al[19] (2007), health care, RCT	111	6–9	64 (c)	24.3 ± 2.6 (I1, I2, and C combined)	I1, D, P, F, M; I2, D, PS, B, F, M; C, wait list	10.3 (I1), 22 (I2)	12 mo (7 mo after treatment) (BMI SDS[c]): I1, −0.15 ± 0.47; I2, −0.24 ± 0.43; C, −0.13 ± 0.40	NR
Doyle et al[25] (2008) and Celio[27] (2006), e-mail and Internet, RCT	83	12–18	63	I, 34.6 ± 7.8; C, 33.9 ± 6.9	I, D, P, B; C, information only	16	8 mo (4 mo after treatment)[d]: I, −0.2 ± 1.8; C, 0.4 ± 2.1	NR
Senediak and Spence[23] (1985), setting NR, RCT	35	6–12	34 (estimated)	% overweight[c]: I1, 32.9 ± 14.0; I2, 35.9 ± 12.2; C, 36.7 ± 5.5	I1, D, P, B, F; I2, D, P, B, F; C, social support, relaxation, mood monitoring	12 (I1, I2, C)	6 mo (3–5 mo after treatment)[b,e] (% overweight[c]): I1, −13.0 ± 6.3 (c); I2, −19.2 ± 5.4 (c); C, −5.9 ± 6.0 (c)	NR
Very low intensity								
Gillis et al[17] (2007), health care, RCT	27	7–16	NR	BMI SDS: I, 1.98 ± 0.21; C, 2.16 ± 0.34	I, D, P, B; C, 1 counseling session	8	6 mo (after treatment) (BMI SDS[c]): I, −0.045 ± 0.19; C, 0.075 ± 0.08	NR
McCallum et al[20] (2005) and McCallum et al[29] (2007), primary care, RCT	163	5–9	52	I, 20.5 ± 2.2; C, 20.0 ± 1.8	I, D, P, B, F, C, usual primary care	4	9 mo (6 mo after treatment): I, 0.5 ± 1.1 (c); C, 0.8 ± 1.0 (c)	15 mo (12 mo after treatment): I, 1.2 ± 1.5 (c); C, 1.2 ± 1.1 (c)
Saelens et al[22] (2002), primary care, RCT	44	12–16	40	I, 31.0 ± 3.5; C, 30.7 ± 3.1	I, D, P, B; C, usual primary care	3.8	7 mo (3 mo after treatment)[b,e]: I, 0.1 ± 2.0 (c); C, 1.4 ± 1.7 (c)	NR

TABLE 1 Continued

Study Reference, Setting, and Design	Participants			Baseline BMI, Mean ± SD	Intervention Components	Net Intervention Hours (I-C)	Short-Term BMI Change, Mean Change (SD of Change)	Maintenance of BMI Change, Mean Change (SD of Change)
	N	Age, y	% Female					
Focused interventions								
Very low or low intensity								
Flodmark et al[38] (1993), health care, CCT	93	10–11	52 (c)	I1, 25.5 ± 2.3 (c); I2, 24.7 ± 1.8 (c); C, 25.1 ± 2.5 (c)	I1, D, P, F; I2, D, P, F, M; C, matched controls, no treatment	12 (I1), 24 (I2)	NR	~48 mo (30–34 mo after treatment)[b,e]: I1, 1.6 ± 2.0 (c); I2, 1.1 ± 1.8 (c); C, 2.8 ± 2.3 (c)
Rooney et al[21] (2005), community, RCT	98 families, 353 people	5–12	51	I1: 21.1 ± 6.2; I2, 22.2 ± 6.2; C, 21.9 ± 6.0	I1, P, F, pedometer; I2, D, P, F, pedometer; C, no treatment	3 (I1), 21 (I2)	9 mo (6 mo after treatment)[d]: I1, −0.4 ± 1.0 (c); I2, −0.9 ± 1.3 (c); C, −0.4 ± 1.1 (c)	NR
Epstein et al[26] (2008), health care, RCT	70	4–7	47 (c)	I, 19.3 ± 2.5; C, 19.1 ± 3.5	I, P, F, use of device to limit TV and computer time; C, F, no device	Hours NR, likely very low	24 mo (after intervention)[b,f] (BMI SDS[c]): I, −0.24 ± 1.9; C, −0.13 ± 2.1	NR

Intensity categories: very low, <10 hours; low, 10 to 25 hours; moderate, 26 to 75 hours; and high, >75 hours. I indicates intervention group; C, control group; (c), calculated; D, dietary counseling; PS, organized physical activity sessions; B, behavioral modification principles used to address diet and physical activity changes; F, family or parent was a target of the intervention; M, mental health treatment beyond behavior modification for diet and physical activity; P, physical activity counseling; CCT, controlled clinical trial; NR, not reported; NS, not significant; TV, television.

[a] *P* < .01.
[b] *P* < .05.
[c] BMI not reported, so other outcome is listed.
[d] Unpublished data supplied by author.
[e] *P* < .05.
[f] Data were not provided for the 12-month midtreatment effect, so the 24-month effect is provided, which is an underestimate of the 12-month effect. Graphical data indicated significant between-group differences at 12 months, so the 24-month data are considered statistically significant and used in the meta-analysis of short-term effects.

over placebo, although not all the results were statistically significant.

KQ2: Do Weight-Management Programs (Behavioral, Combined Behavioral and Pharmacologic) Help Children and Adolescents Who Are Initially Obese or Overweight Maintain BMI, Weight, or Adiposity Improvements After the Completion of an Active Intervention?

Behavioral Interventions

As described above, only 2 trials provided repeated measures to directly assess weight-change maintenance.[18,20] However, 2 other trials[38,39] reported longer-term outcomes that fit our "maintenance" definition. Thus, 4 available studies reported on 562 children and adolescents at least 12 months after completing a weight-management intervention (15–48 months since beginning treatment) (Table 1). We did not combine these trials quantitatively, because they each fell into different a priori groups on the basis of comprehensiveness and intensity. We provide a forest plot of the 4 trials showing standardized effect sizes in Fig 4. Three of the 4 trials revealed that intervention groups had beneficial changes in BMI or percent overweight compared with controls.[18,38,39] In the 2 effective trials for which BMI change was reported,[18,38] BMI increased by 1.7 kg/m² less in the intervention group than in the control group. In the third effective trial in which a non-BMI metric was used,[39] the intervention participants dropped from 36.5% overweight to 26.6% overweight, whereas the degree of overweight in the control participants was unchanged.

