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Effectiveness of Primary Care Interventions for Weight Management in Children and Adolescents: An Updated, Targeted Systematic Review for the USPSTF

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Structured Abstract

Objectives: To examine behavioral and pharmacological weight management interventions for overweight (defined as BMI ≥ 85th to 94th percentile of age- and sex-specific norms) and/or obese (BMI ≥ 95th percentile) children and adolescents which are feasible to conduct in primary care settings or that may be available for referral from primary care in order to update an identified gap in the previous report on childhood obesity for the United States Preventive Services Task Force (USPSTF).

Data Sources: We identified two good quality systematic reviews published after the previous USPSTF review that addressed our research questions. We searched Ovid MEDLINE®, PsycINFO, Database of Abstracts of Reviews of Effects, the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Education Resources Information Center from 2005 (2003 for pharmacological studies) to June 10, 2008 to identify literature that was published after the search dates of prior relevant systematic reviews; we also examined reference lists of five other good-quality systematic reviews and of included trials, and considered experts' recommendations. From the two good quality systematic reviews and 2786 abstracts, we identified 25 trials in 30 publications that addressed our research questions.

Review Methods: After review by two investigators against pre-determined inclusion/exclusion criteria, we included fair-to-good quality trials to evaluate the effects of treatment on weight and weight-related co-morbidities; we would have included large comparative cohort studies to evaluate longer term followup and harms of treatment if they had been available. Investigators abstracted data into standard evidence tables with abstraction checked by a second investigator. Studies were quality-rated by two investigators using established criteria.

Results: Available research primarily enrolled obese (rather than overweight) children and adolescents aged 4 to 18 years and no studies targeted those less than 4 years of age. Comprehensive behavioral interventions involving medium- to high-intensity interventions were the most effective behavioral approach and consistently resulted in small to moderate short-term improvements, with a weighted mean difference in BMI change of 2.4 kg/m^2 between groups. More limited evidence suggests that these improvements can be maintained completely (or somewhat) over the 12 months following the end of treatments, and that there are few harms with behavioral interventions. Two medications (sibutramine, orlistat) combined with behavioral interventions resulted in small to moderate short-term weight loss in very obese adolescents (BMI reduction of 2.6 kg/m^2 more than behavioral treatment plus placebo for sibutramine, 0.85 kg/m^2 for orlistat); however, no studies followed weight changes after medication use ended. Potential side effects were greater than for behavioral interventions and varied in severity. Only one medication (orlistat) is FDA-approved for use in children and adolescents, and it is approved for prescription use in those 12 years and older.

Conclusions: The research evaluating the treatment of obese children and adolescents has improved in terms of quality and quantity in the past several years. While there are still significant gaps in our understanding of obesity and overweight treatment in children and adolescents, current research suggests that behavioral interventions can be effective in managing weight in obese children and adolescents. Combined behavioral-pharmacological interventions may be useful in very obese adolescents, particularly if research confirms that weight loss is maintained.

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Chapter 1. Introduction

Scope and Purpose

This targeted systematic review was undertaken to assist the United States Preventive Services Task Force (USPSTF) in updating its previous recommendation on screening and interventions for overweight in children and adolescents.[1] Based on our previous systematic review in 2005,[2] the USPSTF found insufficient evidence to recommend screening for overweight, due to uncertainties about the effectiveness of behavior counseling or other interventions with overweight children and adolescents that could be conducted in primary care settings or to which primary care clinicians can make referrals. Given recent work on another systematic review, Effectiveness of Weight Management Programs in Children and Adolescents,[3] the USPSTF determined to focus its update on what was considered the critical evidence gap at the time of our last systematic review to allow an efficient and timely updating of their recommendation. Thus, for this targeted updated systematic review, we examine previous and newly available evidence on *behavioral*[*] and pharmacological weight management interventions for *overweight* and/or *obese* children and adolescents (defined as those between 2 and 18 years of age that meet criteria for increased *body mass index [BMI]* appropriate to their age and sex) that are relevant to primary care practice. Readers should note that while this current review builds on our previous USPSTF review, it also differs in scope and definitions of overweight and obesity used in that review. Specifically, the USPSTF has decided to upgrade the terminology it uses to define categories of increased BMI (see Table 1) to align its definitions with other major bodies addressing this issue. Attention to these differences in terminology is key, as children and adolescents defined as "overweight" in the 2005 report would now be defined as "obese".

And, while the current review is intended to fill the critical evidence gap about intervention effectiveness identified during the 2005 review, our previous review also found that there was insufficient evidence to ascertain the magnitude of the potential harms of screening or intervention. In this targeted update, the USPSTF focused our attention on updating both the benefits and potential harms of primary care feasible interventions, but did not choose to update the evidence on screening benefits or harms. Evidence on the harms as well as benefits of BMI screening programs, along with good data on the diagnostic accuracy of BMI as a measure of obesity in children, still appear to be lacking,[4] resulting in arguments against the use of BMI screening of individuals in schools or in other screening programs[5,6] that go beyond its use as a tool by clinicians for monitoring growth and development. The previous review also found fair evidence that obese adolescents and children (i.e., those at or above the 95th BMI percentile for age and sex) aged 8 years and older are at increased risk for becoming obese adults. Evidence on the benefits and harms of screening and on the risk of pediatric obesity persisting into adulthood will not be updated in the current review.

Additionally, in keeping with the USPSTF focus on primary and secondary clinical preventive services, surgical treatment of obesity was considered out of scope for this updated review, since surgical treatment is only considered for extremely obese young people,

[*] Words found in the glossary (located after the text) are italicized on first mention.

particularly those who are experiencing negative health effects as a result of their obesity necessitating treatment. We therefore focus on behavioral and pharmacological interventions, both of which may be appropriate for less obese or overweight children who would be identified and treated in or in coordination with primary care.

While prevention is a critical component of an overall public health strategy to address the dramatic increase in childhood and adolescent overweight in the United States and elsewhere, recent reviews indicate little empirical evidence of effective interventions for preventing development of overweight in clinical settings and are not included in this report.[7,8] Guidance on obesity prevention thereby generally focuses on pragmatic advice for clinicians[8,9] or on settings with evidence, as in schools and, to a lesser extent, community settings.[9,10] The conceptual integration of preventive programs across clinical and community settings have been addressed by several comprehensive reports elsewhere.[11-13]

Background

Definition and Measurement of Overweight and Obesity in Children and Adolescents

Obesity is a condition of excess body fat (adiposity), which is associated with adverse health states and risk for future disease. Despite their colloquial usage, obesity and overweight represent specific conditions in the medical and scientific literature. While these terms are defined primarily based on health risks in adults, the medical definition of obesity in children and adolescents is not as straightforward. At present, there is no universally accepted definition that distinguishes children with normal or healthy weight from those with unhealthy levels of adiposity. This creates significant problems for clinicians, policy makers, and researchers in that while obesity and its health effects are obvious in some children and adolescents, determining those who face health risks from adiposity when their overweight is less extreme is less apparent. In the absence of a clear, health-based definition of obesity, children are instead categorized as "overweight" and "obese" based on how they compare with a normative sample of children of the same age and sex.

Body mass index (BMI) is the most common measure used to define overweight and obesity in children, adolescents, and adults. BMI is a height-adjusted weight measure that is calculated from measured weight (in kg) and height (in meters) as kilograms divided by meters-squared (kg/m^2). Clinicians compare a child's BMI to that of other children of the same age and sex to determine a percentile score based on published norms, such as those developed by the Centers for Disease Control and Prevention (CDC) (see Figures 1 and 2).[14] Because BMI naturally changes with age, percentile scores based on age- and sex-specific norms are used to monitor growth and development in children and adolescents. Percentiles are based on population norms, rather than on health status, and those above the 85^{th} or 95^{th} percentile are categorized as having excess weight. Over time, changes in percentile scores can show clearly when a developing child is moving towards becoming fatter or slimmer.[15] Thus, while the actual BMI might stay the same or increase in an overweight growing child, a decrease in percentile score would indicate a positive outcome, as growth in height outstripped weight gain. Table 1 shows the BMI-based terms that denote different levels of excess weight in children and adolescents and compares them to terms in adults. Figures 1 and 2 also provide comparisons

between various height (inches or centimeters) and weight (pounds and kilograms) measures and absolute BMI, BMI percentiles, and BMI standard deviation scores (SDS).

An Expert Committee (A committee convened by the American Medical Association [AMA] and co-funded in collaboration with the Department of Health and Human Services' Health Resources and Services Administration [HRSA] and the CDC) recently recommended a change to the terminology used to define overweight and obesity in children, while retaining the same percentile cutoffs (Table 1).[11] The group now recommends using the term "overweight" to refer to children aged 2 to 18 years with BMI in the 85th to 94th percentiles for their age and sex. They recommend the term "obese" to refer to children with BMI at or above the 95th percentile for their age and sex or with a BMI at or above 30, which is the adult standard for defining obesity and may apply to older adolescents.[11] The 95th percentile curve for adolescents does not exactly match up with the BMI definition in adults because the adolescent curve is norm-based but the adult cut-off is not. Therefore, the alternate specification of having a BMI at or above 30 is added to the definition for children and adolescents to ensure consistency as adolescents mature into the adult norms.

