JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Obesity and Intervention for Weight Management in Children and Adolescents

Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Obesity is common in children and adolescents in the United States, is associated with negative health effects, and increases the likelihood of obesity in adulthood.

OBJECTIVE To systematically review the benefits and harms of screening and treatment for obesity and overweight in children and adolescents to inform the US Preventive Services Task Force.

DATA SOURCES MEDLINE, PubMed, PsycINFO, Cochrane Collaboration Registry of Controlled Trials, and the Education Resources Information Center through January 22, 2016; references of relevant publications; government websites. Surveillance continued through December 5, 2016.

STUDY SELECTION English-language trials of benefits or harms of screening or treatment (behavior-based, orlistat, metformin) for overweight or obesity in children aged 2 through 18 years, conducted in or recruited from health care settings.

DATA EXTRACTION AND SYNTHESIS Two investigators independently reviewed abstracts and full-text articles, then extracted data from fair- and good-quality trials. Random-effects meta-analysis was used to estimate the benefits of lifestyle-based programs and metformin.

MAIN OUTCOMES AND MEASURES Weight or excess weight (eg, body mass index [BMI]; BMI *z* score, measuring the number of standard deviations from the median BMI for age and sex), cardiometabolic outcomes, quality of life, other health outcomes, harms.

RESULTS There was no direct evidence on the benefits or harms of screening children and adolescents for excess weight. Among 42 trials of lifestyle-based interventions to reduce excess weight (N = 6956), those with an estimated 26 hours or more of contact consistently demonstrated mean reductions in excess weight compared with usual care or other control groups after 6 to 12 months, with no evidence of causing harm. Generally, intervention groups showed absolute reductions in BMI *z* score of 0.20 or more and maintained their baseline weight within a mean of approximately 5 lb, while control groups showed small increases or no change in BMI *z* score, typically gaining a mean of 5 to 17 lb. Only 3 of 26 interventions with fewer contact hours showed a benefit in weight reduction. Use of metformin (8 studies, n = 616) and orlistat (3 studies, n = 779) were associated with greater BMI reductions compared with placebo: −0.86 (95% CI, −1.44 to −0.29; 6 studies; I^2 = 0%) for metformin and −0.50 to −0.94 for orlistat. Groups receiving lifestyle-based interventions offering 52 or more hours of contact showed greater improvements in blood pressure than control groups: −6.4 mm Hg (95% CI, −8.6 to −4.2; 6 studies; I^2 = 51%) for systolic blood pressure and −4.0 mm Hg (95% CI, −5.6 to −2.5; 6 studies; I^2 = 17%) for diastolic blood pressure. There were mixed findings for insulin or glucose measures and no benefit for lipids. Medications showed small or no benefit for cardiometabolic outcomes, including fasting glucose level. Nonserious harms were common with medication use, although discontinuation due to adverse effects was usually less than 5%.

CONCLUSIONS AND RELEVANCE Lifestyle-based weight loss interventions with 26 or more hours of intervention contact are likely to help reduce excess weight in children and adolescents. The clinical significance of the small benefit of medication use is unclear.

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Data from the National Health and Nutrition Examination Survey indicate that an estimated 17% of US 2- to 19-year-olds had obesity in 2011-2104,[1] and 31.8% were either overweight or had obesity in 2011-2012.[2] These data represent substantial increases over the past 3 decades, although the rate of obesity may be stabilizing overall. Excess adiposity in childhood increases the risk of adult obesity, which is associated with many health issues. In addition, obesity during childhood—particularly severe obesity—is associated with problematic cardiometabolic measures such as high blood pressure, dyslipidemia, and insulin resistance[1-7] as well as asthma, obstructive sleep apnea, orthopedic difficulties, early maturation, polycystic ovarian syndrome, and hepatic steatosis.[8]

In 2010, the US Preventive Services Task Force (USPSTF) recommended that clinicians screen children 6 years and older for obesity and offer them or refer them for comprehensive, intensive behavioral interventions to improve weight status (B recommendation).[9] This review was undertaken to provide current evidence to the USPSTF for an updated recommendation on this topic.

Methods

Scope of Review

This systematic review addressed 5 key questions (KQs) about the benefits and harms of screening and treatment for obesity in children and adolescents in primary care or primary care–relevant settings (**Figure 1**). Detailed methods are available in the full evidence report available at https://www.uspreventiveservicestaskforce.org/Page/Document/final-evidence-review151/obesity-in-children-and-adolescents-screening1. Sub-KQs exploring the effect of intervention components (KQ3a) and key patient subgroups (KQ3b) on health outcomes had insufficient data and are presented in the full report but are not discussed here. Similarly, a small group of behavior-based trials that were not lifestyle-based interventions designed to reduce excess weight (eg, maintenance-only trials and those using psychotherapeutic approaches without emphasis on lifestyle factors) are not discussed here.

Data Sources and Searches

In addition to evaluating all studies from the previous USPSTF reviews[11,12] and selected studies from other reviews identified through an initial search for existing systematic reviews, we searched for newly published literature in MEDLINE/PubMed, PsycINFO, Cochrane Central Register of Controlled Trials, PsycINFO, and the Education Resources Information Center. For screening studies we searched from January 1, 2005, through January 22, 2016 (bridging from the 2005 USPSTF review[11]), and for treatment studies we searched from January 1, 2010, through January 22, 2016 (bridging from the 2010 USPSTF review[12]). Reference lists of other relevant publications were also reviewed to identify additional studies published in or after 1985. Since January 2016, we continued to conduct ongoing surveillance through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and therefore the related USPSTF recommendation. The last surveillance was conducted on December 5, 2016, and identified no relevant new studies. The search strategies are listed in the eMethods in the Supplement.

To reduce the risk of reporting bias for trials of metformin and orlistat, both the Drugs@FDA and ClinicalTrials.gov websites were used. Drugs@FDA was searched for the drug approval package for orlistat using the method described by Turner.[13] We did not search for the metformin drug approval package, because it is a generic name and the Food and Drug Administration reviews for generics are focused on bioequivalence rather than efficacy and safety.[13] The package inserts were examined to review known harms and adverse effects of both drugs. ClinicalTrials.gov was searched using the terms "orlistat" and "metformin." For study titles that appeared relevant, the full records were reviewed by 2 investigators; studies meeting eligibility criteria were matched with published articles where possible. One study published results in ClinicalTrials.gov without a subsequent journal publication,[14] although correspondence with study authors indicated that a manuscript submission was expected.

Study Selection

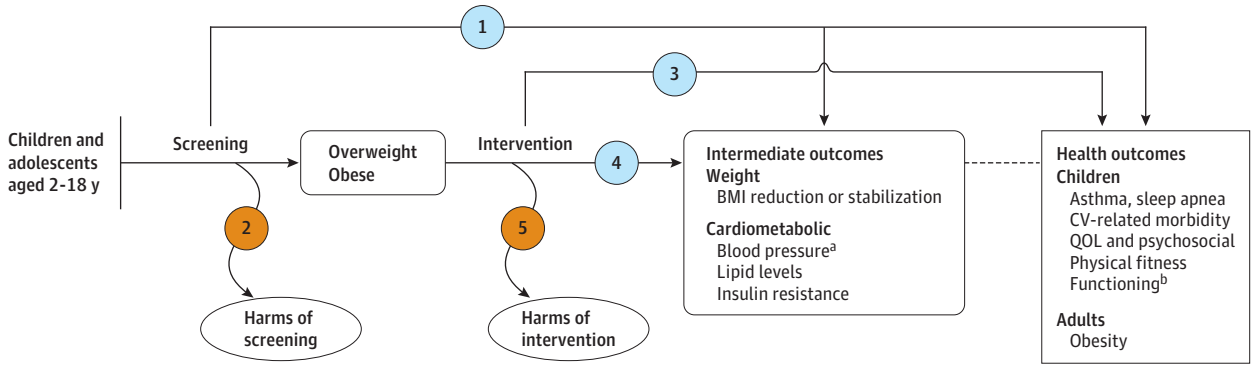
Two investigators independently reviewed 9491 abstracts and 464 full-text articles against inclusion and exclusion criteria (**Figure 2**). Disagreements were resolved through discussion or consultation with a third investigator.

Eligible studies were fair- or good-quality studies published in English that were conducted in "economically developed" countries according to membership in the Organisation for Economic Co-operation and Development.[15] Randomized clinical trials (RCTs) and nonrandomized controlled trials that examined the benefits or harms of screening or weight management interventions (counseling, metformin, orlistat, and health care system–level approaches) among children and adolescents aged 2 to 18 years were included. In addition, large observational studies that examined harms of metformin and orlistat in children or adolescents were eligible; no such studies met the inclusion criteria.

Included trials had to be conducted in or recruited from health care settings and have a primary aim of reducing excess weight (through weight loss or limiting weight gain with growth in height) or maintaining previous reductions in excess weight. Studies of weight management interventions also could take place in telephone, virtual, community, or research settings as long as there was a connection to a health setting (eg, recruitment primarily from a health care setting). We excluded studies conducted in settings that were not generalizable to primary care, such as school classrooms or residential treatment facilities. We excluded studies with components that would not be feasible for an outpatient health care setting, such as interventions that provided most or all of the participants' food or that included community-wide media or built environment components.

Trials were required to target individuals meeting the Centers for Disease Control and Prevention (CDC)[16] or other similar criteria for overweight or obesity, those who had excess weight previously and were engaged in weight maintenance, or high-risk populations with a high proportion of youth with excess weight. Therefore, studies were also included if at least half the sample met the criteria for overweight or obesity and the study targeted a population with elevated risk of obesity (eg, children

Figure 1. Analytic Framework



Key questions

1 Do screening programs for obesity in children and adolescents lead to reductions in excess weight or age-associated excess weight gain, improve health outcomes during childhood, or reduce incidence of obesity in adulthood?

a. Are there effects of screening on cardiometabolic measures, ie, blood pressure, lipid levels, and insulin resistance?

b. Are there common components of efficacious screening programs?

c. Does efficacy differ by key patient subgroups, ie, age, race/ethnicity, sex, degree of excess weight, and socioeconomic status?