Combined Behavioral and Pharmacologic Interventions

Longer-term follow-up of weight loss after active treatment with sibutra-

Study or subcategory	N	Treatment Mean (SD)	N	Control Mean (SD)	SMD (random) 95% CI	Weight, %	SMD (random) 95% CI
01 Comprehensive, Medium-to-High Intensity							
Savoye et al[16] (2007)	105	-1.70(3.14)	69	1.60(3.17)		38.30	-1.04 [-1.37 to -0.72]
Reinehr et al[18] (2006)	174	0.10(1.90)	37	2.00(1.80)		36.49	-1.01 [-1.37 to -0.64]
Nemet et al[24] (2005)	20	-1.50(2.10)	20	0.60(2.50)		25.21	-0.89 [-1.54 to -0.24]
Subtotal (95% CI)	299		126			100.00	-1.01 [-1.24 to -0.78]
Test for heterogeneity: $\chi^2 = 0.17$, $df = 2$ ($P = .92$), $I^2 = 0\%$							
Test for overall effect: $z = 8.70$ ($P < .00001$)							
02 Comprehensive, Low Intensity							
Golley et al[19] (2007)	31	-0.24(0.43)	31	-0.13(0.40)		41.21	-0.26 [-0.76 to 0.24]
Celio Doyle et al[25] (2007)	40	-0.15(1.75)	40	0.39(2.08)		44.47	-0.28 [-0.72 to 0.16]
Senediak et al[23] (1985)	10	-19.22(5.34)	7	-5.86(5.95)		14.32	-2.27 [-3.57 to -0.97]
Subtotal (95% CI)	81		78			100.00	-0.67 [-1.43 to 0.09]
Test for heterogeneity: $\chi^2 = 8.52$, $df = 2$ ($P = .01$), $I^2 = 76.5\%$							
Test for overall effect: $z = 1.72$ ($P = .09$)							
03 Comprehensive, Very Low Intensity							
Gillis et al[17] (2007)	11	-0.04(0.19)	7	0.08(0.08)		20.18	-0.72 [-1.71 to 0.26]
McCallum et al[20] (2007)	73	0.50(1.10)	80	0.80(1.00)		48.55	-0.28 [-0.60 to 0.03]
Saelens et al[22] (2002)	18	0.10(2.00)	19	1.40(1.70)		31.27	-0.69 [-1.35 to -0.02]
Subtotal (95% CI)	102		106			100.00	-0.39 [-0.66 to -0.11]
Test for heterogeneity: $\chi^2 = 1.62$, $df = 2$ ($P = .44$), $I^2 = 0\%$							
Test for overall effect: $z = 2.76$ ($P = .006$)							
04 Focused Interventions, Low or Very Low Intensity							
Epstein et al[26] (2008)	35	-0.24(1.89)	32	-0.13(2.09)		52.48	-0.05 [-0.53 to 0.42]
Rooney et al[21] (2005)	24	-0.87(1.27)	27	-0.43(1.09)		47.52	-0.37 [-0.92 to 0.19]
Subtotal (95% CI)	59		59			100.00	-0.19 [-0.55 to 0.17]
Test for heterogeneity: $\chi^2 = 0.70$, $df = 1$ ($P = .40$), $I^2 = 0\%$							
Test for overall effect: $z = 1.02$ ($P = .31$)							

-4   -2   0   2   4
Favors treatment   Favors control

FIGURE 3
Pooled analysis:short-term weight change effect size (ES) of behavioral interventions (KQ1). SMD indicates standardized mean difference.

mine or orlistat was discontinued was not reported for any trial.

KQ1a and KQ2a. Do Behavioral or Combined Behavioral and Pharmacologic Weight-Management Programs Lead to Other Positive Outcomes (eg, Improved Behavioral or Physiologic Measures, Decreased Childhood Morbidity, Improved Childhood Functioning, or Reduced Adult Morbidity and Mortality)?

Behavioral Interventions

Only approximately half ($n = 7$) of the weight-management studies also reported effects on lipids, blood pressure, glucose/insulin measures, or adiposity. Minimal impact was reported on lipid levels, blood pressure, diet, physical activity level, and psychosocial measures (see full report for greater detail).[40] We have low confidence in these results because of incomplete reporting of these outcomes across studies, including the possibility of selective reporting.

Adiposity was the most common additional measure, reported in 5 of 13 behavioral counseling trials.[16,19,23,24,38] All 5 trials revealed a greater reduction in adiposity after the intervention condition compared with the control condition, including one that did not show differences in the primary weight outcome.[19] Two[16,18] of the 3[16,18,19] trials that reported on fasting insulin and insulin resistance, as measured by the homeostasis model assessment of insulin resistance (HOMA), showed more favorable results in intervention groups relative to the control group. Two[24,38] of the 3 trials[17,24,38] that reported on physical fitness revealed that intervention-group participants were more fit than those in the control groups.

Combined Behavioral and Pharmacologic Interventions

All 7 trials of combined behavioral and pharmacologic interventions measured effects on lipids, and almost all

($n = 6$) also measured blood pressure and waist circumference. Trials of sibutramine generally reported favorable reductions in waist circumference among patients who were taking sibutramine compared with placebo. In addition, the large 12-month trial of sibutramine reported greater improvements in high-density lipoprotein cholesterol and reductions in triglycerides, serum insulin, and the homeostasis model assessment of insulin resistance, compared with the placebo group, although no differences were found for the shorter-term trials. Low-density lipoprotein cholesterol and fasting serum glucose levels were not different between groups for any of the sibutramine trials.

Among patients taking orlistat, Chanoine et al[33] reported that both waist circumference and hip circumference decreased more in those who were receiving active treatment compared with placebo at 12 months ($P = .01$ for

TABLE 2 Characteristics and Results of RCTs of Pharmacologic Antiobesity Treatments Among Adolescents According to Drug Type

| Source Country | Participants | | | Intervention Characteristics | Length of Treatment, mo | Baseline BMI, kg/m² | | Length of Follow-up, mo | Δ BMI, kg/m², (95% CI, if available) | | |
	No. Randomly Assigned	Age, y	% Female			I	C		I	C	P
Sibutramine											
Berkowitz et al[31] (2003), United States	82	13–17	67	5–10 mg of sibutramine + BI or placebo + BI	6	37.5 ± 4.0	38.0 ± 3.6	6	−3.2a	−1.5a	.001b
Berkowitz et al[32] (2006), United States	498	12–16	66	10–15 mg of sibutramine + BI or placebo + BI	12	36.1 ± 3.8	35.9 ± 4.1	12	−2.9	−0.3	<.001
Garcia-Morales et al[34] (2006), Mexico	51	14–18	56	10 mg of sibutramine + BI or placebo + BI	6	35.1 ± 5.3	36.6 ± 5.2	6	−3.4 (−2.5, −4.2)	−1.8 (−0.9, −2.6)	<.005c
Godoy-Matos et al[35] (2005), Brazil	60	14–17	82	10 mg of sibutramine or placebo	6	37.5 ± 3.8 (F), 37.6 ± 4.3 (M)	35.8 ± 4.2 (F), 37.4 ± 1.9 (M)	6	−3.6 ± 2.5	−0.9 ± 0.9	<.001
Van Mil et al[37] (2007), Netherlands	24	12–17	54	5–10 mg of sibutramine + BI or placebo + BI	3d	30.1 ± 4.5	33.3 ± 5.0	6	−0.8e	−1.4e	NR
Orlistat											
Chanoine et al[33] (2005), United States and Canada	539	12–16	67	120 mg of orlistat TID + BI or placebo + BI	12	35.7 ± 4.2	35.4 ± 4.1	12	−0.55	0.3	<.001
Maahs et al[36] (2006), United States	40	14–18	67	120 mg of orlistat TID + BI or placebo + BI	6	39.2 ± 1.2	41.7 ± 2.6	6	−1.3 ± 1.6	−0.8 ± 3.0	NS

I indicates intervention group; C, control group; BI, behavioral treatment; TID, three times per day; NS, not significant; NR, not reported; F, female; M, male.
a Calculated on the basis of average BMI at baseline and average percentage change in BMI for each group (intervention: −8.5% ± 6.8%; control: −4.0% ± 5.4%).
b On the basis of comparison of percentage change in BMI between groups.
c Result of analysis-of-variance testing interaction between treatment group and time.
d Patients were treated with behavioral treatment + sibutramine or placebo for 3 months and then behavioral treatment alone for 3 months.
e Calculated on the basis of differences reported baseline to 3 months and 3 to 6 months.

both in least-squares mean analysis). Adiposity results were inconsistent across 2 orlistat trials. Levels of low-density lipoprotein, high-density lipoprotein, triglycerides, fasting plasma glucose, and insulin were not different between groups in either orlistat trial. Chanoine et al, however, reported a small reduction in diastolic blood pressure (not systolic blood pressure) in the orlistat-treated group (−0.51 mm Hg) compared with an increase in the patients on placebo (1.30 mm Hg) (P = .04).