Although it is not a direct measure of adiposity, BMI-for-age percentile measures in boys and girls correlate reasonably well with percentile rankings of directly measured percent body fat (correlations generally between 0.78 to 0.88).[16] Obesity (primarily defined as BMI ≥ 95th percentile) has also been correlated with childhood health consequences and risk factors for obesity-related morbidity in adults.[17-19] This relationship is complicated, however, by the fact that obesity may not persist into adulthood in as many as half of obese 10 year-olds, and obesity that does not persist has little impact on adult health outcomes.[20] And, since BMI is an imperfect measure of body fat, categorizing individual children and adolescents as obese based on BMI definitions can be problematic;[5] this may be particularly the case for non-white children who are less represented in the populations underlying CDC norms.[21] and who may also differ in normal body composition, growth, or development.[2] Recent data from the Bogalusa Heart Study found that 35 percent of children aged 5 to17 years with BMI ≥ 95th percentile did not have excess body fat.[22] However, almost all (94 percent) of those at or above the 99th percentile had excess body fat. Those with the highest BMI percentiles (≥ 99th) were also much more likely to have two or more cardiovascular risk factors (59 percent), compared with those in the broader group at or above the 95th percentile (39 percent with two or more risk factors). Noting these differences, experts have recently proposed distinguishing the "severely obese," defined by the 99th percentile, as those in particular need of clinical evaluation and treatment.

Since no measure is ideal for every age or degree of weight, many youth obesity researchers report multiple measures, including BMI, BMI percentiles, proportion change in BMI (BMI percentage), or *BMI standard deviation scores* (also known as BMI z-scores or zBMI), or an older measure, "percent overweight." Among these BMI measures, absolute BMI or BMI percentage may be preferable for measuring adiposity change in individual children.[15] For more detail on these measures see Appendix A, Detailed Methods, Literature Synthesis.

Prevalence of Children and Adolescent Obesity in the United States

Childhood and adolescent obesity has increased substantially during the past three decades. Between the early 1970s and 2003 to 2004, the prevalence of child and adolescent obesity (defined as age- and sex-specific BMI ≥ 95th percentile) increased three- to six-fold, depending on age, sex, and ethnicity.[23] During the most recent 2 years, the prevalence plateaued

among all gender, racial/ethnic, and age sub-groups.[24] Updated prevalence figures (2003 through 2006) suggest approximately 12 to 18 percent of 2- to 19-year-old children and adolescents are obese.[24-26]

Obesity prevalence varies somewhat with age and tends to be higher in older children, in males, and in racial and ethnic minorities. Children and adolescents aged 6 to 19 years had a higher prevalence of obesity (17 to 18 percent) than younger children aged 2 to 5 years (12.4 percent), according to data from the 2003 to 2006 National Health and Nutritional Evaluation Survey (NHANES).[24] Additionally, males had slightly higher prevalence of obesity for all age categories than females. When overweight (defined as age- and sex-specific BMI in the 85th to 94th percentile) children and adolescents were included, between one in three and one in four children and adolescents were identified as overweight or obese (24 to 34 percent).[23,24,26] Looking at the youth with the most severe levels of obesity, 3 to 6 percent of boys aged 13 to 17 years were at or above the 99th percentile. The comparable figure for girls was 1 to 3 percent.[22] Other researchers have used the 97th percentile as a cut point for measuring high BMI for age. Using that approach, 9 to 14 percent of boys and 8 to 11 percent of girls aged 2 to 19 years had a BMI at or above the 97th percentile.[24] See Table 2 for BMI and weight measures at median, overweight, obese and very obese BMI percentiles for boys and girls of several ages.

Risk Factors for Child and Adolescent Obesity and Overweight

While childhood and adolescent obesity has increased across the US population as a whole, minority children and adolescents in the US suffer obese and overweight disproportionately at all ages.[23] A recent, large, nationally representative study using NHANES data found that 23 percent of Mexican-American boys aged 2 to 19 years were obese, which was significantly higher than nonHispanic White (16 percent) and nonHispanic Black (17 percent) boys in the same age range.[24] Native American boys were also more likely to be obese—39 percent of Native American adolescent boys in the National Longitudinal Study of Adolescent Health (Add Health) were categorized as obese in the mid-1990s, compared with 10 to 15 percent among other ethnic groups.[27] Among girls in the NHANES study, prevalence of obesity in 2- to 19- year-olds was highest among nonHispanic Black girls (24 percent), followed by Mexican American (18 percent) and then nonHispanic White girls (14 percent).[24] These racial/ethnic disparities are consistent with prevalence figures reported by the Add Health study, which reported higher proportions of obesity in Black (18 percent), Hispanic (13 percent), and Native American (14 percent) adolescent girls, compared with Asian (4 percent) and nonHispanic White girls (10 percent).[27] Statistical tests of these differences, however, were not reported. Racial differences were also apparent in the persistence of obesity into adulthood among children and adolescents aged 5 to 14 years. One study found that among a mixed aged group (5 to 14 years), 65 percent of obese White girls and 84 percent of obese Black girls remained obese into adulthood, with similar results for obese boys (71 percent of White boys versus 82 percent of Black boys).[28]

Disparities in obesity prevalence are also apparent along socio-economic lines. There is a clear inverse correlation between income level and obesity prevalence in nonHispanic White children and adolescents. Obesity prevalence is highest in the lowest income bracket, and those with the highest income levels have the lowest obesity prevalence.[29] This inverse correlation is less clear for Black and Hispanic ethnic groups, however, since data on the relationship between income and obesity are mixed.[29]

Parental obesity is also an important risk factor. Children of obese parents have a higher risk of obesity,[30] with children of two obese parents having the highest risk of obesity.[31] A large-scale epidemiological study published in 1976 found that by age 17, children with two obese parents had three times larger triceps *skinfold* measures as those with two lean parents.[31] Compared to children without obese mothers, children with obese mothers are three to ten times more likely to be obese themselves. White and Black children of obese mothers are three times more likely to be obese, Hispanic children of obese mothers are twice as likely to be obese, and Asian children of obese mothers may be as much as ten times more likely to be obese.[32] In addition, maternal obesity has been associated with earlier age of obesity onset in children of the affected mothers.[32]

Comprehensive reviews have identified additional risk factors, some of which are modifiable (e.g., levels of physical activity and sedentary behavior, consumption of sweetened soft drinks or energy dense food, birth weight) and some of which are not (e.g., genetic variants, rate of maturation).[33-36] Modifiable factors are often the target of intervention. Non-modifiable risk factors, such as those highlighted here, may indicate a need to tailor a treatment approach, or a need for special recruitment efforts to increase participation in treatment programs in some high risk groups.

Prevalence and Burden of Illness

There is growing evidence that childhood and adolescent obesity can have a substantial health impact.[17,19] Causal relationships are difficult to establish, however, as the data on the health and psychosocial consequences of obesity in children and adolescents are almost exclusively observational. Observational data do show some important consistent relationships, however, between childhood obesity and specific health problems. For example, while most children will not experience the health consequences of persistent childhood obesity for decades, data suggest that some of these consequences can occur prior to adulthood, particularly in those who are severely obese.[19] Obese children and adolescents have a higher risk of *type 2 diabetes mellitus*, asthma, and nonalcoholic fatty liver disease, are more likely to have cardiovascular risk factors, such as *hypertension* and hyperlipidemia. These children and adolescents are also more likely to experience other adverse health-related events, such as perioperative adverse respiratory events when undergoing procedures requiring anesthesia.[17,19,37] Obese children may also be more likely to experience mental health and psychological issues, such as depression[38] and low self-esteem,[19,38,39] than nonobese children. The risk of mental health issues increases with age and is higher in girls,[17] likely reflecting the pressures of the social environment. For severely obese children, impacts on quality of life can be severe and other serious conditions such as obstructive sleep apnea, orthopedic problems, infertility, and increased intracranial pressure can occur.[17,19,40,41]

These increased health risks, however, do not necessarily lead to increased expenditures. Despite higher prevalence of health problems in obese children, actual health care expenditures paid by families (including costs of services, devices, and insurance) do not differ between healthy weight and overweight or obese children, when models are adjusted for age, gender, race, poverty status, and insurance type.[42] The authors of the study examining these models hypothesize that there are unmet healthcare needs among obese children, who are disproportionably low-income.

Costs incurred during childhood and adolescence however, may not give us a full representation of obesity's true impact. One of the greatest concerns about childhood obesity is that it may persist into adulthood.[43] Adult obesity, in turn, has a detrimental effect on adult health[9,44,45] and mortality.[44,46] Other systematic reviews have examined the persistence of obesity from childhood into adulthood.[2] Factors associated with greater persistence of obesity from childhood into young adulthood included older age and higher BMI (above the 95th percentile or higher). Recent data from the Bogalusa Heart Study confirm these findings.[43]

Even though it is difficult to disentangle childhood obesity's effects on morbidity and mortality from the effect of adult obesity, a systematic review reporting on the long-term consequences of pediatric obesity concluded that obesity-related cardiovascular disease can originate in childhood obesity.[17] This review, and others, indicate that childhood obesity has also been associated with adverse social and economic outcomes in young adulthood,[17,19,47] although childhood obesity in the absence of adult obesity appears to have little impact on adult socioeconomic, educational, social and psychological outcomes.[20] Much more research is needed to determine long-term health effects of childhood and adolescent obesity independent of adult obesity.

Current Interventions for Child and Adolescent Obesity and Overweight

Behavioral Intervention. Behavioral interventions are the most widely used and studied interventions for childhood overweight and obesity. Behaviorally-based interventions promote weight loss through modifications in diet and activity level without the use of adjuncts, such as pharmacologic agents, and are the first-line treatment for overweight and obesity in children and adolescents.[40] Typical behavioral interventions are designed to modify an individual's food consumption by emphasizing healthy eating and reducing consumption of high-calorie/low-nutrient snack foods. A range of approaches have been used to encourage more healthy patterns of dietary intake and physical activity, which are discussed in detail elsewhere.[11,40,48] Behavioral interventions often involve parents or entire families, particularly for younger children. Optimally, behavioral interventions include cognitive and behavioral management techniques to help participants initiate and sustain needed lifestyle changes, and may include elements such as problem solving, limiting exposure to unhealthy food, healthy thinking about food and the body, and relapse prevention.[40,48] We refer to programs that focus on dietary counseling and brief lifestyle change advice without more extensive use of behavioral management principles as "brief behaviorally-based counseling" interventions. We use the term "behavioral management intervention" to denote more extensive programs that include principles of cognitive and/or behavioral management. We use the term "behavioral intervention" to refer to both behavioral counseling and management interventions.