2 Does screening for obesity in children and adolescents have adverse effects?

3 Do weight management interventions for children and adolescents embedded in primary care, or to which primary care providers refer, improve health outcomes during childhood or reduce incidence of obesity in adulthood?

a. Are there common components of efficacious interventions?

b. Does efficacy differ by key patient subgroups, ie, age, race/ethnicity, sex, degree of excess weight, and socioeconomic status?

4 Do weight management interventions for children and adolescents that are embedded in primary care, or to which primary care providers refer, reduce excess weight or age-associated excess weight gain?

a. Are there effects of interventions on cardiometabolic measures, ie, blood pressure, lipid levels, and insulin resistance?

b. Are there common components of efficacious interventions?

c. Does efficacy differ by key patient subgroups, ie, age, race/ethnicity, sex, degree of excess weight, and socioeconomic status?

5 Do weight management interventions for children and adolescents have adverse effects?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. The dashed line indicates a relationship between an intermediate outcome and a health outcome that is presumed to describe the natural progression of the disease. Refer to USPSTF Procedure Manual for further details.[10] BMI indicates body mass index; CV, cardiovascular; KQ, key question; QOL, quality of life.

[a] Blood pressure, lipid levels, and insulin resistance are secondary outcomes when reported with weight.

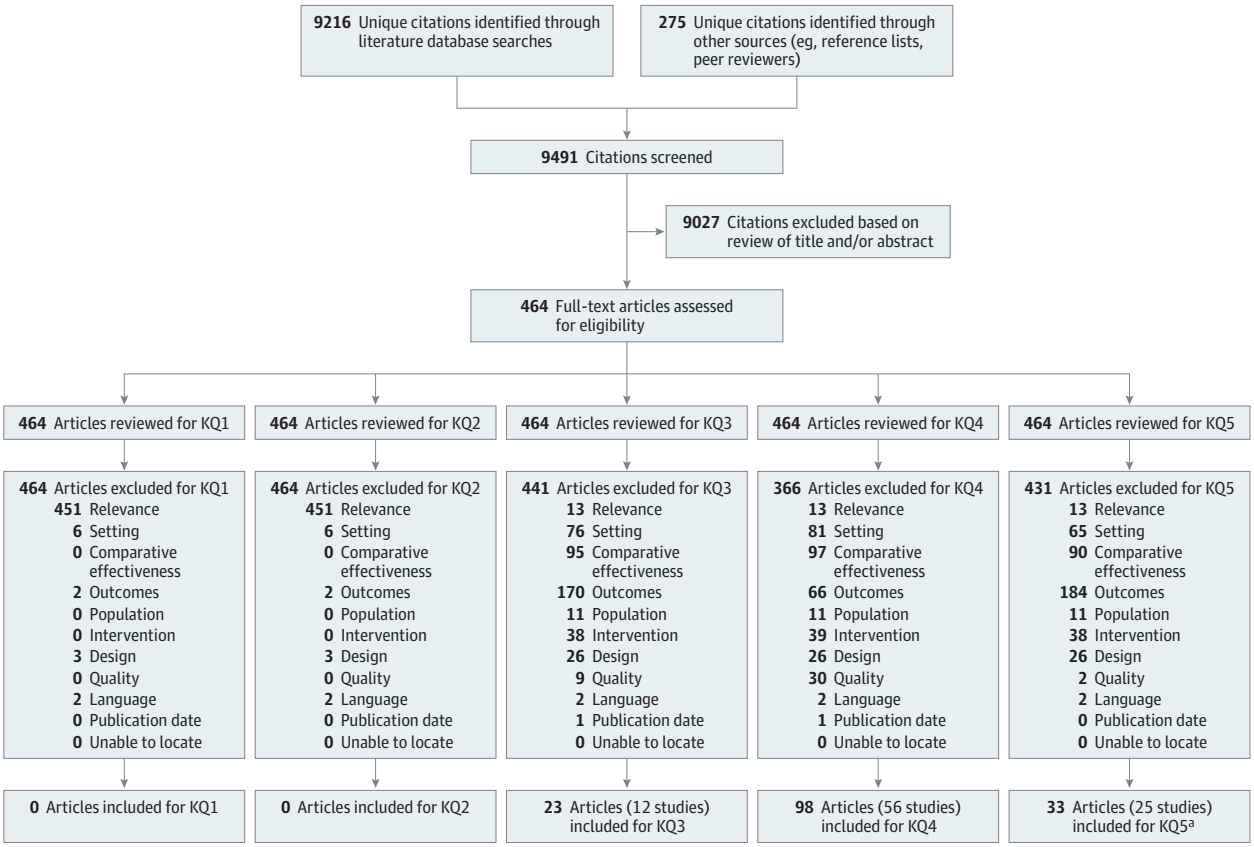
[b] Includes academic, social, or physical functioning.

with overweight parents; Hispanic, black, or American Indian/Alaska Native ethnicity) or with obesity-related medical problems (eg, type 2 diabetes, the metabolic syndrome, hypertension, lipid abnormalities). Studies were excluded if they were limited to youth who had an eating disorder, who were pregnant or postpartum, who were overweight or had obesity secondary to a medical condition, who had an intellectual or developmental disability, or who were in college.

Control groups of behavior-based interventions could include usual care, no intervention, waitlist, attention control, or minimal intervention (eg, pamphlets or 1 to 2 brief sessions with no more than 60 minutes of total estimated direct contact). Pharmacotherapy trials had to include a placebo control. Trials that included a concomitant lifestyle intervention were required to have the same lifestyle intervention in both the pharmacotherapy and the placebo groups.

Trials of screening or treatment benefit had to report at least 1 weight outcome. Other outcomes included health outcomes (eg, reduced orthopedic pain, sleep apnea, or asthma; improved quality of life, functioning, or depression; avoidance of adult obesity), intermediate cardiometabolic outcomes (blood pressure, lipid, insulin/glucose measures), and adverse effects of screening or treatment (eg, labeling, stigma or increased body image concerns, eating disorder, exercise-induced injury). Outcomes other

Figure 2. Literature Search Flow Diagram



Details for reasons for exclusion are as follows. Relevance: Study aim not relevant. Setting: Study was not conducted in a setting or country relevant to US primary care. Comparative effectiveness: Study did not have a control group. Outcomes: Study did not have relevant outcomes or had incomplete outcomes. Population: Study was not conducted in children and adolescents aged 2 to 18 years. Intervention: Study used an excluded intervention/screening approach. Design: Study did not use an included design. Quality: Study did not meet criteria for fair or good quality (ie, was poor quality) using study-design specific criteria developed by the US Preventive Services Task Force for randomized clinical trials; the criteria and definitions of good, fair, poor are provided in eTable 1 in the Supplement. Language: Study was published in a non-English language. Publication date: Article was published before 1985. Unable to locate: Library services could not locate article in which study was published.

[a] Three pharmacotherapy studies included for harms only, because weight outcomes were reported at less than 6 months.

than harms had to be reported at a minimum of 6 months after randomization; 12 months was the preferred outcome point.

Data Extraction and Quality Assessment

Two investigators independently assessed the quality of the included studies by using criteria defined by the USPSTF (eTable 1 in the Supplement).[10] Each study was assigned a final quality rating of good, fair, or poor; disagreements among investigators were resolved through discussion or consultation with a third investigator. We excluded studies as poor quality if there was a major flaw (eg, attrition >40%, differential attrition >20%) or multiple important limitations that could invalidate the results, such as noncomparable groups at baseline, differential reason for dropout, imbalances on important variables due to dropout or baseline differences that were not controlled for, problematic measurement procedures, nonblinded allocation, and attrition of 20% to 39%. One investigator abstracted data from the included studies, and a second investigator checked data for accuracy. We abstracted study design details, population characteristics, intervention characteristics, and outcomes.

Data Synthesis and Analysis

We created summary tables of study, population, and intervention characteristics to examine the consistency, precision, and relationship of effect size with key potential modifiers. Weight-related measures at 12 months' follow-up were the primary outcome, with a body mass index (BMI) *z* score or standard deviation score selected as the primary outcome if available. We refer to either of these measures as BMI *z* score, which is the number of standard deviations the child's BMI differs from the median according to norms such as those of the CDC[16] or International Obesity Task Force.[17] We chose BMI *z* score as the preferred outcome because it was the only widely available measure that could be used to compare relative degree of excess weight across ages. The BMI *z* score values associated with the 85th and 95th percentiles according to CDC standards are 1.036 and 1.645, respectively. If BMI *z* score was

not reported, BMI (calculated as weight in kilograms divided by height in meters squared), weight, waist circumference, or BMI percentile were used. The closest follow-up to 12 months was used (range, 6-24 months).

Hours of contact were estimated based on the number of planned treatment sessions and the length of each session. When information on session length was not provided, assumptions developed a priori were used to estimate contact hours, for example, assigning phone sessions to be 15 minutes and "brief" phone sessions to be 5 minutes. Interventions were grouped by hours of contact (0 to 5 hours, 6 to 25 hours, 26 to 51 hours, ≥52 hours). We carried forward the 26-hour cutoff from the previous review, which was comparable to weekly 1-hour sessions for 6 months. For this review we added 2 additional cutoffs post hoc when heterogeneity in effect sizes remained high and appeared related to contact hours. We selected the 52-hour cutoff to extend the logic of weekly visits from 6 months up to 1 year and selected the 6-hour cutoff because all trials with fewer than 6 hours of contact involved only individual visits, while almost all (25/27) interventions above this cutoff included group sessions. For trials with interventions that lasted longer than 12 months but that reported a 12-month outcome, estimated hours of contact in the first 12 months only are shown in the forest plots.

Random-effects meta-analysis was conducted using the DerSimonian and Laird estimation method to examine group differences in change from baseline.[18] Sensitivity analyses were conducted using a restricted maximum likelihood model with the Knapp-Hartung modification for small samples, which is a more conservative approach when there is substantial statistical heterogeneity or the number of studies is small.[19,20] When only 4 or 5 trials could be included in a meta-analysis, we attempted to use the profile likelihood method[21] for sensitivity analysis, but if this model did not converge, the restricted maximum likelihood model results were used. For the lifestyle-based weight loss trials, we analyzed BMI *z* score, any weight measure, and, among trials with 52 or more contact hours, cardiometabolic outcomes. When pooling any weight measure, standardized mean differences in change between groups were used. Because hours of contact appeared to be a strong effect modifier, separate pooled estimates were generated for each level of contact hours. For metformin, separate meta-analyses were conducted for BMI, BMI *z* score, and cardiometabolic outcomes reported in at least 4 trials.[21]

The I^2 statistic was used to assess statistical heterogeneity.[22] Funnel plots and the Egger test were used to examine the risk of small-study effects for the lifestyle-based weight loss trials, combining trials across all levels of estimated contact hours (36 trials had sufficient data to include in a funnel plot) (eFigure in the Supplement). There were not sufficient data to perform these analyses for other outcomes or for metformin trials.