KQ3: What Are the Adverse Effects of Weight-Management Programs (Behavioral, Combined Behavioral, and Pharmacologic) That Attempt to Stabilize, Reduce, or Maintain BMI?
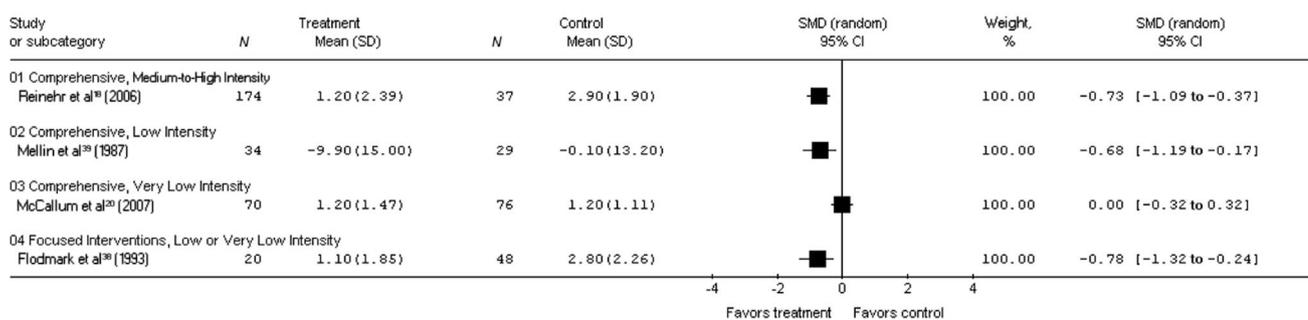
Adverse effects are summarized here, with more detailed accounts in the full evidence review.[40]

Behavioral Interventions

Six[16,19,20,22,25,39] of 13 trials on which weight outcomes were reported also revealed potential harms of behavioral weight-management interventions. Two other trials[41,42] that did not meet treatment inclusion criteria reported injury rates among obese children in exercise programs.

We found no evidence that behavioral intervention programs may be harmful, except they perhaps mildly increase injury risk with exercise. Among the 6 weight-management trials, none showed differences in height,[16,19] eating-disorder pathology,[20,22,25] or depression.[39] From the 2 trials in which injuries in exercise programs were examined, 1 fracture was reported for the intervention groups (n = 114), whereas no children in the control groups reported injuries.[41,42] More robust harms assessment and reporting would reassure us that these programs are as safe as they seem.

Study or subcategory	N	Treatment Mean (SD)	N	Control Mean (SD)	SMD (random) 95% CI	Weight, %	SMD (random) 95% CI
01 Comprehensive, Medium-to-High Intensity							
Reinehr et al[18] (2006)	174	1.20 (2.39)	37	2.90 (1.90)		100.00	-0.73 [-1.09 to -0.37]
02 Comprehensive, Low Intensity							
Mellin et al[39] (1987)	34	-9.90 (15.00)	29	-0.10 (13.20)		100.00	-0.68 [-1.19 to -0.17]
03 Comprehensive, Very Low Intensity							
McCallum et al[20] (2007)	70	1.20 (1.47)	76	1.20 (1.11)		100.00	0.00 [-0.32 to 0.32]
04 Focused Interventions, Low or Very Low Intensity							
Flodmark et al[38] (1993)	20	1.10 (1.85)	48	2.80 (2.26)		100.00	-0.78 [-1.32 to -0.24]

-4   -2   0   2   4
Favors treatment   Favors control

FIGURE 4

Plot of maintenance effect sizes (ES) of behavioral interventions (KQ2). SMD indicates standardized mean difference.

Combined Behavioral and Pharmacologic Interventions

All sibutramine trials evaluated the effects on heart rate and systolic and diastolic blood pressure. Three[31,32,34] of the 5 sibutramine trials revealed greater increases in heart rate and systolic and/or diastolic blood pressure in the sibutramine-treated group compared with the control group after 6 or 12 months of treatment. These differences, however, were small in magnitude. In the 12-month, multicenter sibutramine trial, tachycardia occurred more commonly in the sibutramine-treated group than in the control group (12.5% vs 6.2%; $P = .049$). The number of withdrawals that resulted from tachycardia, however, was similar between groups.

None of the sibutramine trials showed group differences in the overall rates of having any adverse event, any serious adverse event, or discontinuation caused by adverse events. In the large 12-month sibutramine trial, serious adverse events were reported by 2.7% of patients in the sibutramine-treated group and <1% of those in the control group.[32] Only 1 of these events (excessive nausea and vomiting) was thought to be related to sibutramine. No adverse effect on growth and maturation was found.[32,34] Abdominal complaints and constipation were also found to be statistically higher in the sibutramine-treated group in the shorter-term trials.

In the trials in which orlistat was tested, rates of serious adverse effects and discontinuation of therapy resulting from adverse effects were low and similar between groups. In the Chanoine et al trial,[33] only 1 serious adverse event was thought to be study related: asymptomatic cholelithiasis in a 15-year-old girl who had lost 15.8 kg by the time of the event. In the Maahs et al trial,[36] 1 suicide death of a patient who was under a psychiatrist's care occurred in the orlistat-treated group. No deaths occurred in the group on placebo.

Gastrointestinal adverse effects were common among patients taking orlistat. In the largest trial, 50% reported fatty or oily stools compared with 8% of those on placebo, and 20% to 30% reported oily spotting, oily evacuation, abdominal pain, fecal urgency, or flatus with discharge compared with 2% to 11% on placebo. Note that 9% of orlistat patients reported fecal incontinence, compared with <1% of patients on placebo. However, researchers also reported that the gastrointestinal adverse effects were mostly of mild-to-moderate intensity and led to discontinuation of treatment among only 2% of orlistat patients.

Although in both orlistat trials vitamin A, D, and E levels were measured and levels were not different between groups, multivitamin supplementation was provided for all participants in the orlistat trials. No between-group differences were reported in quality of life,[36] growth,[33] bone mineral density,[33] or sexual maturation.[33]

DISCUSSION

We evaluated 13 behavioral intervention trials conducted in 1258 overweight or obese children and adolescents aged 4 to 18 years. We also evaluated 7 trials that combined pharmacologic treatments (sibutramine or orlistat) with behavioral interventions in a total of 1294 obese adolescents aged 12 to 18 years. With the exception of 4 behavioral intervention trials[22,23,38,39] and 1 pharmacologic trial for sibutramine,[31] all of the trials reviewed for this report were newly available since the previous USPSTF review.

Behavioral Interventions

We found that comprehensive medium- to high-intensity behavioral interventions for obese children and adolescents (>95th to 97th percentile for age and gender) aged ≥6 years can effectively produce short-term improvements in weight and probably also in adiposity. The weight change associated with these interventions was generally modest (1.9–3.3 kg/m^2 difference between groups in mean change in BMI after 6–12 months). Modeling this effect on BMI over 1 year suggests a relative reduction in weight gain with continuing growth in treated

participants compared with controls, rather than weight loss per se. For an 8-year-old boy or girl, the largest BMI difference (3.3 kg/m^2) would translate to an ∼13-lb difference after 12 months (assuming the 50th percentile for height for ages 8 and 9 years and ∼2 in of growth). For a 12-year-old boy or girl, this would translate to a 17- to 18-lb difference under similar assumptions. In girls aged 16 years, this BMI difference would translate to ∼19 lb, whereas for boys aged 16 years the difference would be between 22 and 23 lb when using similar assumptions. Limited evidence (1 study) suggests that these improvements can be maintained over the 12 months after treatment. Limited evidence also suggests that reductions in cardiovascular risk factors do not routinely occur, but improvements in insulin resistance may be seen in the setting of medium- to high-intensity comprehensive interventions. Firm conclusions are difficult to draw, because these outcomes were not consistently reported in the behavioral intervention literature, with no more than 4 studies reporting any 1 risk factor. Because children and adolescents included in behavioral interventions tended to be less obese than those in pharmacologic treatment trials, they might also be less likely to have elevated cardiovascular or diabetes risk factors; thus, these differences would be difficult to detect.