Pharmacologic treatment. Pharmacological agents represent another intervention for childhood obesity. Weight loss drugs can be divided into two main categories based on their putative mechanism of action—appetite suppressants and lipase inhibitors. Orlistat is currently the only drug that the United States Food and Drug Administration (FDA) has approved for prescription use in obese children and adolescents (aged 12 and older).[49] Orlistat is a lipase inhibitor that is thought to promote weight loss by reversibly binding to the active center of the enzyme lipase, preventing digestion and absorption of some dietary fats. It also reduces the

absorption of fat-soluble vitamins. In 2007, the FDA approved orlistat for over-the-counter use among adults aged 18 years and older.[50]

Sibutramine is a centrally acting appetite suppressant that selectively inhibits the reuptake of serotonin and norepinephrine, increasing their levels in the brain. Sibutramine has been approved by the FDA for treating obesity in adults, and its labeling indicates that safety and effectiveness is not established in pediatric patients under 16 years of age.[51] Sibutramine and orlistat are the two most well-studied weight loss drugs among adults. Several other appetite suppressants are FDA-approved only for short-term treatment of overweight adults (benzphetamine, diethylpropion, phendimetrazine, and phentermine).[52] These drugs are all structurally similar to amphetamine and pose a theoretical risk for abuse and addiction.[53] Two other amphetamine-like drugs that were widely used during the 1990's, fenfluramine and its active isomer dexfenfluramine, were implicated in unusual cases of left-sided cardiac valve degeneration and were taken off of the market in 1997.[53] Additional drugs that are not FDA-approved for treating overweight or obesity have been considered as potential weight loss agents, such as some antidepressants (fluoxetine, sertraline, and bupropion), antiepileptic drugs (topiramate, zonisamide, lamotrigine), and the antidiabetic biguanide *metformin*.[52]

A recent systematic evidence review found that numerous different drugs produced modest weight loss among adults when combined with dietary recommendations: sibutramine, orlistat, phentermine, bupropion, fluoxetine, topiramate, and probably diethylpropion.[54] The review found that additional weight loss attributable to these drugs was less than 5 kg at 1 year. The drugs were not compared directly against each other, however, and the report found no evidence that any particular drug produced more weight loss than any other. All of the drugs had side effects. Sibutramine was associated with modest increases in heart rate and blood pressure and with preventing decreases in blood pressure that may have occurred with weight loss. Orlistat was associated with numerous gastrointestinal side effects such as diarrhea, flatulence, bloating, abdominal pain, and dyspepsia.

Factors Contributing to the Recent Increase in Childhood Obesity

While many experts have speculated on the causes of the recent increases in childhood obesity,[55,56] data are not available to conclusively determine causality. Evidence does support the relationship between childhood obesity and several lifestyle factors, however, such as overall physical activity, sedentary behaviors, and intake of sweetened beverages.[40] These and other factors, such as self-reported dieting to lose weight (particularly unsupervised, drastic, and/or inconsistent efforts using unhealthy weight loss approaches), are also associated with persistence of obesity between adolescence and adulthood.[57,58] Children (ages 2 to 17) averaged 4.7 hours per day of "screen time" (e.g., television and computer use),[59] and cross-sectional data show that higher prevalence of obesity is associated with more hours per day watching television.[60,61] Likewise, an obesity prevention program that reduced screen time by an average of almost 10 hours per week also resulted in a BMI reduction of 0.45 kg/m^2 in sample of 3rd and 4th grade school children.[62]

Environmental factors also likely reduce children's physical activity. In 1969, for example, 42 percent of children walked or rode their bikes to school. By 2001 this number had fallen to 16 percent.[63] Enrollment in physical education classes has declined from 41.6 percent in 1991 to 28.4 percent in 2003 in high school students.[64] These figures are especially poignant given that longitudinal and cross-sectional observational data have demonstrated that higher

levels of physical activity tend to be associated with lower BMIs in children.[60,65] In one study, for example, an increase in 1 hour/day of physical activity was associated with a BMI decrement of 0.22 kg/m^2 in boys and 0.16 kg/m^2 in girls after 1 year.[65]

Intake of sweetened beverages has also increased and appears to contribute to childhood obesity.[40,66-68] Between the late 1970s and the late 1990s, average daily intake of sweetened beverages increased from 5 ounces to 12 ounces in 6 to 17 year-olds.[68] This 7 ounce daily increase is especially troubling given that BMI increases by an estimated 0.01 kg/m^2 with every 100 grams of regular soda consumed daily in adolescent girls.[66] Stated more clearly, the odds of obesity increase by 60 percent with each additional daily serving of sugar-sweetened soda a child consumes.[69]

Previous USPSTF Recommendation

In 2005, the USPSTF concluded that the evidence was insufficient to recommend for or against routine screening for overweight in children and adolescents as a means to prevent adverse health outcomes ("I" Recommendation). This recommendation was based on the conclusion that while there was fair evidence that overweight adolescents and children aged 8 years and older are at increased risk for becoming obese adults, there was insufficient evidence for the effectiveness of behavioral counseling or other preventive interventions with overweight children and adolescents that could be conducted in primary care settings or to which primary care clinicians can make referrals. The previous report also concluded that there was insufficient evidence to ascertain the magnitude of the potential harms of screening or prevention and treatment interventions.

Chapter 2. Methods

Methods Synopsis

Using the methods of the USPSTF,[70] we developed three key questions (KQ) (with six sub-key questions) and an analytic framework (Figure 3) in conjunction with members of the USPSTF to update its 2005 recommendation on Screening for Childhood Overweight and Obesity. These KQs were designed to evaluate the effectiveness and safety of behavioral and pharmacological treatments for overweight and/or obese children. Key question 1 evaluates the effectiveness of interventions in reducing or stabilizing weight in the short-term (6-12 months since enrolling in treatment), while KQ2 focuses on the maintenance of BMI improvements through medium-term (between 1 to 5 years since enrollment and at least 12 months since treatment ended). Key question 3 assesses adverse effects of behavioral and pharmacological interventions. Key questions 1a and 2a consider other beneficial outcomes arising from the interventions. Key questions 1b, 2b, 1c, and 2c address whether specific program components and population or environmental factors can be identified among effective weight management programs.

We initially searched for systematic reviews and selected relevant, good quality systematic reviews where available to assist in conducting our literature search. A 2006 comprehensive National Institute of Health and Clinical Excellence (NICE) report was based on a series of systematic reviews and addressed the prevention and management of obesity in adults and children.[9] Relevant portions of this report served as a basis for the primary search for the literature included in the current report. Since the NICE report only included orlistat and sibutramine, we used another good-quality review of pharmacological treatments[54] as the basis for our search for pharmacological treatments. We conducted update searches in Ovid MEDLINE®, PsycINFO, Database of Abstracts of Reviews of Effects, the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Education Resources Information Center from 2005 (2003 for pharmacological treatments) to June 10, 2008 to identify literature that was published after the search dates of these reports (Appendix A Table 1). We also hand-searched the reference lists of other good-quality reviews of childhood obesity treatment,[2,7,48,71,72] received suggestions from experts, and searched reference lists of included trials and other relevant reviews and articles. We did not search for data from non-peer-reviewed sources or in non-English literature.

Two investigators independently reviewed 2786 abstracts and 369 articles against specified inclusion/exclusion criteria for each key question. Discrepancies were resolved by consensus. Detailed inclusion/exclusion criteria can be found in Appendix A Table 2. Briefly, we included controlled trials in primary care-relevant settings published in 1985 or later designed to promote weight loss or maintenance in overweight or obese 2 to 18 year-olds. We excluded studies of children with idiosyncratic weight management issues due to behavioral, cognitive, or medical factors. Trials were required to report weight outcomes of at least 6 months, although we included immediate harms when these were also reported. Trials were required to have a minimal intervention, attention control, usual care, placebo, or no-treatment control group and randomize at least 10 participants in each arm. For KQ3 (harms), we abstracted all reports of harms or potential harms in included studies. In addition, weight management programs

reporting adverse events resulting in death, hospitalization, or need for urgent medical or psychiatric treatment were included even if they did not meet the minimum 6-month followup required for the other key questions. We examined other beneficial outcomes (KQ1a and KQ2a), important components of care (KQ1b and KQ2b) and population or environmental factors (KQ1c and KQ3c) using trials that were included for KQ1 (short-term efficacy) or KQ2 (maintenance efficacy). Based on prior literature,[2,10,48,73,74] we limited our examination of specific intervention components (KQ1b and KQ2b) to the use of organized physical activity sessions, behavioral management techniques, and parental or family involvement. Details of how these components were coded can be found in Appendix A Detailed Methods.

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 using established design-specific criteria (Appendix A Table 3). 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 follows: very low (less than 10 hours), low (10 to 25 hours), medium (26 to 75 hours), and high (over 75 hours). Weight outcomes were categorized as short-term (6 to 12 months since beginning treatment) or maintenance (between 1 and 4 years after beginning treatment and at least 12 months after ending active treatment). In addition, we evaluated whether or not 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 provided 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. More detail about how these elements were operationalized can be found in Appendix A Detailed Methods.