Analyses were conducted in Stata version 13.1 (StataCorp). All significance testing was 2-sided, and the results were considered statistically significant at $P \leq .05$.

Results

There were 59 trials identified (N = 8583) that met the inclusion criteria. Study and intervention characteristics are shown in eTables 2 and 3 in the Supplement. Forty-five trials (n = 7099) examined the benefits of behavior-based interventions compared with a control group,[23-66] and 11 examined the benefits of metformin (8 trials, n = 616)[67-74] or orlistat (3 trials, n = 779)[14,75,76] compared with a placebo pill. Three additional trials (n = 89) reported harms of metformin use for weight loss but did not have sufficient follow-up to be included in the examination of treatment benefits.[77-79]

Of the 45 behavior-based interventions, 42 (n = 6956) used counseling on diet, physical activity, or behavior change management with the aim of reducing excess weight in young people (by weight loss or limiting further weight gain as the child grows) and are referred to here as lifestyle-based weight loss interventions.[23,25,26,28-55,57-66] Other behavior-based approaches were studied in 3 small trials that showed neither benefits nor harms and are not discussed further.[24,27,56]

Screening

Key Question 1. Do screening programs for obesity in children and adolescents lead to reductions in excess weight or age-associated excess weight gain, improve health outcomes during childhood, or reduce incidence of obesity in adulthood?

Key Question 2. Does screening for obesity in children and adolescents have adverse effects?

None of the studies that met the inclusion criteria addressed the benefits or harms of screening for obesity.

Effects of Interventions on Health Outcomes

Key Question 3. Do weight management interventions for children and adolescents embedded in primary care, or to which primary care physicians refer, improve health outcomes during childhood or reduce incidence of obesity in adulthood?

Lifestyle-Based Weight Loss Trials

Ten of the lifestyle-based weight loss trials reported measures of health-related quality of life, functioning, or both using the Pediatric Quality of Life Inventory,[23,29,32,39,54,59,62,63] the Child Health Questionnaire,[32,33] or DISABKIDS.[61] Results are shown in **Figure 3** for the 7 studies with data sufficient to show in a plot. These trials involved an estimated 1 to 45 hours of intervention contact; most did not find greater improvement in intervention groups compared with control groups, including the 3 trials not shown in Figure 3 because of insufficient data.[23,62,63] Similarly, measures of depression, self-esteem, or self-perception rarely showed greater improvement with lifestyle-based weight loss interventions.[29,32,39,49,62,63]

Metformin

No trials of metformin reported health outcomes.

Orlistat

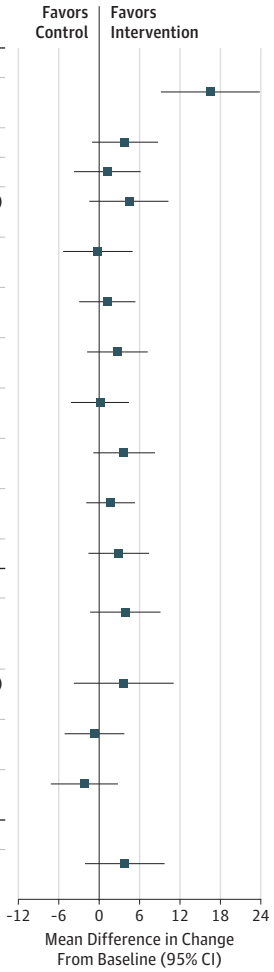
Only 1 orlistat trial reported quality-of-life measures. No differences were found in quality of life between orlistat and placebo groups at 6 months.[76]

Effects of Interventions on Excess Weight

Key Question 4. Do weight management interventions for children and adolescents that are embedded in primary care, or to which primary care physicians refer, reduce excess weight or age-associated excess weight gain?

Figure 3. Change in Quality of Life and Functioning in Behavior-Based Intervention Trials by Estimated Hours of Contact (Key Question 3)

Source	Estimated Contact Hours Through 12 mo	Time Since Randomization (Months After End of Treatment)	Measure	Intervention No.	Intervention Change From Baseline, Mean (SD)	Control No.	Control Change From Baseline, Mean (SD)	Mean Difference in Change From Baseline (95% CI)
PedsQL, parent report (range, 0-100)								
Stark et al,[54] 2011	38	12 (6)	Physical functioning	7	13.8 (8.6)	9	-2.7 (5.6)	16.50 (9.15 to 23.85)
DeBar et al,[29] 2012	37	12 (7)	Total score	85	6.7 (15.2)	76	2.9 (16.5)	3.82 (-1.09 to 8.73)
Hofsteenge et al,[32] 2014	17	6 (0)	Total score	44	3.4 (11.7)	33	2.2 (10.4)	1.20 (-3.75 to 6.15)
			Physical functioning	44	6.6 (13.6)	33	2.2 (12.6)	4.40 (-1.47 to 10.27)
			Psychosocial functioning	44	2.2 (12.3)	33	2.4 (10.7)	-0.20 (-5.36 to 4.96)
Taylor et al,[59] 2015	5	24 (0)	School functioning	89	0.7 (13.3)	92	-0.5 (15.3)	1.20 (-2.97 to 5.37)
			Physical functioning	89	-1.1 (14.9)	92	-3.8 (15.9)	2.70 (-1.80 to 7.20)
			Emotional functioning	89	0.1 (14.6)	92	0 (15)	0.10 (-4.21 to 4.41)
			Social functioning	89	-1.9 (14.7)	92	-5.6 (16.7)	3.70 (-0.89 to 8.29)
			Psychosocial functioning	89	-0.4 (11.9)	92	-2.1 (12.9)	1.70 (-1.92 to 5.32)
McCallum et al,[39] 2007	1	15 (2)	Total score	63	2.9 (13.5)	69	0 (12.9)	2.90 (-1.60 to 7.40)
CHQ, parent report (range, 0-100)								
Kalarchian et al,[33] 2009	44	12 (0)	General health perception	97	5.7 (17.8)	95	1.8 (19.1)	3.88 (-1.35 to 9.11)
			Global health	97	4.1 (24.5)	95	0.5 (27.7)	3.65 (-3.75 to 11.05)
Hofsteenge et al,[32] 2014	17	6 (0)	Psychosocial summary	44	1.7 (10.5)	33	2.4 (9.3)	-0.70 (-5.13 to 3.73)
			Physical summary	44	2 (11.7)	33	4.2 (10.6)	-2.20 (-7.19 to 2.79)
DISAKIDS, child report (range, 0-37)								
Vos et al,[61] 2011	45	12 (NA[a])	Total score	32	6.6 (11)	35	2.8 (13.6)	3.80 (-2.11 to 9.71)



CHQ indicates Child Health Questionnaire; NA, not available; PEDsQL, Pediatric Quality of Life.

[a] Intervention had not yet ended at the 12-month assessment.

Lifestyle-Based Weight Loss Trials

Most of the lifestyle-based weight loss trials were conducted in a primary care (43%) or other health care (43%) setting; the others involved health care–based recruitment, but the intervention was outside of a health care setting. Eight trials were rated as good quality,[28,29,39,57-59,62,63] and the remaining were given a fair rating. Mean baseline BMI *z* score values ranged from 0.94 to 4.3. The weighted mean BMI *z* score was 2.3, well above the BMI *z* score value of 1.645 that corresponds to the 95th percentile for age and sex according to CDC norms. The trials included children as young as 2 years[53,54,57] and up to 18 years[32,38,40] or 19 years.[41] The majority of trials targeted elementary-aged children or both elementary and adolescent ages.

The lifestyle-based weight loss interventions provided at least dietary counseling and some information about behavior change principles, and most also provided information related to physical activity or sedentary behavior. All trials involved parents, except 1 that targeted adolescents. The number of sessions ranged from 1 to 122, and estimated contact hours ranged from 0.25 to 122 over 2.25 to 24 months. The interventions with higher estimated contact hours included group meetings, with or without separate individual family meetings. These group interventions frequently involved separate groups for parents and children as well as joint activities, and they often included supervised physical activity sessions. These interventions typically incorporated behavior change techniques such as goal setting, monitoring diet and activity behaviors, and problem solving. The interventions with fewer than an estimated 6 contact hours did not include group sessions. These interventions were frequently conducted in primary care settings with the involvement of the primary care physician, and several included motivational interviewing–based counseling by the primary care physician or another healthy lifestyle counselor.[28,35,38,48,57,58,60,66]

Weight management interventions above a threshold of 26 estimated contact hours were generally effective in reducing excess weight in children and adolescents after 6 to 12 months,

typically with absolute BMI *z* score reductions of 0.2 or more compared with little or no reduction in control groups (**Figure 4**). There was a general dose-response pattern, with greater contact being associated with larger effects that were more likely statistically significant. However, across all levels of contact, children in both groups showed a wide range of effects, as demonstrated by large SDs relative to the mean change: some children in both groups showed fairly large reductions in excess weight, some showed no or modest changes, and some continued to gain excess weight.

The 7 trials with an estimated 52 or more contact hours (over 6 to 12 months) all showed benefits of treatment,[36,45-47,51,52,64] with a pooled standardized mean difference in change of −1.10 (95% CI, −1.30 to −0.89; 6 trials; I^2 = 43.4%)[45-47,51,52,64] over 6 to 12 months, among those with sufficient data to pool. Absolute BMI *z* score reductions in the pooled intervention groups typically ranged from 0.22 to 0.34, while control groups generally reported small to moderate increases in BMI *z* score. The remaining trial reported a statistically significant between-group difference in BMI *z* score of −0.15 (−0.16 in the intervention group vs −0.01 in the control group).[36] In terms of absolute change in pounds, the range of mean weight change in intervention groups was from +2.6 lb to −7.0 lb, while children in the control groups typically gained a mean of 8 to 17 lb (among children with baseline weights ranging from a mean of 112 to 203 lb). However, 6 of these 7 trials reported results only immediately after the intervention ended, when the effect was likely at its largest.