Medium- to high-intensity interventions were conducted in specialty health care (such as pediatric obesity referral clinics) or similar settings. Although these interventions would likely not be feasible for implementation in a primary care setting, they would be feasible for a health plan to offer, thus making them potentially available for referral from primary care. Lower-intensity interventions that might be feasible for primary care had

a more modest, less consistent BMI benefit.

Behavioral weight-management interventions apparently have few harms. On the basis of limited study reporting, we found no evidence of adverse effects on growth, eating-disorder pathology, or mental health. These findings are consistent with data from several noncomparative studies, including 1 that followed 158 children for 10 years and revealed that weight loss was not related to growth in height in a multivariate model that controlled for child age, gender, baseline height, baseline percent overweight, and midparental height.[43] We also found little risk of exercise-induced injuries from behavioral interventions. Although these findings are reassuring, they are tentative because of incomplete reporting, because fewer than half of the behavioral intervention trials reported any potential adverse effects.

Combined Pharmacologic and Behavioral Interventions

Pharmacologic adjuncts to behavioral interventions have been studied only in obese adolescents aged 12 to 18 years who met adult criteria for class II obesity (mean BMI of 35–40 kg/m^2 at trial entry); these adjuncts provide superior benefits compared with behaviorally based treatment alone. In a large sibutramine trial, participants who received 10 to 15 mg/day of sibutramine treatment plus a behavioral intervention decreased their BMI by 2.9 kg/m^2 after 12 months, corresponding to an average weight reduction of 6.5 kg (14 lb). This is compared with a BMI reduction of 0.3 kg/m^2, corresponding to a weight gain of 1.9 kg (4.2 lb), among trial participants who received a behavioral intervention plus placebo. Although the effect of sibutramine seems to be larger than that of orlistat, direct head-to-head comparisons of pharmacologic agents in combination

with the same, proven behavioral interventions would be required to confirm this impression.

The minimal behavioral intervention provided to all participants in sibutramine and orlistat trials consisted of advice to follow a calorie-restricted diet (eg, 2100 kJ/day [500 kcal/d] deficit) and meet physical activity goals (eg, at least 30 minutes of aerobic activity per day). All but 1 trial[35] also included a behavior-management program that ranged in intensity from 7 to 19 sessions with a dietitian, psychologist, or psychiatrist. Details and fidelity of the behavioral interventions in these combined treatment trials is unknown; therefore, it is difficult to compare the findings of these trials with those of the behavioral trials.

Although trial participants who received sibutramine developed cardiovascular adverse effects (tachycardia or mild relative increases in systolic or diastolic blood pressure), the clinical significance of the effects are unknown. For orlistat, mild-to-moderate gastrointestinal adverse effects were common, but few participants (2%) discontinued treatment because of these adverse effects. The impact that gastrointestinal effects would have on treatment adherences outside a trial setting is unclear. Limited evidence also suggests no adverse effects on growth or maturation for sibutramine or orlistat. Serious adverse effects were also uncommon. Risks of these medications should be weighed against the fact that both drugs lack evidence of persistence of weight reduction after active treatment ends.

Applicability to Real-World Settings

Two of the behavioral intervention programs specifically addressed the use of very low-intensity interventions (∼4 hours of total intervention time) that could be integrated into primary care.[20,22] One of these programs im-

proved short-term weight loss[22] by using support staff to provide adjunctive care through mail and telephone counseling, thus relieving the primary care provider of some of the burden of conducting the intervention. Dissemination research is needed to determine widespread feasibility.

Higher-intensity programs conducted in specialty care settings may also be feasible for many health care settings, perhaps at little extra cost, including adapting the detailed protocols developed for the trials included in this review. The year-long Bright Bodies weight-management program was conducted at a pediatric obesity clinic in the United States and accepted children who ranged in age from 8 to 16 years.[16] The Bright Bodies program involved ~98 total hours of contact through an ongoing educational program (50 minutes/week for 6 months, and then biweekly) that provided information on nutrition, physical activity, behavior-change strategies, coping skills, and relapse prevention and through organized 50-minute exercise sessions twice per week during the first 6 months, then once every 2 weeks during the next 6 months. Parents or caregivers attended all educational sessions. This program was facilitated by a registered dietitian or social worker and an exercise physiologist. A team of professionals in these or related fields would likely have the requisite training to conduct this type of program without extensive additional training. Third-party payment for these types of programs or indication of their cost-effectiveness would assist their uptake in the real world.

The adolescents in whom effective pharmacologic treatments have been studied are in the upper percentiles of the BMI range or have met criteria for class II or III obesity in adults and, thus, represent a small fraction of the 16% of girls and 18% of boys aged 12 to 19

years who are obese. Recent estimates indicated that only 1% to 3% of 13- to 17-year-old girls and 3% to 5% of 13- to 17-year-old boys have BMIs that are at the ≥99th percentile for their age and gender.[44] On the basis of evidence, the use of pharmacologic treatment would be limited primarily to this small group of adolescents.

Limitations

The quality and volume of research on treating child and adolescent obesity has improved substantially since our previous USPSTF review, in which we found study concerns echoed by others,[45] including small sample sizes, high attrition rates (among other quality issues), less-than-ideal outcome measures, and highly heterogeneous treatment approaches. Although several of the newly published trials had >100 participants, retention remains somewhat problematic, with most reporting retention rates of <90%. Although outcome measurement has improved, a lingering quality issue is that the blinding procedures for treatment allocation and outcomes assessment were often not described. Treatment approaches remain heterogeneous, and effective treatment trials should be replicated.

The available treatment data for pharmacologic approaches remain limited. There are only 2 weight-loss medications that have been studied (sibutramine and orlistat), with few randomized trials overall, and only 1 large-scale trial of each of the medications. No trials have been conducted among children aged ≤11 years, so no conclusions can be drawn regarding efficacy or safety for those in that age group. We found no data on maintenance of treatment effect or safety after the 6 to 12 months of active treatment ended.

A limitation to our meta-analysis is that we combined different measures of weight change that had different un-

derlying assumptions and distributions. We attempted to minimize the effects of this by analyzing BMI change whenever it was available so that the majority of the trials did use a common metric. Results of a qualitative examination of the forest plots indicated no obvious bias in the trials that used measures other than BMI change, and the pattern of results was similar when the meta-analysis was limited to studies that reported BMI or BMI change.

CONCLUSIONS

The research on weight-management interventions for obese children and adolescents has improved in terms of quality and quantity in the past several years. Current research suggests that behavioral interventions are probably safe in children aged 4 to 18 years and can be effective, particularly moderate- to high-intensity comprehensive programs. Combined behavioral-pharmacologic interventions may be useful for obese adolescents, particularly if research confirms that weight loss can be maintained after pharmacologic treatment ends.