Where possible, data were synthesized using quantitative methods. For most questions, however, we relied on qualitative synthesis due to 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 type of intervention. We modeled typical cases to more clearly demonstrate the magnitude of weight change in pounds. In these cases, we used growth charts[14] and on-line calculators[75,76] provided by the Centers for Disease Control and Prevention (CDC) to estimate average height for age and to translate between percentile scores, BMI, percent overweight, kilograms, and pounds.

For the behavioral interventions, we conducted meta-analyses of short-term and maintenance outcomes separately. 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 or obtained from the author, 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 examining only those reporting BMI change and found that that pattern of results and magnitude of effects were very similar to those seen in the primary meta-analysis that included all trials (and allowed different measures of weight change). All meta-analyses were conducted using RevMan 4.2. We did not quantitatively pool the results of the pharmacological trials due to the heterogeneity in the specific drug studied, length of treatment, and length of follow-up, in addition to differences in how outcomes were reported.

USPSTF Involvement

The authors worked with four USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework and key questions, resolve issues around scope and approach, and will work with them to finalize this draft report. Research was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the USPSTF and AHRQ staff provided oversight throughout the project.

Chapter 3. Results

We begin the results section by reporting the short-term (KQ1) and maintenance (KQ2) results, for behavioral and then pharmacological studies. We then discuss the questions of other positive outcomes (KQ1a and KQ2a), important components of treatment (KQ1b and KQ2b), and the impact of population and environmental factors (KQ1c and KQ2c) on the combined evidence of KQ1 and KQ2. We only identified four trials that met our criteria for maintenance for the behavioral trials, and two of these were also part of KQ1. Thus, the evidence base was too sparse to explore the subquestions of other positive outcomes (KQ2a), important components of treatment (KQ2b), and other factors (KQ2c) for the maintenance trials alone. And, as these trials were divided on the basis of time to followup only, the two groups of trials were not fundamentally different bodies of literature.

Finally, we discuss harms of behavioral and pharmacological interventions (KQ3) as reported in the trials reviewed in KQ1 and 2. In this section, we report on two additional behavioral trials that did not meet inclusion criteria for either KQ1 or KQ2, but did meet criteria for KQ3.

KQ1. Do weight management programs (behavioral, combined behavioral and pharmacological) lead to BMI, weight, or adiposity stabilization or reduction in children and adolescents who are obese (≥ 95th BMI percentile) or overweight (84–94th percentile)?

Behavioral Interventions

Summary of findings. Of the 11 behavioral interventions trials which measured short-term weight outcomes (6 to 12 months after entry), only two were included in the previous (2005) USPSTF review. All 11 behavioral intervention trials were consistent with a beneficial effect on BMI, BMI SDS, or on percentage overweight among the 1099 obese or overweight children or adolescents aged 4 to 18 years studied, although not all differences were statistically significant (Table 3; Figure 4). Differences between intervention and control groups ranged from 0.3 to 3.3 kg/m^2 and reflected weight loss as well as weight gain prevention among treated participants. Intervention effectiveness tended to increase with more intensive interventions. The largest effects (between-group BMI differences of 1.9 to 3.3 kg/m^2) were seen in three comprehensive weight management programs (including dietary or weight loss counseling, physical activity counseling or program, and use of behavioral management technique to assist in behavior change) with at least medium (26 to 75 contact hours) or high (76+ contact hours) intensity. Meta-analysis confirmed that among comprehensive weight management programs, medium-to-high intensity interventions had a significantly larger effect on weight outcomes than did very low-intensity (under 10 hours) interventions. Data were limited about non-comprehensive weight management programs, and showed mixed results.

Intervention descriptions from the seven effective comprehensive programs and two effective non-comprehensive programs are described in Table 4, with two representative "best-case" programs in specialty healthcare and in primary care further detailed in the text below.

Study Details. Eleven trials[77-90] (in 14 publications) measured short-term weight outcomes (6 to 12 months after entry into treatment) (Figure 4), with only two[83,84] available at the time of our 2005 review.[2] These trials randomized a total of 1099 overweight or obese children and adolescents (Table 3). Ages enrolled in trials varied substantially, with some trials focusing only on younger children, some only on adolescents, and others spanning a wide age range. Trial participants were evenly divided between males and females: most trials were between 40 and 60 percent female, but two trials were more than 60 percent female and one was only 34 percent female. Only four trials reported a substantial proportion of nonWhite or Hispanic participants, ranging from 24 to 63 percent. The remaining either did not report race or ethnicity, or were predominantly nonHispanic White. Before treatment the mean BMI indicated that most participants in these trials exceeded the 95th percentile for BMI, and in some cases met adult criteria for Class I obesity.

Trial characteristics are listed in Table 3. All but three of the interventions provided comprehensive programs, which included dietary counseling, physical activity program or counseling, and behavior modification principles. Many involved families. Unique intervention elements included specialty mental health treatment that was not focused solely on weight management, pedometers, and screen monitoring devices to limit television and computer use. Settings included primary care,[81,83] specialty health care or similar,[77-80,85,87] the internet,[86] a community setting,[82] or the setting of one trial could not be ascertained.[84] Studies were conducted in the United States, Australia, Germany, Israel, and Sweden

We evaluated a total of 14 different active treatment arms. Treatment duration ranged from 3 to 24 months, with the exception of one study using a "rapid pace" treatment arm that lasted only 4 weeks.[84] Treatment intensity (estimated in hours of contact) ranged from 3.8 to almost 100 hours. We could not calculate exact hours of contact for one trial that involved a device limiting the television viewing and computer use, but the number of contact hours with the study staff was estimated to be very low. Control groups varied from no treatment to 1 to 2 brief counseling sessions to usual care (in primary care settings), and one older trial[84] matched the number of contact hours in the intervention group with social support, relaxation, and mood monitoring activities rather than healthy lifestyle counseling.

All trials were consistent with a beneficial effect on BMI or weight change, compared with controls. Not all of these differences, however, were statistically significant. Across all trials, short-term BMI changes in intervention groups ranged from dropping 1.7 kg/m^2 [77] to increasing by 0.5 kg/m^2.[81] Control group BMI changes ranged from dropping 0.4 kg/m^2 [82] to increasing by 2.0 kg/m^2.[79] Thus, differences in short-term improvements in BMI between intervention and control groups ranged from 0.3 to 3.3 kg/m^2 and these differences reflected weight loss and weight gain prevention among treated participants. Comprehensive medium- to high-intensity programs showed the largest effects and were consistently statistically significant.[77,79,85] BMI change in comprehensive medium- to high-intensity programs were 1.9 to 3.3 kg/m^2 greater in the interventions than the control conditions.

Seven of 11 trials reported BMI changes from baseline or post-intervention, while three reported changes in BMI SDS[78,80,87] and one reported changes in percent overweight.[84] Meta-

analyses of all 11 trials reporting standardized mean differences for short-term, weight-related outcomes after behavioral interventions were conducted after grouping the trials on the basis of comprehensiveness and intensity (Figure 4). A parallel analysis was also conducted on the subset of trials reported BMI change, calculating weighted mean differences, which resulted in a very similar pattern of results, though with greater statistical heterogeneity (Figure not shown).

Standardized effect sizes ranged from -1.01 ($p<0.001$, I^2=0 percent, weighted mean BMI difference of -2.4 with $p<0.001$, I^2=64%) for the comprehensive, medium- to high-intensity programs to -0.19 ($p=0.31$, I^2=0 percent) for low- to very low-intensity focused interventions. The standardized effect size for comprehensive, low-intensity programs was not statistically significant ($p=0.08$) and showed a high degree of statistical heterogeneity (I^2=77 percent). One[84] of these three trials had a much larger effect than the other two,[80,86] but was also much older (published in 1985 compared with 2007 for both of the others), smaller (n=35 randomized), and suffered from high attrition. Thus, the two more recent, better quality trials represent better estimates of the effects of low-intensity comprehensive interventions, which were small (-0.26 and -0.28) and not statistically significant.

Although comprehensive low-intensity interventions did not produce statistically significant treatment benefits, the standardized effect of comprehensive very low-intensity trials was statistically significant at -0.39 ($p=.006$, I^2=0 percent, weighted mean difference of -0.63, $p=0.18$ I^2=60%). Two of these were conducted in primary care settings and recruited participants through primary care. The third was conducted in a primary care setting, though the participants had all been referred to one of the researchers for weight management, and are therefore more akin to a specialty care population. Though data are very sparse and must be interpreted cautiously, these data suggest that very low-intensity interventions may result in improved weight management in primary care settings in the short term.

The non-comprehensive (focused) interventions were all estimated to be low or very low-intensity. Results showed that the use of pedometers without a comprehensive weight management program was not effective in improving weight management.[82] Devices to monitor and limit weekly screen time (computer or television) in young children (4-7 year old) who spend an average of 2 hours or more per day in front of a screen, however, were effective weight management tools at 12 months, even without a comprehensive weight management program, although data reporting limited our ability to report effect sizes at 12 months.[87] At the end of the two-year intervention, BMI SDS had declined by 0.24 in the treatment group (n=35) and only 0.13 in the control group (n=32). Post-hoc analyses showed that socioeconomic status moderated the effect of the intervention, with children from lower SES families showing a greater benefit than those from higher SES families.[87]

Study design and quality. We rated six[77,80,81,83,86,87] of the trials good-quality, while the remaining trials were rated fair-quality (see Appendix A Table 3 for quality criteria). Most trials were randomized controlled trials, but one was a nonrandomized controlled trial.[79] Most trials using randomization failed to report whether treatment allocation was blinded and most trials did not report whether those conducting followup assessments were blind to the treatment condition. Many of the trials were also quite small; only three trials had treatment arms with more than 40 participants at followup. While most trials reported retention of 90 percent or higher, retention in three trials was below 70 percent.[77,78,84] One of these three trials[77] included statistical methods to compensate for attrition. Several trials statistically tested for differential attrition (none found differential attrition between treatment and control groups), but most did not. Two smaller

trials[78,85] appeared to have differential attrition, but these differences were not tested statistically. The majority of trials were published in 2005 or later, and only two[83,84] were included in the previous USPSTF review.