The 9 interventions with an estimated 26 to 51 contact hours (over 2.25 to 12 or more months)[26,29,33,34,42,49,53,54,61] generally showed smaller effects than trials with contact hours estimated at 52 or more, with a pooled standardized mean difference in change of −0.34 (95% CI, −0.52 to −0.16; 9 trials; I^2 = 24%) (Figure 4) over 6 to 12 months. Change in BMI *z* score in the 7 of these studies reporting BMI *z* scores ranged from −0.11 (SD, 0.16)[26] to −0.59 (SD, 0.75)[53] in the intervention groups, whereas the control groups generally showed mean reductions of 0.10 or less. Absolute weight changes were highly variable, but typically intervention groups showed mean 1- to 5-lb weight gains compared with mean 5- to 10-lb gains in control groups (with baseline mean weights ranging from 58 to 190 lb). Seven of the 9 demonstrated statistically significant group differences based on either study-reported analyses or calculations using reported means and SDs.[29,34,42,49,53,54,61] Five of these trials reported results from 3.75 to 9 months after the last treatment session, and all 5 demonstrated a statistically significant benefit of treatment, suggesting some degree of postcontact maintenance of weight benefit.[29,42,49,53,54]

Only 4 of the 26 interventions with fewer than an estimated 26 hours of contact over 3 to 24 months showed statistically significant benefits (based on either study-reported analyses or calculations using reported means and SDs) at 6- to 12-month follow-up,[28,48,50,55] and the standardized effect sizes were usually small, generally reflecting absolute BMI *z* score reductions of 0.10 or less in the intervention groups. Pooled effects for the 21 trials that provided sufficient information to be included in the meta-analysis are shown in Figure 4, with separate results for those with an estimated 6 to 25 hours and fewer than 6 hours. Two of the 4 lower-intensity interventions that showed a benefit of treatment targeted children who were overweight but did not have obesity.[28,55] However, even though results were statistically significant in only 4 trials, the intervention group children showed statistically nonsignificantly greater mean reductions in excess weight than control group children in 21 of these 24 trials.

Four of the included trials reported outcomes at 18 to 24 months in addition to 12-month outcomes, allowing exploration of longer-term trajectories.[28,33,45,59] With estimated contact hours ranging from 1 to 78, beneficial effects were fully maintained (or improved on) at 24 months in 2 trials, with estimated contact hours of 6 (over 24 months)[59] and 78 (over 12 months).[45] In the highest-contact trial, there was a BMI *z* score difference between groups of −0.30 at both 12- and 24-month assessments, when the intervention had ended at 12 months. However, group differences were attenuated at longer-term follow-up in the other 2 trials.

Metformin

One good-quality[69] and 7 fair-quality[67-74] trials (n = 616) compared the use of metformin for weight loss with a placebo pill. None of these trials was conducted in primary care; all were conducted in pediatric obesity or endocrine clinics or other types of clinical research settings. Included ages were 6 to 19 years.

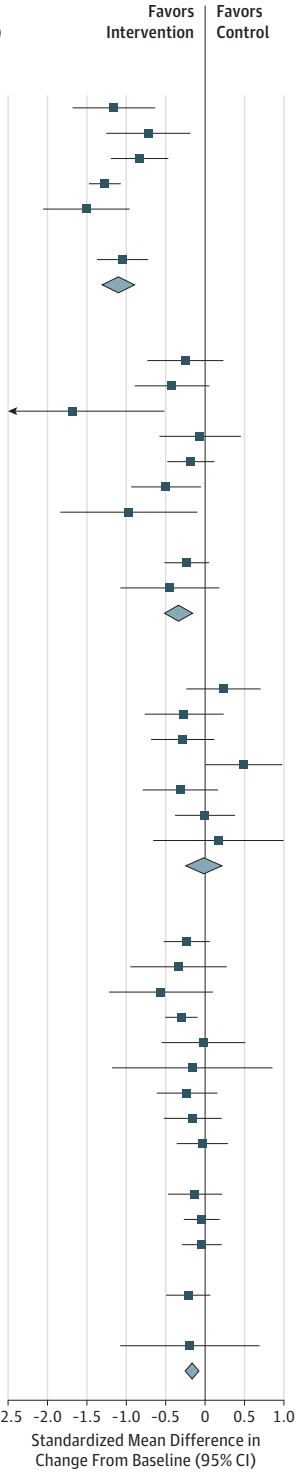
Participants in metformin trials had a higher BMI than those in behavior-based interventions, with a weighted mean baseline BMI of 36.0. Six of the 8 metformin trials required abnormalities of insulin or glucose metabolism, such as hyperinsulinemia, insulin resistance, or impaired glucose tolerance[67,69-73]; 1 trial explicitly excluded participants with elevated levels of fasting or 2-hour glucose or hemoglobin A1c (HbA_{1c}).[74] One metformin trial restricted inclusion to participants with a previous unsuccessful lifestyle intervention, defined as BMI change less than 2 points over 6 months and persistent insulin resistance.[67]

The total daily metformin dose ranged from 1 to 2 g.[68] The lowest adherence rate occurred in a trial reporting that 60% of the metformin group and 75% of the control group filled 4 prescriptions over 6 months, equating to a maximum dose for 2 months.[70] Adherence was greatest in a trial in which 93.2% of pills were taken in the metformin group and 92.2% in the placebo group.[69] All but 1 of the metformin trials[73] also provided a concomitant counseling intervention to all participants. The estimated number of contact hours was highly variable, ranging from 15 minutes to 86 hours. Two trials provided physical activity sessions.[67,74]

Metformin was associated with a small but statistically significant reduction in weight, with minimal statistical heterogeneity in trials of 6 to 12 months' duration. In pooled analyses, metformin was associated with a lower BMI *z* score (−0.10 [95% CI, −0.17 to −0.03]; 6 trials; I^2 = 13.1%) and lower BMI (−0.86 [95% CI, −1.44 to −0.29]; 6 trials; I^2 = 0%) (**Figure 5**). Results were almost identical when using the more conservative profile likelihood pooling method to account for the small number of trials being pooled: BMI *z* score weighted mean difference (WMD), −0.10 (95% CI, −0.19 to −0.04); BMI weighted mean difference, −0.86 (95% CI, −1.45 to −0.28). Results of trials that could not be pooled were generally consistent with pooled results.[70,72,73]

Figure 4. Change in Weight (BMI *z* Score, BMI, Weight in Kilograms, or BMI Percentile) in Behavior-Based Weight Loss Intervention Trials, by Estimated Hours of Contact, Showing DerSimonian and Laird Pooled Estimates (Key Question 4)