The research we reviewed is generally consistent with a recently proposed model of a stepped-care approach to weight-management treatments that increases intensity (and treatment-associated risk) according to degree of excess weight, age/maturation, health risks, and motivation.[4,6] This stepped-care model, has been recommended by the Expert Committee (which was convened by the American Medical Association and co-funded in collaboration with the Department of Health and Human Services' Health Resources and Services Administration and the Centers for Disease Control and Prevention [CDC]). Approaches range from simple preventive messages aimed at younger children and those who are not overweight, to weight-management interventions that

increase in intensity as the child becomes more obese or has more weight-related health problems.

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APPENDIX 1: DETAILED METHODS

KQs and Analytic Framework

Using the methods of the USPSTF,[10] we developed 3 KQs (with 6 sub-KQs) and an analytic framework (Fig 3) in conjunction with members of the USPSTF to update its 2005 recommendation on screening for childhood overweight and obesity.[30] These KQs were de-

signed to evaluate the effectiveness and safety of behavioral and pharmacologic treatments for overweight and/or obese children. Each KQ focused on a different area of the evidence. KQ1 evaluates the effectiveness of interventions in reducing or stabilizing weight that use short-term outcomes (6–12 months since enrolling in treatment), whereas KQ2 focuses on the maintenance of BMI improvements through medium-term outcomes (between 1 and 5 years since enrollment and at least 12 months since treatment ended). KQ3 assesses adverse effects of behavioral and pharmacologic interventions. KQ1a and KQ2a consider other beneficial outcomes that arise from the interventions. KQ1b, KQ2b, KQ1c, and KQ2c evaluate whether specific program components and population or environmental factors can be identified for short- or longer-term effective weight-management programs.

Literature Search Strategy

We searched for systematic reviews in Ovid Medline, PsycINFO, the Database of Abstracts of Reviews of Effects (DARE), the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CCRCT), and the Education Resources Information Center (ERIC) from 2004 to 2007. We selected relevant, good-quality systematic reviews when available to assist in conducting our literature search. Quality criteria were based on USPSTF methods,[10] supplemented by NICE methodology.[11] A 2006 comprehensive NICE report was based on a series of systematic reviews and addressed the prevention and management of obesity in adults and children.[11] Relevant portions of this report served as a basis for the primary search for the literature included in the current report. The NICE report only included orlistat and sibutramine. Therefore, we used another good-quality review of pharmacologic treatments[9] as the basis for our search for pharmacologic treatments. We conducted update searches in Ovid Medline, PsycINFO, DARE, CDSR, CCRCT, and ERIC from 2005 (2003 for pharmacologic treatments) to June 10, 2008, to identify literature that was published after the search dates of these reports (Appendix 2). The literature search and reports[9,11] were supplemented by hand-searching the reference lists of other good-quality reviews of childhood obesity treatment,[5,12,13,30,46] suggestions from experts, and reviewing reference lists of included trials. We did not search for data from non–peer-reviewed sources.

Article Review and Data Abstraction

Two investigators independently reviewed 2786 abstracts and 369 articles. Every abstract was considered for inclusion in each KQ. Discrepancies were resolved by consensus. Detailed inclusion/exclusion criteria can be found in Appendix 3. Briefly, the study population included overweight or obese 2- to 18-year-olds. We excluded studies of children with idiosyncratic weight-management issues that were a result of behavioral, cognitive, or medical factors. Trials were required to be designed to promote weight loss or maintenance and report weight outcomes of at least 6 months, although we included immediate harms when they were reported. Interventions that used mazindol were excluded, because it is no longer used in current practice. Trials were required to have a minimal intervention or control group and randomly assign at least 10 participants in each arm. Only controlled trials (RCTs and controlled clinical trials) were included for efficacy (short-term and maintenance) of behavioral and pharmacologic treatments. Weight-management programs for which pre-specified adverse events that resulted in death, hospitalization, or need for urgent medical or psychiatric treatment were reported were included to assess harms (KQ3) for all treatment modalities, even if 1 of our specified weight outcomes was not reported or did not meet the minimum 6-month follow-up required for the other KQs. In addition, we abstracted all reports of harms or potential harms in included studies.

We limited our consideration of behavioral interventions to those published in or after 1985. We did this because of the dramatic increases in overweight in children that occurred during the 1980s and 1990s and changes in environmental and social factors related to weight gain, such as types and quantities of food readily available to children (eg, fast-food purveyors in school cafeterias, vending machines with soft drinks and candy widely available in schools) and the increased availability of sedentary activities in the home (such as computers, home DVD/video players, and video games), made the generalizability of studies to the current environment questionable.

We only examined other beneficial outcomes (KQ1a and KQ2a), important components of care (KQ1b and KQ2b), and population or environmental factors (KQ1c and KQ3c) by using trials that were included for KQ1 (short-term efficacy) or KQ2 (maintenance efficacy). When reported, we abstracted data on beneficial outcomes, including their impact on comorbidities.

We used a 2-step process to determine which specific intervention components we examined for KQ1b and KQ2b. First, we examined previous literature and identified several factors that may affect weight outcomes in behavioral interventions. These include whether the studies included organized physical activity sessions,[47] behavioral management techniques[30,45] (for dietary and physical activity), or involved parents or families in addition

to the child (clarifying the extent to which parental involvement is important and for what ages).[5,45,48] Second, we examined the distribution of treatment elements between successful and unsuccessful treatment trials. To do this, we coded the age of the participants (C, children only [only included children aged ≤12 years]; A, adolescents only [only included those aged ≥10 years]; and B, both age groups [age range included both younger children and adolescents]). We coded the 3 main components of behavioral interventions as follows: (1) presence of organized physical activity sessions (0, did not provide organized physical activity session; 1, provided organized physical activity); (2) use of behavioral modification principles (0, no or minimal use of behavioral modification principles; and 1, applied behavioral modification principles in treatment); and (3) family involvement (0, no parental involvement beyond consent/receiving materials; 1, parent attended 1–3 sessions, less intensive involvement than child; and 2, parent was also a primary recipient of treatment).

One investigator abstracted data from included studies into evidence tables. A second investigator verified the evidence tables' content. Two investigators independently quality rated all studies by using established design-specific criteria (Appendix 4). Discrepancies were resolved by consensus or consultation with a third investigator. Poor-quality studies were excluded. Eight trials of behavioral interventions[49–56] and 1 of pharmacologic treatment[57] were excluded because they did not meet our quality criteria. See Appendix 5 for more detail on quality rating.

Treatment intensity was categorized according to hours of contact: very low intensity (<10 hours), low intensity (10–25 hours), medium intensity (26–75 hours), or high intensity (>75 hours). Thus, at the least, a high-intensity program would amount to twice-weekly hour-long meetings for 6 months and once-weekly hour-long meetings for the following 6 months, assuming that no more than 2 sessions were missed. The lowest end of the medium-intensity range would involve weekly hour-long meetings for 6 months. Weight outcomes were categorized as short-term (6–12 months since beginning treatment) or medium-term (between 1 and 4 years after beginning treatment and at least 12 months after ending active treatment). The longest follow-up reported in any of the included trials was 4 years. Maintenance was evaluated when possible by using multiple measurements in the same individuals at least 12 months after an active intervention ended or by using single postbaseline measurements in the medium-term. Weight outcomes were abstracted as reported and included many different measures: end-point BMI; absolute change in BMI from baseline; percent change in BMI from baseline; absolute change in BMI SDS from baseline; end point-weight; and absolute change in weight from baseline.