It is difficult to determine how well the results of these trials would generalize to patients in real-world treatment settings. Several studies relied at least in part on media advertisements for recruitment, and may therefore have enrolled participants who are more motivated to lose weight than a typical obese young person. One trial[81] recruited participants via primary care screening. Because they attempted to find and enroll all eligible primary care patients, rather than relying on interested patients to contact them, generalizability to primary care settings is improved. However, only 32 percent who met weight criteria actually enrolled in the trial. There may be unmeasured differences between children who did and children who did not participate that influence how well they respond to the intervention. For example, children and adolescents who participated may have higher levels of motivation, more free time, more involved parents, more failed attempts at weight loss, or any number of factors that may moderate the intervention's effectiveness.

Best average intervention effect from a specialty healthcare setting. One good-quality trial conducted by Savoye and colleagues[77] provides a realistic best-case scenario. This trial reported one of the largest effect sizes of the outpatient programs included in this review and a comprehensive program in which many families with overweight children could realistically participate. This year-long program (Bright Bodies Weight Management) was conducted at a pediatric obesity clinic in the United States and accepted children ranging from age 8 to 16 years, with an average age of 12.1 years. Sixty-one percent of the 174 participants were girls. The Bright Bodies program involved about 98 hours of contact and an extensive educational program providing information on nutrition, physical activity, behavior change strategies, coping skills, and relapse prevention. The program provided organized exercise sessions twice per week during the first 6 months, then once every two weeks during the next 6 months. Parents or caregivers attended all educational sessions. Children and adolescents in the intervention group began the program with an average BMI of 35.8 kg/m^2, which dropped by an average of 1.7 kg/m^2 by the end of the intervention, compared with an average increase of 1.6 kg/m^2 in the control group. This trial suffered from somewhat low retention (77.6 percent at 6 months and 66.7 percent at 12 months), but took statistical measures to examine and combat the effects of attrition, including comparing results in completers only with results involving multiple imputation and data replacement methods.

To provide a more concrete example of the average impact of the Bright Bodies program, we modeled the impact on a 12-year-old girl who began the program at an assumed height of 5'0", with the average entry BMI of 35.8, and who experienced the average reduction in her BMI by 1.7 kg/m^2 over the course of the intervention year, while growing 2 inches (an average for this age and sex). This would amount to a change from 183 pounds to 186 pounds 1 year after she participated in the program, compared with an expected 21 pound weight gain and an increase of 1.6 BMI kg/m^2 if she had not participated.

Best average intervention effect from a primary healthcare setting. One good-quality primary care-based trial showed a statistically significant effect in overweight and obese adolescents. This trial would likely be feasible for implementation in many primary case settings, with some additional resources and institutional support.[83] The Healthy Habits intervention began with a computerized assessment and planning tool that assessed eating, physical activity,

and sedentary behavior in 12 to 16 year olds, average age of 14 years. The intervention then developed a personalized plan to improve each participant's habits in these areas. The computer program helped the youth identify benefits, barriers, and specific strategies to reach identified goals. The youth were also given a non-tailored treatment manual covering behavioral skills for weight control. The pediatrician discussed the summary and action plan generated by the computer program. Telephone counselors contacted the adolescents weekly for 8 weeks and biweekly for the last three calls to help them implement their treatment plan and troubleshoot adjustments to the plan. As calls lasted 10 to 20 minutes, we estimated that the entire program involved approximately 3.8 hours of contact.

Youth in the intervention group began the trial with an average BMI of 31.0 kg/m^2 (obese by adult standards, and well above the 95th percentile). This average, however, dropped to 30.9 kg/m^2 at the end of the 4-month treatment phase, and averaged 31.1 kg/m^2 3 months later. The control group participants had an average baseline BMI of 30.7 kg/m^2, which increased to 31.8 kg/m^2 4 months later, and ended up with an average BMI of 32.1 kg/m^2. We modeled the impact of the program on a 14-year-old girl (average baseline age was 14.2) who began the program at an assumed height of 5'4" and who grew 1 inch from baseline to 7-month assessment. Based on the average BMIs at baseline and 7-month assessment for each group, she would have gained 7 pounds (from 180 to 187 pounds) if she had been in the intervention group, and 14 pounds (179 to 193) in the control group.

Combined Behavioral and Pharmacological Interventions

Summary of Findings. Among 691 obese adolescents aged 12 to 18 years, BMI was reduced 2.9 to 3.6 kg/m^2 in those treated with 6 to 12 months of sibutramine plus behavioral intervention compared with a BMI reduction of 0.3 to 1.8 kg/m^2 in those receiving placebo plus behavioral intervention (between group BMI differences of 1.6 to 2.7 kg/m^2) (Table 5). In a very small study (n=24) of obese adolescents, shorter-term (3 month) sibutramine treatment within a 6-month behavioral intervention was not more effective than behavioral intervention alone. Among 539 obese adolescents aged 12 to 18 years, 12 months of orlistat plus behavioral intervention reduced weight gain (0.53 kg) compared with behavioral intervention alone (3.14 kg), resulting in a small, but statistically significant between-group BMI difference (0.85 kg/m^2). In a smaller study (n=40), 6-month orlistat plus behavioral intervention resulted in a smaller (0.55 kg/m^2) non-significant BMI reduction compared with behavioral intervention alone. In a small number (n = 145) of very selected obese children and adolescents aged 9 to 19 years (all with additional risk factors for developing type 2 diabetes mellitus), 6 months of metformin therapy led to a statistically significant net reduction in BMI SDS in two of three studies (between-group difference in BMI of -0.79 to -1.4 kg/m^2).

Study Details. We identified seven trials (all fair- or good-quality RCTs)[91-97] evaluating a pharmacological agent's effect (either sibutramine or orlistat) on overweight or obesity in a total of 1,294 adolescents aged 12 to 19 years (Appendix B Table 2). Five obesity treatment trials[91,92,94,95,97] evaluated the effectiveness of 10-15 mg/day of sibutramine in 715 patients. Two trials[93,96] evaluated the effectiveness of orlistat (120 mg three times a day) in 579 patients. All pharmacological obesity treatment trials compared the active medication plus behavioral counseling (with or without a behavioral management program) to the effects of placebo plus the same behavioral counseling. Multivitamin supplementation was provided for all participants in both of the orlistat trials. Although these are not broadly generalizable, we also describe weight-

related and other outcomes from three small trials testing the effect of metformin on preventing glucose intolerance or improving insulin sensitivity in 145 selected obese adolescents with additional risk factors for diabetes.[98-100] The trials compared the effect of metformin to placebo therapy, either with minimal[100] or no[98,99] concurrent behavioral counseling intervention. (see Table 6)

Participants in the sibutramine and orlistat trials all met a BMI-based criteria for obesity (either above the age- and sex-specific 95 to 97th percentile or above a BMI of 30 kg/m^2), and mean BMI in these trials was typically 35 to 38 kg/m^2 at baseline. Most trials excluded those at or above the midpoint for Class III (morbid) obesity (BMI exceeding 44 kg/m^2) and those with type 1 or type 2 diabetes mellitus. The sibutramine trials also generally excluded patients who had cardiovascular disease or hypertension. About two-thirds of participants in these trials were females. The majority of trials did not report race/ethnicity of participants. In the two largest multi-center RCTs, however, almost half of the sibutramine patients were racial/ethnic minorities,[92] as were one-quarter of orlistat patients.[93] The sibutramine trial included 21 percent Black participants, 16 percent Hispanic participants, and 7 percent other nonWhite patients. The orlistat trial included 17 percent Black participants and 7 percent of other race-ethnicity. Additionally, a small (n=52) sibutramine trial conducted in Mexico could have applicability to adolescents of Mexican heritage living in the United States.[94]

The minimal behavioral intervention provided to all participants in sibutramine and orlistat trials consisted of advice to follow a calorie-restricted diet (e.g., 500 kcal/day deficit) and meet physical activity goals (e.g., at least 30 minutes of aerobic activity per day). All but one trial[95] also included a behavior management program, ranging in intensity from seven to 19 sessions with a dietitian, psychologist, or psychiatrist. Family members attended behavioral management sessions in only two of the seven trials.[91,97] The length of drug therapy was 3, 6, or 12 months (in one, four, and two trials, respectively). We report the followup results at 6 months in the single trial evaluating 3 months of drug therapy (sibutramine). No other trials reported followup results describing weight patterns after pharmacologic treatment ended.

Of the six trials that reported their funding sources, all but one was funded completely or partially by the pharmaceutical industry. Two of these pharmaceutical-industry sponsored trials were large (about 500 participants) multi-center RCTs (over 30 study sites) conducted in the United States and Canada. One evaluated sibutramine[92] and the other evaluated orlistat.[93] The remaining trials randomized much smaller samples (n = 24 to 82), were conducted at single sites, and reported outcomes after only 6 months of treatment.