Source	Estimated Contact Hours Through 12 mo	Months Since Randomization (Months Since End of Treatment)	Intervention No.	Intervention Change From Baseline, Mean (SD)	Control No.	Control Change From Baseline, Mean (SD)	Standardized Mean Difference in Change From Baseline (95% CI)
Estimated contact ≥52 h							
Outcome: BMI *z* score							
Weigel et al,[64] 2008	114	12 (0)	36	-0.34 (0.48)	30	0.26 (0.57)	-1.15 (-1.68 to -0.63)
Savoye et al,[51] 2014	78	6 (0)	31	-0.05 (0.13)	27	0.04 (0.12)	-0.72 (-1.25 to -0.19)
Reinehr et al,[45] 2006	78	12 (0)	174	-0.30 (0.35)	37	0 (0.41)	-0.83 (-1.19 to -0.47)
Reinehr et al,[46] 2009	78	12 (0)	288	-0.22 (0.35)	186	0.15 (0.17)	-1.27 (-1.47 to -1.07)
Reinehr et al,[47] 2010	67	6 (0)	34	-0.26 (0.22)	32	0.05 (0.19)	-1.50 (-2.05 to -0.96)
Outcome: BMI							
Savoye et al,[52] 2007	82	12 (0)	105	-1.7 (3.1)	69	1.6 (3.2)	-1.05 (-1.37 to -0.72)
Subtotal (I^2 = 43.4%; P = .12)							-1.10 (-1.30 to -0.89)
Estimated contact 26-51 h							
Outcome: BMI *z* score							
Vos et al,[61] 2011[a]	45	12 (NA[b])	32	-0.40 (1.3)	35	-0.1 (1.1)	-0.25 (-0.73 to 0.23)
Kalavainen et al,[34] 2007	44	12 (6)	35	-0.30 (0.15)	35	-0.20 (0.30)	-0.42 (-0.89 to 0.05)
Stark et al,[54] 2011	38	12 (6)	7	-0.37 (0.41)	9	0.40 (0.49)	-1.68 (-2.85 to -0.52)
Croker et al,[26] 2012	38	6 (0)	31	-0.11 (0.16)	27	-0.10 (0.16)	-0.06 (-0.58 to 0.45)
DeBar et al,[29] 2012[a]	37	12 (7)	90	-0.15 (0.41)	83	-0.08 (0.36)	-0.18 (-0.48 to 0.12)
Sacher et al,[49] 2010	36	6 (3.75)	37	-0.30 (0.51)	45	-0.01 (0.65)	-0.49 (-0.94 to -0.05)
Stark et al,[53] 2014	30	12 (16)	11	-0.59 (0.75)	12	-0.03 (0.36)	-0.97 (-1.84 to -0.10)
Outcome: BMI							
Kalarchian et al,[33] 2009	44	12 (0)	97	0.50 (3.0)	95	1.1 (2.2)	-0.23 (-0.52 to 0.05)
Nemet et al,[42] 2005[a]	33	12 (9)	20	-1.6 (4.3)	20	0.60 (5.5)	-0.45 (-1.07 to 0.18)
Subtotal (I^2 = 24.0%; P = .23)							-0.34 (-0.52 to -0.16)
Estimated contact 6-25 h							
Outcome: BMI *z* score							
Bryant et al,[25] 2011	24	12 (0)	35	0.03 (0.24)	35	-0.03 (0.27)	0.23 (-0.24 to 0.70)
Golley et al,[31] 2007	24	12 (7)	31	-0.24 (0.43)	31	-0.13 (0.40)	-0.26 (-0.76 to 0.24)
Hofsteenge et al,[32] 2014	17	6 (0)	53	-0.12 (0.46)	44	0.02 (0.53)	-0.28 (-0.68 to 0.12)
Gerards et al,[30] 2015	17	12 (8.5)	35	0.05 (0.26)	32	-0.08 (0.27)	0.49 (0.00 to 0.98)
Nowicka et al,[41] 2008	16	12 (0)	65	-0.06 (0.46)	23	0.09 (0.53)	-0.31 (-0.79 to 0.16)
Norman et al,[65] 2016	12	12 (0)	53	-0.10 (0.36)	53	-0.10 (0.44)	0.00 (-0.38 to 0.38)
Arauz Boudreau et al,[23] 2013	11	6 (0)	13	-0.03 (0.14)	10	-0.05 (0.08)	0.17 (-0.66 to 1.00)
Subtotal (I^2 = 37.4%; P = .14)							-0.02 (-0.25 to 0.21)
Estimated contact 0-5 h							
Outcome: BMI *z* score							
Taylor et al,[59] 2015	5	12 (NA[b])	91	-0.19 (0.52)	90	-0.08 (0.43)	-0.23 (-0.53 to 0.06)
Stettler et al,[55] 2015[a]	4	12 (0)	46	-0.06 (0.50)	24	0.10 (0.41)	-0.34 (-0.95 to 0.27)
Saelens et al,[50] 2002[a]	4	7 (3)	18	-0.05 (0.22)	19	0.06 (0.17)	-0.56 (-1.22 to 0.10)
Broccoli et al,[28] 2016	4	12 (9)	186	-0.12 (0.38)	185	-0.01 (0.35)	-0.30 (-0.51 to -0.10)
Sherwood et al,[66] 2015	3	6 (0)	26	-0.02 (0.37)	29	-0.01 (0.54)	-0.02 (-0.55 to 0.51)
Looney and Raynor,[37] 2014	3	6 (0)	7	-0.16 (0.48)	8	-0.07 (0.61)	-0.16 (-1.18 to 0.85)
Wake et al,[63] 2013	3	12 (0)	56	-0.20 (0.50)	49	-0.10 (0.36)	-0.23 (-0.61 to 0.16)
Taveras et al,[58] 2015	1	12 (0)	164	-0.09 (0.33)	171	-0.04 (-0.32)	-0.16 (-0.52 to 0.21)
McCallum et al,[39] 2007	1	15 (12)	70	0 (0.61)	76	0.02 (0.55)	-0.03 (-0.36 to 0.29)
Outcome: BMI							
Taveras et al,[57] 2011	3	12 (0)	253	0.30 (1.4)	192	0.50 (1.4)	-0.13 (-0.47 to 0.21)
van Grieken et al,[60] 2013	2	24 (12)	277	1.4 (1.5)	230	1.4 (1.7)	-0.04 (-0.27 to 0.18)
Wake et al,[62] 2009	1	12 (9)	127	0.60 (2.6)	115	0.70 (2.2)	-0.04 (-0.29 to 0.21)
Outcome: BMI percentile							
Resnicow et al,[48] 2015[a]	3	24 (0)	154	-4.9 (15.2)	158	-1.8 (13.8)	-0.21 (-0.49 to 0.07)
Outcome: Weight							
Kong et al,[35] 2013	4	9 (0)	28	1.7 (4.0)	23	2.5 (4.3)	-0.19 (-1.08 to 0.69)
Subtotal (I^2 = 0.0%; P = .91)							-0.17 (-0.25 to -0.08)



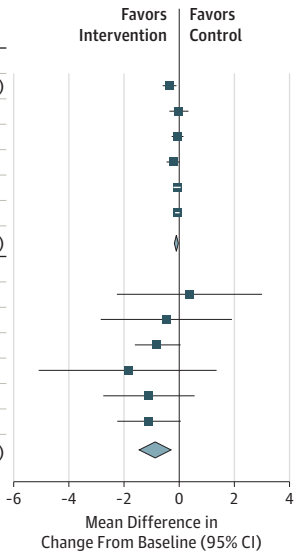
BMI indicates body mass index.

[a] Study-reported repeated-measures or adjusted analysis demonstrated a statistically significant benefit.

[b] Intervention had not yet ended at 12-month assessment.

Figure 5. Change in Weight (BMI *z* Score and BMI) in Metformin Trials (Key Question 4)

Source	Metformin, mg/d	Age, y	Time Since Randomization, mo[a]	Intervention No.	Intervention Change From Baseline, Mean (SD)	Control No.	Control Change From Baseline, Mean (SD)	Mean Difference in Change From Baseline (95% CI)
Outcome: BMI *z* score								
Freemark and Bursey,[73] 2001	1000	12-19	6	14	-0.12 (0.30)	15	0.23 (0.39)	-0.35 (-0.60 to -0.10)
Wiegand et al,[67] 2010	1000	10-17	6	34	-0.03 (0.70)	29	-0.02 (0.70)	-0.01 (-0.36 to 0.34)
Kendall et al,[71] 2013[b]	1500	8-18	6	55	-0.09 (0.61)	55	-0.03 (0.52)	-0.06 (-0.27 to 0.15)
Clarson et al,[74] 2014[b]	2000	10-16	12	23	-0.17 (0.44)	24	0.05 (0.40)	-0.22 (-0.46 to 0.02)
Wilson et al,[68] 2010	2000	13-18	12	27	-0.09 (0.25)	27	-0.01 (0.25)	-0.08 (-0.21 to 0.05)
Yanovski et al,[69] 2011[b]	2000	6-12	6	53	-0.11 (0.20)	47	-0.04 (0.21)	-0.07 (-0.15 to 0.01)
Subtotal (I^2 = 13.1%; P = .33)								-0.10 (-0.17 to -0.03)
Outcome: BMI								
Wiegand et al,[67] 2010	1000	10-17	6	34	0.10 (5.1)	29	-0.30 (5.5)	0.38 (-2.25 to 3.01)
Kendall et al,[71] 2013[b]	1500	8-18	6	55	-0.20 (6.3)	55	0.20 (6.4)	-0.46 (-2.84 to 1.92)
Love-Osborne et al,[70] 2008	1700	12-19	6	48	-0.20 (1.9)	16	0.60 (1.3)	-0.79 (-1.62 to 0.04)
Clarson et al,[74] 2014[b]	2000	10-16	12	23	-0.60 (5.6)	24	1.3 (5.7)	-1.86 (-5.08 to 1.36)
Wilson et al,[68] 2010[b]	2000	13-18	12	27	-0.90 (3.1)	27	0.20 (3.1)	-1.10 (-2.75 to 0.55)
Yanovski et al,[69] 2011[b]	2000	6-12	6	53	-0.80 (2.8)	47	0.30 (3.0)	-1.10 (-2.25 to 0.05)
Subtotal (I^2 = 0.0%; P = .90)								-0.86 (-1.44 to -0.29)



Weights are from random-effects analysis. BMI indicates body mass index.

[a] For all studies in figure, time since randomization equals months since end of treatment.

[b] Study-reported repeated-measures or adjusted analysis demonstrated a statistically significant benefit.

When individual trials adjusted for characteristics such as baseline weight, age, sex, or race/ethnicity, several trials became statistically significant, which was not reflected in the unadjusted analyses.[68,69,71] The trial with the most intensive concomitant lifestyle therapy, with an estimated 86 contact hours, showed a statistically nonsignificant net difference in BMI *z* score between the intervention and placebo groups at 12 months (−0.22 [95% CI, −0.46 to 0.02]).[74] Despite the intensive lifestyle intervention in both groups, mean BMI *z* score increased by 0.05 (SD, 0.40) in the placebo group; BMI *z* score decreased by 0.17 for participants taking metformin. The estimated weight change for this study, based on baseline BMI and assuming the median height for age, amounted to a mean reduction of 3.1 lb with metformin compared with 1.4 lb with placebo. This was the largest reduction in BMI *z* score of all included metformin interventions; the remaining interventions showed reductions of 0.12 lb or less, generally compared with extremely small reductions or BMI *z* score increases in the placebo groups. Across all metformin trials, mean weight change ranged from a 5-lb reduction to a 5-lb weight gain with metformin, and from a 2-lb reduction to an 11-lb weight gain with placebo. Baseline mean weight ranged from 168 to 239 lb. Despite differences in metformin dose and concomitant therapy between trials, statistical heterogeneity was very low, and dose did not appear to modify the weight effect of metformin. Limited data were available about the persistence of metformin effect after discontinuation.

Orlistat

Three fair-quality trials (n = 779) examined the use of orlistat (360 mg/d) for weight loss compared with a placebo pill over 6 to 12 months; trials were collectively limited to adolescents aged 12 to 18 years.[14,75,76] The baseline weighted mean BMI across the 3 orlistat studies was 37.4. One orlistat study required the presence of 1 or more obesity-related comorbidities (including type 2 diabetes),[14] but the other 2 had no health-related requirements beyond excess weight. Concomitant counseling interventions ranged from an estimated 3.5 to 15 hours of contact. Adherence to orlistat based on pill counts was 72% to 73% in 1 trial[75] and greater than 80% in another trial[76]; the third trial did not report adherence level.[14]

Orlistat trials reported small between-group BMI differences ranging from −0.94 (95% CI, −1.58 to −0.30) to −0.50 (95% CI, −7.62 to 6.62) (**Table 1**).[14,75,76] Over 6 to 12 months, mean BMI change with orlistat ranged from −1.44 (SD, 2.6) to −0.55 (SD not reported), whereas control groups had BMI changes ranging from −0.8 (SD, 13.4) to 0.31 (SD not reported). In terms of absolute weight, mean changes ranged from 1-lb weight gain to 12-lb weight loss with orlistat, compared with 7-lb weight gain to 4-lb weight loss, with very wide variability within studies. Youth in these trials had baseline mean weights of 215 and 244 lb in the 2 studies reporting baseline weight. BMI reduction was statistically significant in the 2 larger trials (n = 539 and n = 200)[14,75] but not in the smallest trial (n = 40).[76] Only 1 trial reported change in BMI *z* score, which was a reduction of 0.12 (SD, 0.2) with the use of orlistat compared with a reduction of 0.06 (SD, 0.2) in the placebo group over 6 months (P = .007).