In addition, we evaluated whether a treatment was comprehensive. Interventions were considered comprehensive if they included all of the following elements: (1) counseling for weight loss or healthy diet; (2) counseling for physical activity or a physical activity program; and (3) instruction in and support for the use of behavioral management techniques to help make and sustain changes in diet and physical activity. An intervention was considered to use behavioral management techniques if any of the following elements were described: self-monitoring (having the child document diet-related behaviors or physical activity); stimulus control (modifying factors that seem to serve as cues that lead to inappropriate eating, such as watching television); eating management (techniques specifically aimed at modifying the act of eating, such as eating slowly); contingency management (contingency contracting, with which rewards are given for desired eating or exercise behaviors, weight loss, or treatment adherence); cognitive-behavioral techniques (the attempt to alter maladaptive cognitions related to health behaviors or to use cognitive approaches to enhance behavior change, such as problem-solving to cope with high-risk situations).

Literature Synthesis

This review included studies of both behavioral interventions and pharmacologic agents. We address each type of intervention for each of the 6 KQs listed in our analytic framework. We discuss each pharmacologic agent as a separate intervention.

When possible, data were synthesized by using quantitative methods. For most questions, however, we relied on qualitative synthesis because of significant heterogeneity in setting, age range, intervention approach, weight outcome reported, and timing of outcome reporting among the limited number of studies available for each overall type of intervention. We modeled typical cases to more clearly articulate the magnitude of weight or weight change in pounds. In these cases, we used growth charts published by the CDC[58] to estimate average height for age and to translate between-percentile scores, BMI, and percent overweight (based on CDC-published 50th-percentile scores for weight or BMI). We also used online calculators provided at the CDC Web site[59,60] for calculating BMI and BMI percentiles. We used the following formula to convert BMI to pounds for an illustrative child of a given age and height: pounds $= (\text{BMI} \times \text{inches}^2)/703$.

Studies have reported a variety of weight outcomes including BMI, BMI percentile scores, BMI SD or z scores,

and percent overweight. All of these measures have strengths and limitations. Although BMI is reliably measured and widely used, it can be problematic when averaging BMI change over a wide age range at which younger children would naturally show smaller changes. Percentile scores are helpful when describing weight change in children of many ages, because they are a measure of relative overweight rather than absolute weight. The limitation of percentile scores, however, is that there can be a large range in the highest extremes (>99th percentile).

To avoid the difficulties with a limited upper range of BMI percentile scores, many researchers report BMI SDSs (also known as z scores) or measures of "percent overweight." Both of these are measures of the relative degree of overweight similar to percentile scores but without a truncated upper limit. BMI SDS is calculated as the number of SD units above or below the median, based on statistically derived curves.[61] BMI SDS requires the use of published computer programs that access reference data and formulae such as that published by the CDC.[62] Percent overweight is calculated by a simple formula: 100(child's BMI/50th percentile BMI for child's age and gender).

This method was used chiefly in earlier studies that were published before computer programs were available to calculated BMI SDS. The disadvantage of using percent-overweight scores is that they do not account for the known weight distribution.

Quantitative Synthesis

For the behavioral interventions, we conducted meta-analyses of short-term and maintenance outcomes separately. Most trials reported weight outcomes as postintervention BMI or changes in BMI from baseline and compared those changes between in-

tervention and control groups. Among trials for which BMI or change in BMI were not reported, 3 trials reported weight outcomes as changes in BMI SDSs,[17,19,26] and 1 trial reported changes in percent overweight.[23] Three[18,19,26] of the trials that reported BMI or related measures between groups at follow-up statistically tested only whether shape and slope of the curves from baseline through follow-up were significantly different. For 1 of these trials[26] we used 24-month outcomes as an estimate for 12-month outcomes, which were shown graphically, but the means and SDs were not reported. The 24-month outcome is a slight underestimate of the 12-month effect, and although the 24-month effect was not statistically significant cross-sectionally, we show it as being statistically significant in Table 3 and in the text descriptions because the graphical display in the article indicated nonoverlapping CIs at a 12-month follow-up.

We focused on the change in BMI from baseline as the preferred measure of weight change when it was available. If BMI change was unavailable and could not be calculated, we used change in BMI SDS as our second choice and change in percent overweight as the third choice. Because we combined different outcomes, we analyzed standardized effect sizes. We also ran a meta-analysis to examine only those reporting BMI change and found that that pattern of results and magnitude of effects were similar to those seen in the primary meta-analysis that included all trials (and allowed different measures of weight change). We report the more comprehensive results in the meta-analysis including all trials.

The number of observations included in the analysis of interest to this review (as opposed to, eg, the number randomized or the number with complete data) was used as the n in the

meta-analysis. If both intention-to-treat and completers-only analyses were reported, we selected the intention-to-treat analysis for inclusion in the meta-analysis. If a trial involved 2 active treatment arms, the arm with the greater number of treatment hours or that was judged to be most comprehensive was selected for the meta-analysis. If outcomes were reported at multiple time points in the short-term, we chose the one closest to 12 months after baseline. Maintenance outcomes at more than 1 time point for both intervention and control groups were not reported for any trials. We used random-effects models because the trials varied considerably along many dimensions that would affect both baseline BMI (eg, age, minimum overweight inclusion criteria) and change in BMI (eg, intensity of intervention, comprehensiveness of treatment program). All meta-analyses were conducted by using Rev-Man 4.2.

Trials were grouped according to comprehensiveness and intensity into 4 categories: (1) comprehensive, medium (26–75 hours of contact) to high (≥76 hours) intensity; (2) comprehensive, low intensity (11–25 hours); (3) comprehensive, very low intensity (<10 hours); and (4) focused interventions. Interventions were considered to be comprehensive if they provided dietary counseling and physical activity counseling and used behavior-modification principles to assist with behavior change. Trials were only statistically combined within category. All trials for which maintenance outcomes (KQ2) were reported fell into different categories and, therefore, were not statistically combined, although the forest plot is presented to facilitate comparison with across trials.

If mean change scores from baseline for each group were not reported, we calculated an unadjusted differ-

ence between the mean baseline and mean follow-up scores for each group by using simple subtraction. SDs of the change scores were reported in 5 trials with posttreatment outcomes and 1 trial with follow-up outcome. In addition, 2 authors who did not report them in published articles provided us with these unpublished data.[21,27] We calculated SDs for trials that did not report them. Baseline BMI is highly correlated with posttreatment and follow-up BMI, and we had to take this correlation into account when calculating the SDs of the change scores. To estimate the degree of correlation, we examined data from a recently published trial in a school setting[63] in which both the SDs of the change scores (which we were attempting to calculate) and the SDs of the baseline and posttreatment BMIs (which we would use to calculate of the SDs of the change scores) were reported. Although this trial was excluded from the current review because of the setting, it used an intervention approach and population comparable to those targeted by this review. From this trial, we ascertained that the correlation between the baseline and posttreatment BMI was ~0.90. Therefore, we assumed a correlation of 0.90 for the remaining trials and calculated SDs of BMI change by using the following formula: $SD_{baseline-follow-up} = sqrt(SD^2_{baseline} + SD^2_{follow-up} - [2 \times 0.90 \times SD_{baseline} \times SD_{follow-up}])$.

When given SEs rather than SDs, we calculated SDs by multiplying the SE by the square root of n. When given symmetric confidence limits rather than SDs, we determined the SD by using the following formula: $SD = CI\ width\sqrt{n}/2(1.96)$.