Sibutramine. Five trials reported outcomes 6 or 12 months after starting sibutramine treatment (in seven publications) (Table 4).[91,92,94,95,97,101,102] One of these was a small trial (n=24) that evaluated 3 months of a behavioral intervention plus sibutramine (10 mg) or placebo treatment, followed by 3 months of a behavioral intervention alone.[97] Based on our calculations, BMI was not reduced more in those receiving sibutramine plus a behavioral intervention compared with placebo treatment plus a behavioral intervention. Both groups had similar, modest (-0.8 kg/m^2 to -1.4 kg/m^2) mean reduction in BMI at 6 months. All of the three trials reporting weight outcomes immediately after 6 months of treatment with sibutramine plus a behavioral intervention found a statistically significant difference between the intervention and control groups, favoring a greater reduction in BMI in the group treated with sibutramine.[91,94,95] Among patients treated with sibutramine plus a behavioral intervention, the mean reduction in BMI ranged from -3.2 kg/m^2 to -3.6 kg/m^2. In contrast, the mean reduction in BMI among

patients treated with placebo plus behavioral therapy ranged from -0.9 kg/m^2 to -1.8 kg/m^2. Budd and colleagues[101] presented a secondary analysis of the data from one of these trials,[91] reporting outcomes separately for the 34 Black and 45 White participants. At month 6, there were no statistically significant differences in the outcomes between racial groups. This trial, however, was not designed to have adequate power to detect differences between racial groups.

The single large trial that reported weight outcomes after 12 months of sibutramine plus a behavioral intervention also found statistically significant results in favor of the sibutramine group.[92] The mean reduction in BMI in the sibutramine group was -2.9 kg/m^2 compared to -0.3 kg/m^2 in the control group ($p < 0.001$). As noted, this trial had higher attrition in the placebo control group (38 percent) than the sibutramine group (24 percent, $p = 0.001$), somewhat reducing our confidence in these findings. BMI measures over time, however, were also analyzed using a linear mixed-effects model to predict missing values. In these analyses, the mean change in BMI between treatment and control groups was also statistically significantly different at all study visits from week 1 through month 12. The difference between the changes in BMI z-scores was also statistically significant. The mean change in body weight (± standard error [SE]) at month 12 was -6.5 ± 0.31 kg in the sibutramine group versus 1.9 ± 0.56 kg in the placebo group (difference, -8.4 kg, or 18.5 pounds (CI: -9.7 ,-7.2 kg); $p < 0.001$ by linear mixed-effects model).

Orlistat. Two trials reported the weight outcomes after 6 or 12 months of orlistat therapy plus a behavioral intervention and results were mixed. The large (n=539), multi-center trial evaluating 12 months of orlistat therapy found a statistically significant difference between the change in BMI favoring the orlistat plus a behavioral intervention group (-0.55 kg/m^2 vs. 0.3 kg/m^2, $p < 0.001$).[93] The absolute mean body weight increased in both groups during the 12-month trial, but increased less in the orlistat group (0.53 kg vs. 3.14 kg, $p < 0.001$). Attrition in this trial was quite high (33 to 34 percent), but analyses of primary weight outcomes included over 98 percent of randomized participants and replaced missing data using the last observation carried forward (LOCF) method. Also, baseline characteristics were not different for completers or those who dropped out within each group. Nevertheless, the high level of attrition in the trial somewhat limits its validity. A smaller trial (n=40) that evaluated the effects of 6 months of orlistat plus a behavioral intervention found that the orlistat group had a larger BMI reduction than the control group (-1.3 kg/m^2 vs. -0.8 kg/m^2), but this difference was not statistically significant.[96]

Study design and quality. All included studies of sibutramine and orlistat were double-blinded, placebo-controlled RCTs of fair- or good- quality (see Appendix A Table 3 for quality criteria). Most trials used appropriate randomization methods and took explicit measures to conceal allocation assignment. Intervention and control groups were similar at baseline for age, sex, and anthropometric characteristics in all of the trials. Descriptions of drug protocols were clear. Descriptions of behavioral interventions were generally adequate, but much less detailed than trials evaluating behavioral interventions. Adherence to medication protocols (measured by pill counts) was 80 percent or higher in the majority of the trials. Adherence was slightly lower (72 to 73 percent) in the large multi-center orlistat RCT. Most of the trials did not report how the behavioral intervention program was supervised, or if it was delivered as intended. Most trials also did not report any data on adherence to diet, physical activity, or other behaviors. Most of the trials specified that outcomes were assessed by personnel blinded to treatment status.

Attrition rates ranged from 10 to 35 percent. Notably, both of the large, multi-center trials had fairly high attrition. Overall attrition was 35 percent in the large orlistat trial. In the large sibutramine trial, the attrition rate was 28 percent overall and was differential between groups (24 percent in the sibutramine group and 38 percent in the control group, p=0.001). All of the trials analyzed main weight outcomes among the *intent-to-treat* (ITT) or modified ITT population. The modified ITT population included any participant who had at least one post-baseline efficacy measurement. Missing values were replaced using the LOCF method in most trials and/or a linear mixed-effects model for repeated measures over time. One trial[94] excluded 10 percent of patients, even in the modified ITT population analyses, because they left the trial in less one month.

Metformin. Two of three trials among obese adolescents with additional risk factors for developing type 2 diabetes mellitus evaluating Metformin found statistically significant differences between groups for BMI or BMI SDS at 6 months, with results favoring the metformin group. The third trial found that a statistically higher proportion of adolescents in the metformin group had a greater than 5 percent BMI reduction, compared to those in the placebo group.

Study design and quality. Results should be interpreted with caution, however, as these were very small studies and because analyses in these trials included only patients who completed the trial (attrition rates were 9 and 25 percent), which could have caused bias. In one trial, attrition was also quite different between intervention and control groups (20 percent versus 36 percent).

KQ2. Do weight management programs (behavioral, combined behavioral and pharmacological) 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

Summary of Findings. Data from fewer studies (four trials, 562 patients) suggests BMI or other weight change improvements can persist longer-term (15 to 48 months after beginning a behavioral intervention and at least 12 months since the intervention ended)(Figure 5; Table 3). Of the two trials that conducted repeated measures in participants to assess weight change maintenance, BMI reduction was maintained for 12 months after a high-intensity behavioral intervention ended.

Study Details. Four trials in six publications[79,81,89,90,103,104] reported medium-term outcomes at least 12 months after the intervention ended and 15 to 48 months since beginning treatment (see Table 3). Two studies measured short-term as well as maintenance outcomes [79,81] while two measured maintenance outcomes only.[103,104] Three of the four trials found that intervention groups had beneficial changes in BMI or percent overweight compared to controls at least 1 year after treatment ended.[79,103,104] We did not combine any of the trials quantitatively as they each fell into different a priori groups based on comprehensiveness and intensity. We do provide a forest plot of the four trials showing standardized effect sizes (see Figure 5). The two

trials[79,103] with statistically significant group differences in BMI change found that the intervention group BMI increased by 1.7 kg/m^2 less in the intervention group than in the control group. In the third trial showing group differences,[104] the intervention participants dropped from 36.5 percent overweight to 26.6 percent overweight (a 9.9-point difference), while the degree of overweight in the control participants was unchanged. This trial testing a low-intensity (24 hours), short-duration (3 month) intervention found a greater difference in overweight measures between intervention and controls at 15 months than at 3 months.[104] This result was the only one to suggest that treatment effects could be enhanced beyond the end of active treatment. This result should be interpreted with caution since we excluded trials reporting only outcomes before 6 months, and therefore cannot determine whether this 3-month outcome was typical.

One of the two comprehensive weight management trials reporting both short-term and maintenance outcomes confirmed that BMI benefits after a high-intensity behavioral intervention seen at 12 months post-treatment were largely maintained 12 months later.[79] The second trial with both short-term and maintenance outcomes did not find improved weight outcomes at either 9 or 15 months and was a very low-intensity (4 hours), short-duration (3 month) treatment.[81]

Study design and quality. Two were fair-or-good quality randomized controlled trials, and two were fair-quality controlled clinical trial.[79,103] Two had 40 or fewer participants per arm,[103,104] however the other two had over 75 to 100 per arm.[79,81,90] Quality issues included failure to report blinding for treatment allocation and outcome assessment.

Three trials were set in specialty health care treatment settings[79,103,104] and one in primary care.[81] Three trials involved comprehensive interventions with high-,[79] low-,[104] and very low-[81] intensity interventions. The remaining trial involved a low-intensity intervention focused on providing family therapy.[103]

Combined Behavioral and Pharmacological Interventions

No trials reported on maintenance of weight loss after active treatment with sibutramine or orlistat was discontinued. Cross-over results from one small metformin trial were available graphically only, and did not meet inclusion criteria (maintenance of results at least 12 months after intervention end).

KQ1a & 2a. Do behavioral or combined behavioral and pharmacological weight management programs lead to other positive outcomes (e.g., improved behavioral or physiological measures, decreased childhood morbidity, improved childhood functioning, or reduced adult morbidity and mortality)?

Behavioral Interventions

All of the 13 trials reporting either short-term (KQ1) or maintenance (KQ2) outcomes also reported one or more beneficial outcomes, including measures of adiposity, cardiovascular risk factors, physical fitness, behavioral outcomes, and psychosocial outcomes (see Table 7 for studies reporting cardiovascular risk factors and adiposity outcomes). Results in all areas were

mixed, but the outcomes that were most likely to show greater improvement in the intervention group were insulin-related measures, measures of adiposity, and measures of physical fitness. Limits to findings include incomplete reporting of these outcomes across studies, including the possibility of selective reporting, and possible bias in measurements where lack of blinding of outcome assessors could affect results (e.g. waist circumference).

Measures of adiposity. Five of the trials[77,80,84,85,103] reported measures of adiposity and all found that the intervention groups showed greater improvement in adiposity than the control groups. Four of these five trials[77,84,85,103] also found positive effects in the primary weight outcome as well as either skinfold measures or body fat (as measured by *bio-electrical impedance*). The remaining trial,[80] which did not have a positive primary weight outcome, showed improvement in adiposity as measured by *waist circumference*.