Effects of Interventions on Cardiometabolic Measures

Key Question 4a. Do weight management interventions affect cardiometabolic measures?

Table 1. Weight Outcomes of Included Orlistat Trials (Key Question 4)[a]

Source	Follow-up, mo	No. of Participants	Outcome	Mean Difference (95% CI)		Between-Group Difference		Adjustment Details
				Intervention	Control	Calculated (95% CI)	Study-Reported *P* Value	
Yanovski,[14] 2012	6	100	BMI[b]	−1.44 (2.6)	−0.50 (2)	−0.94 (−1.58 to −0.30)	NR	
			Weight, kg	−2.9 (7)	−0.6 (7)	−2.30 (−4.24 to −0.36)	NR	
			BMI *z* score	−0.12 (0.2)	−0.06 (0.2)	−0.06 (−0.12 to −0.00)	.007	
Chanoine et al,[75] 2005	12	352	BMI[b]	−0.55 (NR)	0.31 (NR)	−0.86 (NA)	.001	Treatment center, treatment × center interaction, body weight <80 or ≥80 kg Weight loss during run-in Corrected for age and sex by BMI *z* score
			Weight, kg	0.53 (NR)	3.14 (NR)	−2.61 (NA)	<.001	
			Waist circumference, cm	−1.33 (NR)	0.12 (NR)	−1.45 (NA)	<.05	
Maahs et al, 2006[76]	6	16	BMI[b]	−1.3 (7.16)	−0.8 (13.42)	−0.50 (−7.62 to 6.62)	.70	
			Weight, kg	−5.5 (23.91)	−1.6 (39.39)	−3.90 (−25.54 to 17.74)	.76	

Abbreviations: BMI, body mass index; NA, not available; NR, not reported.

[a] All studies in this table were of fair quality.

[b] Calculated as weight in kilograms divided by height in meters squared.

Table 2. Pooled Results for Continuous Intermediate Cardiometabolic Outcomes of Included Lifestyle-Based Weight Loss Trials With 52 or More Estimated Hours of Contact Intervention Trials (Key Question 4)[45-47,51,52,64]

Outcome	Pooled Mean Difference in Change Between Groups (95% CI)	No. of Trials	I^2	No. Included in Analysis		Model
				Intervention	Control	
Blood pressure, mm Hg						
Systolic	−6.4 (−8.6 to −4.2)	6	51.3	973	688	DerSimonian and Laird
Diastolic	−4.0 (−5.6 to −2.5)	6	17.3	973	688	DerSimonian and Laird
Lipids, mg/dL						
LDL-C	−10.0 (−21.1 to 1.1)	4	56.6	685	407	REML
HDL-C	0.4 (−2.2 to 3.0)	4	0	798	509	REML
Triglycerides	−9.1 (−27.8 to 9.6)	4	36.9	797	509	REML
Fasting plasma glucose, mg/dL	−0.8 (−3.0 to 1.2)	4	0	798	508	REML

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; REML, restricted maximum likelihood with Knapp-Hartung modification.

SI conversion factors: To convert LDL-C and HDL-C values to mmol/L, multiply by 0.0259; triglyceride values to mmol/L, multiply by 0.0113; fasting plasma glucose values to mmol/L, multiply by 0.0555.

Lifestyle-Based Interventions

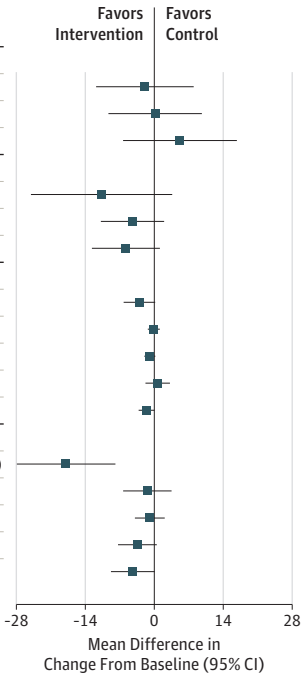
The interventions offering an estimated 52 or more hours of contact showed fairly consistent improvements in blood pressure (systolic blood pressure [SBP] pooled mean difference in change between groups, −6.4 mm Hg [95% CI, −8.6 to −4.2]; 6 trials; I^2 = 51.3%; diastolic blood pressure [DBP] pooled mean difference in change between groups, −4.0 mm Hg [95% CI, −5.6 to −2.5]; 6 trials; I^2 = 17.3%) but no statistically significant improvement for lipids (**Table 2**). Some improvements in insulin and glucose measures other than fasting plasma glucose (homeostatic model assessment, 2-hour oral glucose test, insulin levels) were found in individual trials. Neither the individual trials nor the pooled estimate for fasting plasma glucose showed any benefit. Fasting plasma glucose was the only insulin or glucose measure with sufficient data to pool. Cardiometabolic outcomes were sparsely reported in trials of less intensive interventions and were generally not associated with improvements in blood pressure, lipid levels, or insulin or glucose levels.

Metformin

Four of 5 trials reporting fasting glucose values reported a small or no decrease in fasting glucose level with the use of metformin (ranging from −1.6 to 0.6 mg/dL [to convert glucose values to mmol/L, multiply by 0.0555]) and small increases with placebo (ranging from 0.2 to 3.5 mg/dL) (**Figure 6**). Pooled analyses showed a between-group difference in fasting glucose levels of −3.7 mg/dL with wide confidence intervals (95% CI, −9.9 to 2.5; 5 trials; I^2 = 64.0%; **Table 3**). One outlier study showed a statistically significant difference of −17.9 mg/dL (95% CI, −27.9 to −7.9) between the metformin and placebo groups.[73] This small, fair-quality study without lifestyle modification components also exhibited the largest metformin effect on BMI *z* score; however, this trial

Figure 6. Change in Insulin and Glucose Outcomes in Metformin Trials (Key Question 4)[a]

Source	Metformin, mg/d	Age, y	Time Since Randomization, mo[a]	Intervention No.	Intervention Change From Baseline, Mean (SD)	Control No.	Control Change From Baseline, Mean (SD)	Mean Difference in Change From Baseline (95% CI)
Outcome: 2-h Oral glucose tolerance test, mg/dL								
Wiegand et al,[67] 2010	1000	10-17	6	34	2.0 (16.3)	29	3.9 (22.7)	-1.90 (-11.81 to 8.01)
Kendall et al,[71] 2013	1500	8-18	6	55	-5.6 (25.4)	55	-5.8 (25.4)	0.18 (-9.31 to 9.67)
Clarson et al,[74] 2014	2000	10-16	12	23	3.4 (18.0)	24	-1.8 (22.3)	5.23 (-6.33 to 16.78)
Outcome: Insulin, μIU/mL								
Freemark and Bursey,[73] 2001	1000	12-19	6	14	-12.3 (11.0)	15	-1.6 (25.9)	-10.70 (-25.05 to 3.65)
Kendall et al,[71] 2013	1500	8-18	6	55	-0.60 (16.3)	55	3.8 (18.1)	-4.42 (-10.85 to 2.01)
Yanovski et al,[69] 2011	2000	6-12	6	53	3.2 (17.1)	47	9.0 (18.0)	-5.76 (-12.67 to 1.15)
Outcome: HOMA[b]								
Freemark and Bursey,[73] 2001	1000	12-19	6	14	-3.1 (2.6)	15	-0.10 (5.8)	-3.01 (-6.21 to 0.19)
Kendall et al,[71] 2013	1500	8-18	6	55	0.20 (3.2)	55	0.30 (3.3)	-0.09 (-1.30 to 1.12)
Clarson et al,[74] 2014	2000	10-16	12	23	-0.90 (1.9)	24	0 (2.0)	-0.90 (-2.02 to 0.22)
Wilson et al,[68] 2010	2000	13-18	12	27	-0.10 (5.0)	27	-0.80 (4.3)	0.70 (-1.79 to 3.19)
Yanovski et al,[69] 2011	2000	6-12	6	53	0.70 (4.0)	47	2.2 (4.2)	-1.55 (-3.17 to 0.07)
Outcome: Fasting plasma glucose, mg/dL								
Freemark and Bursey,[73] 2001	1000	12-19	6	14	-9.2 (14.6)	15	8.7 (12.8)	-17.90 (-27.91 to -7.89)
Wiegand et al,[67] 2010	1000	10-17	6	34	0.60 (8.5)	29	2.0 (11.0)	-1.40 (-6.32 to 3.52)
Kendall et al,[71] 2013	1500	8-18	6	55	-0.70 (8.3)	55	0.20 (7.9)	-0.90 (-3.93 to 2.13)
Clarson et al,[74] 2014	2000	10-16	12	23	-1.6 (5.7)	24	1.8 (7.9)	-3.42 (-7.36 to 0.52)
Yanovski et al,[69] 2011	2000	6-12	6	53	-0.90 (10.9)	47	3.5 (11.7)	-4.35 (-8.80 to -0.10)



Weights are from random-effects analysis. FPG indicates fasting plasma glucose; HOMA, Homeostasis Model Assessment; OGTT, oral glucose tolerance test.

[a] For all studies in figure, time since randomization equals months since end of treatment.

[b] HOMA (insulin resistance) = insulin (μIU/mL) × glucose (mmol/L)/22.5.

Table 3. Pooled Results for Continuous Intermediate Cardiometabolic Outcomes of Included Metformin Trials (Key Question 4)[67-69,71,73,74]

Outcome[a]	Pooled Mean Difference in Change Between Groups (95% CI)	No. of Trials	I^2	No. Included in Analysis	
				Intervention	Control
Fasting plasma glucose, mg/dL	−3.7 (−9.9 to 2.5)	5	64.0	179	170
Lipids, mg/dL					
Total cholesterol	−2.5 (−13.7 to 8.7)	4	0.0	156	146
LDL-C	−0.3 (−8.4 to 7.8)	6	21.4	206	197
HDL-C	0.2 (−2.4 to 2.8)	6	11.9	206	197
Triglycerides	3.1 (−17.6 to 23.8)	5	0.0	206	197

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert fasting plasma glucose values to mmol/L, multiply by 0.0555; total cholesterol, LDL-C, and HDL-C values to mmol/L, multiply by 0.0259; triglyceride values to mmol/L, multiply by 0.0113.