APPENDIX 2 Search Strings

1	exp "Obesity"/
2	"Weight-Gain"/
3	"Weight-Loss"/
4	(obesity or obese).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
5	(weight gain or weight loss).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
6	(overweight or over weight or overeat$ or over eat$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
7	weight change$.mp.
8	((bmi or body mass index) adj2 (gain or loss or change)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
9	weight maintenance.mp.
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	limit 10 to child <6 to 12 years>
12	limit 10 to adolescent <13 to 18 years>
13	limit 10 to preschool child <2 to 5 years>
14	(child$ or adolescen$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
15	(teenage$ or young people or young person or young adult$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
16	(schoolchildren or school children).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
17	(pediatr$ or paediatr$).ti,ab.
18	(boys or girls or youth or youths).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
19	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20	exp "Behavior-Therapy"/
21	Social Support/
22	Family-Therapy/
23	exp "Psychotherapy-Group"/
24	((psychological or behavio?r$) adj (therapy or modif$ or strateg$ or intervention$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
25	(group therapy or family therapy or cognitive therapy).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
26	((lifestyle or life style) adj (chang$ or intervention$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
27	counsel?ing.mp.
28	social support.mp.
29	(peer adj2 support).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
30	((children adj3 parent$) and therapy).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
31	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	exp OBESITY/dt [Drug Therapy]
33	exp Anti-Obesity Agents/
34	lipase inhibitor$.mp.
35	(orlistat or xenical or tetrahydrolipstatin).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
36	(appetite adj (suppressant$ or depressant$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
37	sibutramine.mp. or meridia.ti,ab. [mp = title, original title, abstract, name of substance word, subject heading word]
38	(dexfenfluramine or fenfluramine or phentermine).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
39	bulking agent$.mp.

APPENDIX 2 Continued

40	(methylcellulose or celevac).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
41	((antiobesity or anti obesity) adj (drug$ or agent$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
42	guar gum.mp.
43	(metformin or glucophage).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
44	(fluoxetine or prozac).mp.
45	(Sertraline or zoloft).mp.
46	Diethylpropion.mp.
47	zonisamide.mp.
48	topiramate.mp.
49	(Octreotide or somatostatin or sandostatin).mp.
50	(Amantadine or symmetrel).mp.
51	(Glucagon-Like Peptide 1 or glp-1).mp.
52	(rimonabant or acomplia).mp.
53	(SLV 319 or SLV319).mp.
54	exenatide.mp.
55	liraglutide.mp.
56	vildagliptin.mp.
57	sitagliptin.mp.
58	(qnexa or contrave or excalia).mp.
59	exp OBESITY/dh [Diet Therapy]
60	"Diet-Fat-Restricted"/
61	"Diet-Reducing"/
62	"Diet-Therapy"/
63	"Fasting"/
64	(diet or diets or dieting).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
65	(diet$ adj (modif$ or therapy or intervention$ or strateg$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
66	(low calorie or calorie control$ or healthy eating).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
67	(fasting or modified fast$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
68	exp "Dietary-Fats"/
69	(fruit or vegetable$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
70	(high fat$ or low fat$ or fatty food$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
71	formula diet$.mp.
72	59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71
73	"Exercise"/
74	"Exercise-Therapy"/
75	exercis$.mp.
76	(aerobics or physical therapy or physical activity or physical inactivity).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
77	(fitness adj (class$ or regime$ or program$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
78	(physical training or physical education).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
79	dance therapy.mp.
80	sedentary behavio?r reduction.mp.
81	73 or 74 or 75 or 76 or 77 or 78 or 79 or 80
82	exp OBESITY/su [Surgery]
83	"Surgical-Staplers"/
84	"Surgical-Stapling"/
85	"Lipectomy"/
86	"Gastric-Bypass"/
87	"Gastroplasty"/
88	(dental splinting or jaw wiring).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
89	(gastroplasty or gastric band$ or gastric bypass).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
90	(intragastric balloon$ or vertical band$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
91	(stomach adj (stapl$ or band$ or bypass)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
92	biliopancreatic diversion$.mp.
93	liposuction.mp.
94	82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93
95	exp "Alternative-Medicine"/
96	(alternative medicine or complementary therap$ or complementary medicine).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
97	(hypnotism or hypnosis or hypnotherapy).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
98	(acupuncture or homeopathy).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
99	(chinese medicine or indian medicine or herbal medicine or ayurvedic).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
100	95 or 96 or 97 or 98 or 99

101	((diet or dieting or slim$) adj (club$ or organi?ation$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
102	(weightwatcheR$ or weight watcher$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
103	(correspondence adj (course$ or program$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
104	(fat camp$ or diet$ camp$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
105	101 or 102 or 103 or 104
106	(family intervention$ or parent$ intervention$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
107	(parent$ adj2 (behavio?r or involve$ or control$ or attitude$ or educat$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
108	106 or 107
109	(systematic$ review$ or systematic$ overview$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
110	(quantitative$ review$ or quantitative$ overview$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
111	Evidence-Based Medicine/
112	evidence based review$.mp.
113	exp "Controlled-Clinical-Trials"/
114	exp "Research-Design"/
115	((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
116	(CONTROLLED-CLINICAL-TRIAL or RANDOMIZED CONTROLLED TRIAL or META-ANALYSIS).pt.
117	(control$ and (trial$ or stud$ or evaluation$ or experiment$)).ti,ab.
118	(comparison group$ or control group$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
119	random$.ti,ab.
120	matched pairs.mp.
121	(outcome study or outcome studies).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
122	(quasiexperimental or quasi experimental or pseudo experimental).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
123	(nonrandomi?ed or non randomi?ed or pseudo randomi?ed).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
124	cohort studies/
125	(cohort adj (study or studies)).ti,ab.
126	cohort analys$.ti,ab.
127	case series.ti,ab.
128	longitudinal studies/
129	longitudinal$.ti,ab.
130	follow-up studies/
131	(follow up adj (study or studies)).ti,ab.
132	prospective studies/
133	prospective$.ti,ab.
134	109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133
135	10 and 19
136	32 or 33 or 34 or 36 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58
137	134 and 135 and 136
138	limit 137 to yr = "2003–2007"
139	31 or 35 or 37 or 72 or 81 or 94 or 100 or 105 or 108
140	134 and 135 and 139
141	limit 140 to yr = "2005–2007"
142	138 or 141
143	limit 142 to animals
144	limit 142 to humans
145	143 not 144
146	142 not 145
147	limit 146 to english language

Databases: Medline, the Database of Abstracts of Reviews of Effectiveness, the Education Resource Information Center, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, NICE, and PsycInfo: 2003 to June 2008.