Cardiovascular risk factors and physical fitness outcomes. Physiologic outcomes included lipid levels, glucose tolerance, insulin-related measures, blood pressure, and physical fitness. Results for all of these outcomes were quite mixed. Reduced fasting insulin and reduced *insulin resistance* were the most commonly found group differences. Two[77,79] of the three[77,79,80] trials reporting on fasting insulin found reductions of fasting insulin in the intervention groups relative to the control group. Two of these three trials[77,79] also reported significant reductions in insulin resistance, as measured by the *homeostasis model assessment of insulin resistance (HOMA)*. By contrast, none of the four trials[77-80] reporting lipid levels found group differences in *HDL* or triglyceride levels, and only one found reductions in *LDL* levels.[79]

Neither of the two trials[79,80] reporting on blood pressure found group differences on diastolic blood pressure and only one[79] reported reductions in systolic blood pressure. Similarly, none of the three trials[77,79,80] reporting on glucose levels found any group differences.

Three trials[78,85,103] reported on physical fitness, each using a different measure, and two[85,103] of these found that participants the intervention groups were more fit than those in the control groups. Nemet and colleagues[85] reported increased endurance in the participants in their intervention group after completing a 14-week, twice-weekly exercise program along with up to six meetings with a dietitian. This study measured endurance by the number of seconds participants were able to continue a treadmill test. Another trial[103] reported improvement in physical fitness without organized exercise sessions. The third trial[78] did not include organized exercise sessions and did not see group differences in scores on the Harvard Step Test.

Behavior changes. The interventions in these trials appeared to have a minimal impact on the intermediate outcomes of diet and activity level. While five trials[78,81,83,85,87] explored dietary changes, only two[81,87] found group differences. The study of the screen-time monitoring and limiting device[87] found that the intervention group showed greater reductions in energy intake than the control group at 18 and 24 months (but not at 6 or 12 months). The only dietary differences found in the other trial[81] were that children in the intervention group reported consuming less whole milk and consuming more skim milk and water.

Six trials[78,81-83,85,87] reported changes in physical activity levels and/or sedentary behavior. Only two reported positive effects.[85,87] One of these[85] provided organized physical activity sessions during the 3-month intervention and measured the amount of sedentary and physical activity participants reported 1 year later. Groups did not differ in average reduction in amount of screen time per day, but participants in the intervention group reported an average increase of 9.1 weighted metabolic-equivalent (MET) units of habitual activity, compared with a

7.3 unit drop in the control group ($p<0.05$). The authors did not describe how these data should be interpreted, but in general 1.0 MET is considered a resting metabolic rate, and brisk walking (4.0 miles per hour) is estimated at 5.0 MET.[105] This suggests that long-term changes in physical activity can be sustained after only 3 months of intervention, though the magnitude of the change is unclear. The other trial,[87] examining the use of a screen time limiting and monitoring device, found no differences in the amount of physical activity, but greater reductions in the target sedentary behaviors of television viewing and computer use. The remaining four trials, which did not show group differences, included one trial targeting physical activity,[82] two low-intensity primary care-based trials,[81,83] and a small (n=27) low-intensity trial involving weekly brief contact with a case manager which showed mixed results.[78]

Psychosocial outcomes. Finally, several trials measured psychosocial constructs. The only group differences were found in either of the two trials[83,86] reporting on eating disorder pathology are that Doyle and colleagues[86] reported reduced levels of shape concern (one of four eating disorder dimensions assessed) in the intervention participants in their trial. Mellin and colleagues[104] found reductions in depression scores among intervention participants and no changes in depression scores in control participants. They did not, however, directly test the groups against each other. Also, Mellin and colleagues did not find group differences in change in self-esteem; both groups showed improvement in repeated measures tests.

Combined Behavioral and Pharmacological Interventions

Sibutramine. Physiological outcomes in the sibutramine trials are also presented in Table 5. Three of the four trials that reported changes in waist circumference found statistically significant differences favoring the sibutramine groups. In these three trials, the sibutramine groups reduced the waist circumference on average by 7 to 8 cm. In contrast, the placebo groups reduced waist circumference on average by 2 to 3 cm ($p <0.001$ for all three trials). Four trials reported the effects on lipid profiles or glycemic parameters at 6 or 12 months followup. Of these, statistically significant differences were only reported in the large, multi-center that found greater improvements in HDL cholesterol and reductions in triglycerides, serum insulin, and HOMA, compared to the placebo group. Differences in LDL cholesterol and fasting serum glucose were not statistically different between groups.

Orlistat. Chanoine and colleagues[93] reported that both waist circumference and hip circumference decreased significantly more in those receiving orlistat and a behavioral intervention, compared with placebo plus behavioral intervention controls at 12 months ($p=0.01$ for both in least squares mean analysis). The LSM reduction for waist and hip were -2.67 and -1.52 cm, respectively, for the orlistat group, compared with -0.89 and -0.10 cm the control group. In a subset of patients evaluated with *dual-energy x-ray absorptiometry (DEXA)*, patients in the orlistat group lost significantly more fat mass than patients in the placebo group (-2401 g vs. -380 g; $p =0.03$). In contrast, percent body fat at 6 months was measured using bioelectrical impedance analysis in the Maahs trial, and no statistically significant differences were found between groups. Levels of LDL, HDL, TG, *FPG*, and insulin were measured in both Orlistat trials, and no significant differences were found between groups in either trial. The Chanoine and colleagues trial, however, reported a small reduction in diastolic blood pressure in the orlistat group (-0.51 mm Hg), compared to an increase in the placebo patients (+1.30 mm Hg; $p=0.04$). Change in systolic BP was similar in both groups and not statistically different.

Metformin. One of the trials[99] found statistically significant improvements favoring the metformin group for waist circumference and *subcutaneous adipose tissue*, but no difference for *visceral abdominal adipose tissue*. These parameters were not reported in the other trials. Two trials reported improvements in fasting glucose and insulin, either between groups or only within the metformin group. Neither of these two trials found statistically significant differences between groups for insulin sensitivity when using minimal model analyses, glucose effectiveness, acute insulin response disposition index, or glucose disposal. The third trial found no differences between in fasting glucose, insulin, or 2-hour glucose. One trial reported on lipid parameters and found to be statistically different between groups.[98]

KQ1b & KQ2b. Do specific components of the weight management programs influence the effectiveness of the programs?

Behavioral Interventions

We examined the results of the full group of 13 KQ1 (short-term) and KQ2 (maintenance) trials to identify important components of treatment. Treatment approaches generally focused on making healthy lifestyle improvements, emphasizing healthy eating, and increased physical activity. Specific interventions and the components of treatments, however, were quite heterogeneous (Table 3). For example, participants engaged in organized physical activity sessions as part of the intervention in of five of the trials.[77,79,80,85,104] Five additional trials[78,81,83,84,86] applied behavioral modification principles to help participants increase their physical activity on their own time. Two trials provided only information and encouragement for physical activity, but did not appear to apply behavioral modification principles.[82,103] The final trial[87] attempted to increase physical activity indirectly through reducing sedentary behavior.

Many of the trials involved the parents as primary participants in the intervention, in most cases along with the overweight or obese child.[77,79-82,84,85,87,103] All but one[77] of these trials involved children aged 11 years and younger on average. Parental involvement took many forms in these trials, including weight control educational sessions (with or without their overweight child),[77,81,82,84,85] family therapy,[79,103] or parenting skills training.[80] Family involvement in the remaining trials ranged from no involvement to including parents in one to three counseling sessions. The trials with less parent involvement targeted older children, although one included children as young as 7 years old.[78]

The number of trials was too small to permit quantitative examination of the variation in treatment components through meta-regression. Therefore, we coded three treatment components possibly related to treatment success: the provision of organized physical activity sessions as part of the intervention (shown as "PA+" on Table 3, third column), parental involvement within age groups ("Fam" on Table 3, third column), and the use of behavior modification principles ("BehMod" on Table 3, third column). We then sorted the trials by each of these variables and qualitatively examined the overall patterns of variation in treatment components and their association with statistically significant effects on weight outcomes (see Appendix C Tables 1-3).

While we discuss our findings from this exercise, they should be considered primarily as hypothesis-generating. The degree of variability among this small number of treatment

programs, including important differences in effects due to setting, age, and treatment intensity, greatly limits our ability to examine treatment components. In summary, none of the component clearly improved the chance of showing a positive weight management effect. While organized physical activity sessions did increase the likelihood of treatment success, it was confounded with treatment intensity, and it was therefore impossible to determine whether it was the exercise sessions or the overall intensity of the treatment program that improved the chances of success.

Organized physical activity sessions. Programs that provided organized physical activity sessions (rather than encouraging participants to exercise at home) appeared to be more likely to improve BMI. Group differences were seen in four of five programs with organized physical activity sessions, compared to four of eight programs without organized physical activity sessions. The one trial[80] with organized physical activity that did not see beneficial changes in BMI reported greater improvements in other weight and adiposity measures in intervention participants compared with control participants. We did not have sufficient data to determine whether programs with organized physical activity or those that improved physical activity or fitness were more likely to have a positive impact on other health outcomes (such as fasting insulin or blood pressure). The physical activity sessions ranged from seven 1-hour sessions at 2- to 4-week intervals, which consisted of fun, noncompetitive physically active games and activities,[80] to twice-weekly 60-minute sessions for 6 months (and bi-weekly sessions for the subsequent 6 months).[77] Efforts were generally made to present a variety of enjoyable activities, including team sports, noncompetitive games, dancing, swimming, walking, jogging, and obstacle courses. Two trials[80,85] employed activities to help develop motor skills. One trial[77] used exercise physiologists to facilitate the exercise sessions and help children maintain a target heart rate of 65 to 80 percent of their age-adjusted maximal heart rate. However, programs offering organized physical activity also tended to be more intensive programs, and therefore it is difficult to determine whether the exercise itself or the generally greater hours of contact that improved the likelihood of success.