[a] All outcomes reported in table were based on restricted maximum likelihood with Knapp-Hartung modification.

had a statistically significant BMI imbalance between groups at baseline and questionable fasting glucose balance between groups that were not adjusted for. Between-group change in fasting glucose levels in other studies was small and generally statistically nonsignificant (range, −0.90 to −4.35 mg/dL).[67,69,71,72,74] This pattern of results was similar for other glucose- and insulin-related outcomes. None of the trials reporting lipid or blood pressure outcomes showed a benefit with metformin.

Orlistat

Two of the 3 orlistat trials reported cardiometabolic outcomes.[75,76] Changes in glucose, insulin, and lipid levels were statistically nonsignificant in both reporting trials. In the 1 trial that reported blood pressure, the orlistat group achieved a greater DBP reduction (mean difference in change, −1.81 mm Hg [95% CI not reported]; $P = .04$); changes in SBP were not statistically significant (mean difference in change, −0.22 [95% CI not reported]; $P = .84$).[75]

Components of Efficacious Interventions

Key Question 4b. Are there common components of efficacious interventions?

For lifestyle-based weight loss trials, the relationship between weight outcomes and a number of intervention-related variables were explored, including estimated hours of contact; number of sessions; intervention duration; whether group, individual, or supervised physical activity sessions were offered; and whether sessions were offered to children with or without parents present. Estimated contact hours and number of sessions were the only intervention components associated with effect size ($P < .001$ in both cases).

Efficacy of Interventions by Patient Subgroups

Key Question 4c. Does efficacy differ by key patient subgroups (ie, age, race/ethnicity, sex, degree of excess weight, and socioeconomic status)?

Across all interventions, subgroup analysis of the prespecified subpopulations of interest (ie, age, race/ethnicity, sex, degree of excess weight, socioeconomic status) was sparse, so that no conclusions could be drawn about differential effectiveness on weight outcomes. Analyses were generally limited by small study sizes and the absence of statistical interaction testing.

Harms of Interventions

Key Question 5. Do weight management interventions for children and adolescents have adverse effects?

Lifestyle-Based Interventions

Three of the lifestyle-based weight loss intervention trials reported no adverse events in the intervention group,[26,47,49] and 2 additional trials (published in the same article) reported that there were no serious adverse events.[44] Five trials similarly found no group differences on measures of disordered eating or body dissatisfaction.[29,39,50,62,63]

Metformin

We included 3 trials reporting harms in addition to the trials included for benefits of treatment.[77-79] The 3 trials had follow-up of less than 6 months, so they were not included with benefits of treatment. Gastrointestinal adverse effects were common but not serious in participants taking metformin. Adverse effects were also frequently reported by those receiving placebo. For example, vomiting was reported by 15% and 42% of those taking metformin in 2 trials and by 3% and 21% of control group participants.[68,69] Discontinuations due to adverse effects, however, were relatively rare (<5%) and occurred in relatively similar proportions between groups. Reporting trials generally showed no differences in liver or kidney function, and there were no reported cases of lactic acidosis.[68,69,71-73,78,79] None of the trials reported on hypoglycemia.

Orlistat

Gastrointestinal adverse effects were very common among patients taking orlistat. For example, abdominal pain or cramps were reported by 16% to 65% of participants taking orlistat and by 11% to 26% of those taking a placebo. Flatus with discharge was reported by 20% to 43% of those taking orlistat and 3% to 11% of those receiving placebo. In 2 trials, fecal incontinence was reported in 9% to 10% of participants taking orlistat and 0% to 1% of those receiving placebo.[75,76] Nevertheless, discontinuations due to adverse effects were relatively rare (<5%) but about twice as common among participants taking orlistat than in those taking placebo.

Discussion

The summary of evidence for this review is shown in **Table 4**. There was no direct evidence on the benefits or harms of screening children and adolescents for excess weight, but a fairly large and recent body of evidence suggests that lifestyle-based weight loss programs with at least 26 hours of contact are likely to promote reductions in excess weight in children and adolescents. The literature also revealed no evidence of these programs causing harm. Relative reductions in BMI *z* score of 0.20 or more were typical, but the absolute amount of weight loss was highly variable within studies, suggesting a wide possible range of benefit. Those with the most contact hours also demonstrated approximately 6-mm Hg reductions in SBP relative to the control groups, smaller reductions in DBP, and some improvement in insulin and glucose measures, but typically no improvements in levels of fasting plasma glucose or lipids. Behavior-based interventions with fewer estimated hours of contact rarely demonstrated benefit, although limited evidence suggested that briefer interventions may be effective in children who are overweight but who do not have obesity. Estimated hours of contact was the only characteristic clearly related to effect size, with larger effects seen in trials with more contact hours.

Use of metformin or orlistat was associated with very small reductions in excess weight in youth, amounting to less than 1 BMI unit difference between groups and absolute reductions in BMI *z* score of less than 0.20 in all cases. Medications provided small or no benefit for intermediate cardiometabolic outcomes, including fasting glucose level. Evidence for metformin was primarily limited to youth with abnormalities of insulin or glucose metabolism, most of whom met adult criteria for severe obesity. The evidence base was small for metformin and even smaller for orlistat, with only 3 trials.

The clinical importance of these changes in weight is difficult to determine. A German expert panel considered a BMI *z* score reduction of 0.2 to be associated with clinically significant improvement,[80] but the current review found no data to support any particular cutoff. Several small prospective studies of children who had obesity have reported larger improvements in cardiometabolic measures among those who reduced their BMI *z* score over time—and reported statistically significant linear trends in some cases—across 4 levels of BMI *z* score improvement.[81-83] These studies typically found a great likelihood of statistically detectable change in cardiometabolic risk factors, starting with BMI *z* score reductions of 0.125 to 0.50. However, there was no clear or consistent threshold for benefit. Similarly, a study showing greater improvement in insulin sensitivity with an 8% reduction in BMI did not provide data showing that this level of BMI change is an important threshold (eg, compared with 6% or 10%) or whether the amount of improvement in insulin sensitivity reported was clinically important.[84] Analysis of participants who completed a short-term, family-based behavioral weight management program showed that the mean 0.15 BMI *z* score reduction achieved in the intervention group was associated with statistically significant improvements in

Table 4. Summary of Evidence

Topic	No. of Studies (Design), No. of Participants	Summary of Findings	Consistency/Precision	Limitations (Includes Reporting Bias)	Overall Study Quality	Applicability
KQ1, KQ1a, KQ1b, KQ1c: Benefits of Screening						
	0 (NA)	NA	NA	NA	NA	NA
KQ2: Harms of Screening						
	0 (NA)	NA	NA	NA	NA	NA
KQ3: Health Benefits of Treatment						
Behavior-based interventions	11 (RCTs) n = 1523	11 trials reported generally small statistically nonsignificant relative increases in health-related QOL or functioning scores, using a variety of specific measures, except for 1 trial in young children that reported improved physical functioning with a larger effect size. High variability in effects suggests a wide range of benefit to individuals within trials. In addition, 5 trials each reported self-esteem and body satisfaction, with most finding no group differences. One trial reported no differences in percentage screening positive for depression.	Consistency: QOL or functioning results reasonably consistent. Other outcomes either inconsistent or had insufficient data to rate consistency. Precision: QOL or functioning results imprecise, primarily owing to confidence intervals that straddle 1.0 and a wide variety of specific measures. Other outcomes imprecise owing to inconsistency or insufficient data to rate precision for other outcomes.	Wide variety of measures and specific outcomes reported, raising concerns about reporting bias. However, since most results were not statistically significant, this concern is mitigated.	Fair to good (5 good, 6 fair)	Five trials conducted in the United States, 3 involved primary care
Pharmacologic interventions	1 (RCT) n = 40	No difference in quality of life between users of orlistat and placebo.	Consistency: NA Precision: imprecise	Single small study, short follow-up (6 mo)	Fair	Conducted in the United States, but not in primary care.
KQ4, KQ4a: Benefits of Behavior-Based and Pharmacologic Interventions on Weight and Cardiometabolic Outcomes						
Lifestyle-based weight loss interventions	42 (3 CCTs, 39 RCTs) n = 6956	Interventions with an estimated ≥26 h of contact generally reported greater reductions in excess weight than control groups over 6 to 12 mo. Intervention groups receiving ≥26 h of contact generally reported BMI *z* score reductions of 0.10 to 0.77, while control group youth showed reductions of ≤0.20 or increased BMI *z* score at follow-up. Trials reported high variability in effects, suggesting a wide range of benefit to individuals within trials. In trials with ≥52 h of estimated contact, improvements were seen in SBP (−6.4 [95% CI, −8.6 to −4.2] mm Hg) and DBP (−4.0 [95% CI, −5.6 to −2.5] mm Hg) and some insulin or glucose measures in some trials, but benefits were rare and cardiometabolic outcomes were sparsely reported in trials of lower-contact interventions.	Consistency: reasonably consistent for weight outcomes, reasonably consistent for blood pressure and lipids, inconsistent for insulin/glucose measures Precision: imprecise	No evidence of reporting bias was identified, but many included trials limited by small sample sizes (n <40 per treatment group) and fairly high (2%-40%) attrition. Sixteen trials were excluded for poor quality. For cardiometabolic outcomes, reporting bias was not apparent because most of the highest-contact trials reported these outcomes. Reporting was sparest in trials with fewer than 52 h of contact, in which benefits were rarely found.	Fair to good (8 good, 34 fair)	Almost half of the trials were conducted in the United States, and more than one-third were conducted in primary care settings, but trials with the most contact hours and largest effects were not conducted in primary care. Access to similar programs is likely limited.
Metformin	8 (RCTs) n = 616	Metformin was associated with a small, statistically significant weight reduction with very low statistical heterogeneity, despite differences in dose and background therapy. In pooled analyses, metformin reduced BMI *z* score by −0.10 (95% CI, −0.17 to −0.03; 6 studies; I^2 = 13.1) and BMI by −0.86 (95% CI, −1.44 to −0.29[a]; 6 studies; I^2 = 0) vs placebo over 6 to 12 mo. Results of trials that could not be pooled were generally consistent with pooled results. Metformin was associated with no statistically significant benefit for fasting glucose, lipid, or blood pressure outcomes.	Consistency: Reasonably consistent Precision: imprecise	Small studies with wide CIs Short trials, primarily of 6-mo duration Limited data about persistence of effect after discontinuation	Fair (1 good, 7 fair)	Most trials conducted in the United States, but none in primary care. Seventy-five percent of trials required abnormalities of insulin or glucose values for inclusion and a mean baseline BMI of 36.0.[a] Reasonable representation of black and Hispanic youth.