APPENDIX 3 Study Eligibility Criteria

1. Populations: the following apply to all KQs
   a. Age 2–18 y. If a study substantially overlapped our age range (eg, 14–65 y), included article if results for younger participants were reported separately. For study of "young adult" or "college aged," excluded unless average age was <19 y or "college freshmen" was specified.
   b. Either (1) entire sample was overweight or obese (85th percentile for age and gender-specific BMI or who meet previously accepted criteria for overweight on the basis of ideal body weight) or (2) ≥50% of the sample were overweight or obese and ≥80% of the sample had 1 of the following risk factors for overweight or obesity-related medical problems: children of overweight parents; Hispanic, black, or American Indian/Alaska Native; children with the following medical conditions: diabetes, metabolic syndrome, hypertension, lipid abnormalities, or other cardiovascular-related disorders.
   c. Primary care population or comparable.
   d. Excluded trials in which the sample was limited to youth: (1) with eating disorders; (2) pregnant/postpartum; (3) overweight/obesity secondary to genetic or medical condition, including polycystic ovarian syndrome, hypothyroid, Cushing disease, growth hormone deficiency, insulinoma, hypothalamic disorders (eg Frohlich syndrome), Laurence-Moon-Biedl syndrome, Prader-Willi syndrome, weight gain secondary to medications (eg, antipsychotics), or (4) other idiosyncratic weight-loss issues.
2. Study design
   a. All studies for KQ1 and KQ2 (including sub-KQs) must have had an outcomes assessment at 6 mo or later after baseline. No minimum follow-up is required for serious (ie, requiring urgent medical care) adverse events (KQ3).
   b. Behavioral interventions: limited to RCTs or CCTs with minimal intervention or placebo control, with a minimum of 10 subjects per treatment arm.
   c. Pharmacologic interventions: RCTs with placebo pill control, with a minimum of 10 subjects per treatment arm.
3. Setting
   a. For behavioral interventions: all KQ except serious (ie, requiring urgent medical care) adverse effects (KQ3): limited to countries listed as "high" human development on Human Development Index (>0.90): Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Hong Kong, Iceland, Ireland, Israel, Italy, Japan, Korea, Luxembourg, Netherlands, New Zealand, Norway, Portugal, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom, and United States.
   b. Excluded trials in settings not feasible for implementation in primary care or health care systems to which primary care providers could refer, such as schools and inpatient settings.
4. Intervention
   a. Included behavioral (published in 1985 or later), pharmacologic, complimentary/alternative, or health care system interventions, singly or combined, designed to promote weight control/loss or weight maintenance, or an important components of weight loss (eg, physical activity).
   b. Intervention must have been conducted in primary care, feasible for conduct in primary care, or comparable to programs widely available for referral from primary care. We also accepted programs that would be feasible for implementation in a health care system and, therefore, could be available for referral from primary care, if available.
   c. Excluded trials in which the intervention focused on primary prevention, changes in the build environment, mazindol.
5. Outcomes
   a. KQ1 and KQ2 (and sub-KQs): must have provided acceptable adiposity outcome (2-C, 3-C, or 4-C models, except 2-C models not using Lohman's age and gender-specific equation or using the measurement of total body fat K^+) or weight outcome (eg, baseline and postintervention weight, weight change, net weight change over control group, or a related measures (such as BMI, BMI SDS, etc).
   b. KQ3: All potential harms reported in KQ1 and KQ2 trials were included. For trials that were not included for KQ1 or KQ2, outcomes were limited to serious adverse events such as death, need for medical or psychiatric treatment, or growth retardation.

CCT indicates controlled clinical trial.

Study Reference, Study Quality	Study Characteristics	Patient Characteristics	CONSORT Numbers, Retention	Inclusion/Exclusion Criteria	Description of Intervention Groups	Intervention Components
	Trial design	Age	Assessed for eligibility			List any of the following components address in the each study arm: Diet, Physical activity, Behavior modification, Family counseling, Parent training
	No. of participants	% female	Excluded			
	Setting for enrollment/ assessment	Race	Randomized			
	Location	Socioeconomic status	Retention			
	Recruitment strategy	Comorbidities				
	Study aim					
	Treatment Target	Treatment Intensity	Mean Entry Weight (Mean ± SD)	Intervention Phase, 2–11 mo	Intervention Phase, 12–23 mo	Intervention Phase, ≥24 mo
	Individual/Family vs Group Treatment	No. of sessions				
	Child, Parent, or Family	Amount of time				
	Format of intervention: individual or group	Duration				
	Follow-up (≥3 mo After Intervention)	Data Used for Meta-analysis (BMI Change [Mean ± SD], if Available)	Physiological Outcomes	Other Anthropomorphic Outcomes (List)	Other Beneficial Outcomes	Adverse Effects (Report Findings)
			Lipids	None	Abstract any of the following outcomes that are reported: dietary intake, physical activity, sedentary behavior, body image/self-esteem	
			Glucose tolerance			
			Blood Pressure			
			Physical fitness			

CONSORT indicates Consolidated Standards of Reporting Trials.

APPENDIX 5 Quality-Rating Criteria

Design	USPSTF Quality-Rating Criteria[10]	National Institute for Health and Clinical Excellence Methodology Checklists[64]
Systematic reviews and meta-analyses	Comprehensiveness of sources considered/search strategy used	The study addresses an appropriate and clearly focused question
	Standard appraisal of included studies	A description of the methodology used is included
	Validity of conclusions	The literature search is sufficiently rigorous to identify all the relevant studies
	Recency and relevance are especially important for systematic reviews	Study quality is assessed and taken into account
		There are enough similarities between the studies selected to make combining them reasonable
Case-control studies	Accurate ascertainment of cases	The study addresses an appropriate and clearly focused question
	Nonbiased selection of cases/controls with exclusion criteria applied equally to both	The cases and controls are taken from comparable populations
	Response rate	The same exclusion criteria are used for both cases and controls
	Diagnostic testing procedures applied equally to each group	What percentage of each group (cases and controls) participated in the study?
	Measurement of exposure accurate and applied equally to each group	Comparison is made between participants and nonparticipants to establish their similarities or differences
	Appropriate attention to potential confounding variables	Cases are clearly defined and differentiated from controls
		Is it clearly established that controls are noncases?
		Measures have been taken to prevent knowledge of primary exposure influencing case ascertainment
		Exposure status is measured in a standard, valid, and reliable way
		The main potential confounders are identified and taken into account in the design and analysis
		Have CIs been provided?
RCTs	Initial assembly of comparable groups uses adequate randomization, including first concealment and whether potential confounders were distributed equally among groups	The study addresses an appropriate and clearly focused question
	Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)	The assignment of subjects to treatment groups is randomized
	Important differential loss to follow-up or overall high loss to follow-up	An adequate concealment method is used
	Measurements: equal, reliable, and valid (includes masking of outcome assessment)	Subjects and investigators are kept "blind" about treatment allocation
	Clear definition of the interventions	The treatment and control groups are similar at the start of the trial
	All important outcomes considered	The only difference between groups is the treatment under investigation
		All relevant outcomes are measured in a standard, valid, and reliable way
		What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?
		All the subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis)
		Where the study is carried out at >1 site, results are comparable for all sites
Cohort studies	Initial assembly of comparable groups uses consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts	The study addresses an appropriate and clearly focused question
	Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)	The 2 groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation
	Important differential loss to follow-up or overall high loss to follow-up	The study indicates how many of the people asked to take part did so, in each of the groups being studied
	Measurements: equal, reliable, and valid (includes masking of outcome assessment)	The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis
	Clear definition of the interventions	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?
	All important outcomes considered	Comparison is made between full participants and those lost to follow-up, by exposure status
		The outcomes are clearly defined
		The assessment of outcome is made blind to exposure status
		When blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome

Design	USPSTF Quality-Rating Criteria[10]	National Institute for Health and Clinical Excellence Methodology Checklists[64]
		The measure of assessment of exposure is reliable
		Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable
		Exposure level or prognostic factor is assessed more than once
		The main potential confounders are identified and taken into account in the design and analysis
		Have CIs been provided?
Diagnostic accuracy studies	Screening test relevant, available for primary care, adequately described	The nature of the test being studied is clearly specified
	Study uses a credible reference standard, performed regardless of test results	The test is compared with an appropriate gold standard
	Reference standard interpreted independently of screening test	When no gold standard exists, a validated reference standard is used as a comparator
	Handles indeterminate result in a reasonable manner	Patients for testing are selected either as a consecutive series or randomly from a clearly defined study population
	Spectrum of patients included in study	The test and gold standard are measured independently (blind) of each other
	Sample size	The test and gold standard are applied as close together in time as possible
	Administration of reliable screening test	Results are reported for all patients who are entered into the study
		A prediagnosis is made and reported

Hierarchy of research design: (I) properly conducted RCT; (II-1) well-designed controlled trial without randomization; (II-2) well-designed cohort or case-control analytic study; (II-3) multiple time series with or without the intervention; dramatic results from uncontrolled experiments; and (III) opinions of respected authorities based on clinical experience; descriptive studies or case reports; reports of expert committees.