(continued)

Table 4. Summary of Evidence (continued)

Topic	No. of Studies (Design), No. of Participants	Summary of Findings	Consistency/Precision	Limitations (Includes Reporting Bias)	Overall Study Quality	Applicability
Orlistat	3 (RCTs) n = 779	Orlistat was associated with small between-group reductions in BMI ranging from −0.94 (95% CI, −1.58 to −0.30) to −0.50 (95% CI, −7.62 to 6.62)[a] and weight ranging from −3.90 (−25.54 to 17.74) to −2.61 (95% CI not reported, $P < .001$) kg over 6 to 12 mo. The 1 trial reporting BMI *z* score showed a between-group difference of −0.06 (95% CI, −0.12 to 0.00) favoring orlistat. Where reported, changes in cardiometabolic risk factors were generally statistically nonsignificant, except for DBP reduction in a large trial (mean between-group difference, −1.81 mm Hg [CI not reported], $P = .04$).	Consistency: reasonably consistent Precision: imprecise	Small body of evidence (n = 3). One study was small (n = 40); the other 2 had short duration (6 mo). No study assessed weight change after medication use ended.	Fair (all fair)	All trials conducted in the United States, but none in primary care. Mean baseline BMI of 37.4.[a] Reasonable representation of black and Hispanic youth.
KQ4b: Common Components of Efficacious Interventions						
Lifestyle-based weight loss interventions	42 (3 CCTs, 39 RCTs) n = 6956	Hours of contact was the only treatment characteristic clearly associated with effect size. Most successful interventions took place outside of the primary care setting, targeted both the parent and child, provided didactic information, helped parents and children engage in stimulus control (eg, limiting access to tempting foods, limiting screening time), identified or helped participants identify specific goals, encouraged self-monitoring and problem-solving to help achieve the goals, and included supervised physical activity sessions.	Consistency: apparent dose-response effect for hours of contact; could not determine for other components Precision: NA	Interventions were highly variable, and the effect of specific components could not be evaluated.	Fair to good (8 good, 34 fair)	Almost half of the trials were conducted in the United States. More than one-third were conducted in primary care settings, but trials with the highest contact hours and largest effects were not conducted in primary care. Access to similar programs is likely limited.
KQ4c: Differences in Efficacy by Key Patient Subgroups						
Lifestyle-based weight loss interventions	42 (3 CCTs, 39 RCTs) n = 6956	Six trials reported subgroup analyses. Neither these analyses nor evidence in trials limited to important subpopulations suggested that lifestyle-based weight loss interventions were more or less effective in subpopulations defined by age, race/ethnicity, sex, degree of excess weight, or socioeconomic status.	Consistency: inconsistent Precision: imprecise	Six trials included subgroups analyses. Definitions of subpopulations varied across studies. Many subgroups involved small sample sizes. Statistical interaction testing was missing in several trials.	Fair to good (8 good, 34 fair)	Almost half of the trials were conducted in the United States. More than one-third were conducted in primary care settings, but trials with the highest contact hours and largest effects were not conducted in primary care. Access to similar programs was likely limited.
KQ5: Harms of Behavior-Based and Pharmacologic Treatment						
Behavior-based interventions	10 (RCTs) n = 1232	Among 10 trials reporting something related to adverse effects, 5 reported no adverse or serious adverse effects associated with the interventions. No group differences on eating disorder pathology or body dissatisfaction.	Consistency: consistent Precision: imprecise	Sparsely and inconsistently reported.	Fair to good (4 good, 6 fair)	Four US-based trials, 3 conducted in primary care, covering elementary school–aged children and adolescents.
Metformin	11 (RCTs) n = 705	Gastrointestinal adverse effects were common but not serious in participants taking metformin. Adverse effects were also frequently reported by those receiving placebo. Discontinuations due to adverse effects were relatively rare (<5%) and similar between groups.	Consistency: despite difference in how adverse effects were reported, results reasonably consistent Precision: imprecise	Inconsistent definitions of adverse effects across studies.	10fair,1good	Most trials conducted in the United States but none in primary care.
Orlistat	3 (RCTs) n = 779	Gastrointestinal adverse effects were very common among patients taking orlistat. Discontinuations due to adverse effects were relatively rare (<5%) and were about twice as common with orlistat compared with placebo.	Consistency: despite difference in how adverse effects were reported, results reasonably consistent Precision: imprecise	Evidence limited to 3 studies, 1 of which was small (n = 40).	Fair (all fair)	All trials conducted in the United States but none in primary care.

Abbreviations: BMI, body mass index; CCT, controlled clinical trial; KQ, key question; DBP, diastolic blood pressure; NA, not applicable; QOL, quality of life; RCT, randomized clinical trial; SBP, systolic blood pressure.

[a] BMI calculated as weight in kilograms divided by height in meters squared.

lipid and insulin measures as well as normalization of blood pressure and levels of total cholesterol and low-density lipoprotein cholesterol in a significant portion of participants with initially abnormal levels of these measures.[85] Setting aside the issue of degree of excess weight needed to improve cardiometabolic health, in many trials children in the control groups were more likely to continue gaining excess weight, in contrast to children in the intervention groups. Arresting the gain in excess weight likely constitutes a clinically important benefit for many of the interventions.

The results of this review are consistent with a recent review commissioned by the Canadian Task Force on Preventive Health Care, which included a different but overlapping body of evidence, including trials with no connection to a health care setting and limiting evidence to RCTs.[86] They found that behavioral weight management interventions were associated with a small but robust mean reduction in BMI (pooled mean difference, −1.15 [95% CI, −1.59 to −0.72]) as well as small improvements in blood pressure (SBP pooled mean difference, −4.64 [95% CI, −7.46 to −1.82]; DBP pooled mean difference, −4.08 [95% CI, −6.07 to −2.09]) and quality of life (pooled mean difference, 2.05 [95% CI, −0.31 to 4.40], based on instruments with possible ranges of 0 to 100 and 0 to 37). Those pooled effect sizes were entirely consistent with the findings of the current review. Differences in BMI change in the current review were typically greater than 1.0 for interventions with 26 or more hours of contact and most commonly less than 1.0 for those with fewer hours of contact. Other reviews have reported similar favorable effects of lifestyle-based weight management interventions, particularly comprehensive programs involving parents and at least a moderate level of intervention intensity.[87-89]

For metformin, the results for BMI change were generally similar to but smaller in magnitude than those reported in a recent systematic review that showed a pooled BMI reduction of −1.16 (95% CI, −1.60 to −0.73).[90] That review included trials that the current review excluded based on duration,[77-79] setting,[91] no use of a placebo pill in control groups,[92,93] quality,[94] and study aim other than weight loss.[95] It nevertheless reached similar conclusions: that the magnitude of BMI change was small compared with the reductions needed for long-term health benefits.[90]

Limitations

We identified several limitations to the evidence base, including no evidence related to the benefits or harms of screening for obesity. In the trials of treatment for excess weight, limitations included minimal follow-up beyond 12 months, many studies with small numbers of participants, methodologic limitations, and sparse reporting of health outcomes. Given the propensity for people to regain lost weight, the lack of long-term follow-up is a serious limitation. In addition, it was difficult to interpret average effects in the presence of high within-study variability in results. Results rarely allowed determining the proportion of children falling below obesity and overweight thresholds after participating in the interventions. The degree to which control group children independently sought out and participated in formal weight management programs is unknown but could attenuate the apparent benefit of the intervention. In addition, heterogeneity in population, study, and intervention characteristics, along with inconsistent reporting, precluded assessing how most of these characteristics affected the study results. The evidence base for pharmacologic studies was small, and one of the orlistat trials has not yet been published in a peer-reviewed journal. Most pharmacotherapy trials followed up children for only 6 months, and only 1 trial had planned follow-up after the medication was discontinued.

There was a relationship between estimated hours of intervention contact and effect size, although the estimate of contact hours was imperfect. First, not all studies reported a detailed description that included hours of contact, so session duration had to be estimated in many cases. Planned hours of intervention were estimated, but generally there was no access to actual hours received by participants. In addition, the continuous variable for estimated contact hours was divided into categories post hoc on the basis of maintaining methods of the previous review, extending similar logic, and the distributional properties of the included studies rather than on clear differences in effectiveness at specific cutpoints. Thus, it is not apparent that a 25-hour intervention would be substantially less effective than a 26-hour intervention.

Some bodies of literature not included in this review may provide relevant information. We limited the review to trials in which either the intervention or recruitment occurred in a health care setting, thereby increasing applicability to primary care, but interventions in some of the excluded studies were likely very similar to those in the included studies and at least somewhat applicable. In addition, multilevel trials, such as those that involve school- and community-level interventions as well as individually targeted interventions, may have included components in health care settings that were very similar to interventions in the included trials but that were not included because of the presence of other non–health care components. These trials might highlight the ability of health care–based interventions to potentiate other initiatives. Also, this review did not include a systematic search for observational evidence of harms of behavior-based interventions, although these interventions are unlikely to cause serious harms. In addition, the review did not include comparative effectiveness studies, which might have enabled better identification of specific components associated with effectiveness.

Conclusions

Lifestyle-based weight loss interventions with 26 or more hours of intervention contact are likely to help reduce excess weight in children and adolescents. The clinical significance of the small benefit of medication use is unclear.

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Concept and design: O'Connor, Evans, Burda, Eder, Lozano.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: O'Connor, Evans, Burda, Walsh, Eder.
Critical revision of the manuscript for important intellectual content: Burda, Eder, Lozano.
Statistical analysis: O'Connor.
Administrative, technical, or material support: Burda, Walsh, Eder.

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