Parental involvement. The role of parental involvement in weight management programs can only be considered in the context of the child's age. None of the three trials that focused on adolescents included parents as the intervention's primary participants. However, one of the trials[104] in adolescents invited parents to one or more intervention sessions, and this trial did show positive weight outcomes. The two remaining trials lacked parental involvement and one[83] was successful in improving weight and the other was not.[86] Thus, we had insufficient evidence to evaluate whether parental participation increases the likelihood of successful weight loss in adolescents.

All seven of the trials limited to children aged 12 or younger had high levels of parental involvement, as did two of the trials that included both younger children and adolescents. Due to the lack of variability we could not explore the importance of parental involvement further than concluding that weight-loss researchers consider parental involvement crucial for successful weight loss in young children. Parental involvement took many forms in the trials with high levels of involvement. In some trials parents and children attended weight control educational sessions together,[81,84,85] while others provided family therapy,[79,103] or parenting skills training[80] in addition to traditional weight control topics.

Behavior management techniques. The inclusion of behavior management techniques did not clearly have an impact on the probability of effectiveness. Sixty percent of the 10 programs including behavior management techniques had a significant positive treatment effect,

as did two (67 percent) of the three trials lacking behavior management techniques. There were too few trials that lacked behavior management techniques, however, to provide confidence in any conclusions regarding the impact of behavioral management techniques on weight outcomes.

Combined Behavioral and Pharmacological Interventions

Sibutramine. Data were largely insufficient to explore the importance of specific treatment components. Based on the limited number of trials, shorter treatment (3 months, compared with 6 or 12 months) may be related to reduced beneficial effects on BMI. There are other possible explanations for these between trial differences, however, such as lack of placebo run in or differences in population or setting.

Orlistat and Metformin. Data were insufficient to explore the importance of specific treatment components.

KQ1c & KQ2c. Are there population or environmental factors that influence the effectiveness of the weight management programs?

Behavioral Interventions

Data were insufficient to explore the importance of population or environmental factors.

Combined Behavioral and Pharmacological Interventions

Data were insufficient to explore the importance of population or environmental factors.

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

Behavioral Interventions

Summary of Findings. Available evidence suggests little to no harm associated with behavioral weight management interventions (Table 8). Very limited data from one small trial suggests possible increased risk of injury with exercise programs in obese children. Most trials (seven of 13) did not report harms, thus our conclusions about the safety of behavioral weight management interventions with respect to growth, eating disorders, body image, and depression need to be confirmed through further research.

Study Details. Six[77,80,81,83,86,104] of 13 trials addressing weight outcomes also reported potential harms of behavioral weight management interventions (Table 8). In order to more fully illuminate serious adverse events (i.e., those requiring urgent medical treatment), we eliminated the minimal followup time criterion of 6 months for beneficial outcomes based on the assumption that adverse effects could happen well before a treatment effect is apparent. We also eliminated the requirement that the trial be conducted in a country with a United Nations Human Development Index (HDI) (http://hdrstats.undp.org/indicators/1.html) of >0.90, based on our

assumption that cultural conditions are unlikely to affect likelihood of injury. Thus, two additional supplementary trials[106,107] reporting on injury rates in exercise programs with obese children were included. These trials did not meet criteria for inclusion for the previous questions because they only reported weight outcomes of less than 6 months, and one was also excluded because it took place in China, which was not on our list of included countries.

We found no evidence that behavioral intervention programs may be harmful, except perhaps mildly increasing injury risk with exercise. Among the eight trials, two[77,80] reported no group differences in change in height measured at 10 to 12 months. Three trials[81,83,86] reported either favorable or no effects on several measures of eating disorder pathology or body image. One trial[104] reported that depression symptomatology improved in intervention group participants, but did not change in the control group, which represents an added benefit rather than an adverse effect. In the two trials examining injuries in exercise programs, Sung and colleagues reported that none of the 41 obese children in their exercise condition were injured, however, one of the 73 obese children in the trial by Davis and colleagues fractured a bone. No children in the control groups of either of these trials reported any injuries.

In addition to the eight trials shown in Table 6, Nemet and colleagues[85] reported that no adverse events were noted, but did not describe what events they examined or how they elicited information on adverse events.

Combined Behavioral and Pharmacological Interventions

Summary of Findings. Over 6 to 12 months, adolescent users of sibutramine or orlistat were no more likely to discontinue treatment due to adverse effects than those on placebo. Serious adverse events were reported in 2.7 percent of sibutramine patients compared with less than 1 percent of placebo patients and in 3 percent of those on orlistat and on placebo. Adolescent sibutramine users were more likely to develop small increases in heart rate, and in some cases, blood pressure, although the clinical significance of these is not clear. Adolescent orlistat users commonly experienced mild-to-moderate gastrointestinal side-effects, with 20 to 30 percent reporting oily spotting, oily evacuation, abdominal pain, fecal urgency or flatus with discharge and 9 percent reporting fecal incontinence. Oily spotting, fatty or oily stools, and cramping improved with time, although fecal incontinence did not. Available data suggests that neither medication adversely affects growth and maturation over the short-term (6 to 12 months), and orlistat does not adversely affect fat-soluble vitamin levels. Trials of metformin reported no serious adverse effects and no abnormalities in serum lactate, liver function or renal function among selected obese children and adolescents after six months of treatment. Twenty-nine percent of patients who took metformin reported some type of gastrointestinal side effect.

Sibutramine. Adverse effects results are reported in Table 5. A more detailed account is included in Appendix B Table 3. All sibutramine trials evaluated the effects on heart rate and systolic and diastolic blood pressure. Three of the five sibutramine trials found statistically greater increases in heart rate and systolic and/or diastolic blood pressure in the sibutramine group compared to the control group after 6 or 12 months of treatment. These differences, however, were small in magnitude. In the 12-month, multi-center sibutramine trial, tachycardia occurred more commonly in the sibutramine than the control group (12.5 percent vs. 6.2 percent, $p = 0.049$). Withdrawals due to tachycardia, however, were similar between groups.

None of the sibutramine trials reported statistically significant differences between groups in the overall rates of having any adverse event, any serious adverse event, or discontinuation due to adverse events. In the large, 12-month sibutramine trial, serious adverse events were reported by 2.7 percent of patients in the sibutramine group and less than 1 percent of the control group. Only one of these events (excessive nausea and vomiting) was thought to be related to sibutramine. Two trials examined short-term effects on growth and maturation, including the 12-month, multi-center trial. Neither trial found a significant difference between the groups. Abdominal complaints and constipation were also found to be statistically higher in the sibutramine group in the shorter-term trials.

Orlistat. Rates of serious adverse effects and discontinuation of therapy due to adverse effects were low in both trials and were not reported to be statistically different between groups. In the Chanoine and colleagues trial,[93] one or more serious adverse effects occurred in 3 percent of both groups. Discontinuation of therapy due to a serious adverse event occurred among 12 of 357 (3 percent) of orlistat patients and three of 182 (2 percent) patients in the placebo group. In the orlistat group, only one event was thought to be study-related— asymptomatic cholelithiasis in a 15-year-old female who had lost 15.8 kg by the time of the event. In the Maahs and colleagues trial,[96] two of 20 patients in the orlistat group and zero of 20 patients in the placebo group withdrew from the trial due to adverse effects. One suicide death occurred in the orlistat group to a patient who was under a psychiatrist's care. No deaths occurred in the placebo group.

Gastrointestinal (GI) side effects were very common among patients taking orlistat. Chanoine and colleagues reported that among patients taking orlistat, 50 percent reported fatty or oily stools compared to 8 percent of those on placebo; 20 to 30 percent reported oily spotting, oily evacuation, abdominal pain, fecal urgency, or flatus with discharge compared to 2 to 11 percent on placebo; and 10 to 15 percent experienced soft stool, nausea, and increased defecation compared to 9 to 13 percent on placebo. Notably, 9 percent of orlistat patients reported fecal incontinence, compared with less than 1 percent of placebo patients. Chanoine and colleagues also reported that the GI side effects were mostly mild- to moderate-intensity and led to discontinuation of treatment among only 2 percent of orlistat patients. In the smaller 6-month orlistat trial, Maahs and colleagues also reported that numerous adverse gastrointestinal effects occurred significantly more frequently in the orlistat group than the placebo group, including: soft stools, oily spotting, fatty or oily stools, oily evacuation, liquid stools, cramping, flatus with discharge, and fecal incontinence. Soft stools, oily spotting, fatty or oily stools, oily evacuation, and liquid stools all occurred in over 50 percent of patients treated with orlistat. Flatus with discharge occurred in 20 to 47 percent of patients treated with orlistat (varying by study month), in contrast to 0 percent in all but the first month for the control group. Fecal incontinence occurred in 6 to 13 percent of the orlistat group at each month, in contrast to 0 percent of the control group during any month. The authors report that the oily spotting, fatty or oily stools, and cramping improved more over time in the orlistat group than in the placebo group.

Both orlistat trials measured vitamin A, D, and E levels and reported that levels were not different between groups. It is important to note, however, that multivitamin supplementation was provided for all participants in the orlistat trials. In the Maahs trial, quality of life measured using four different scales showed no statistically significant differences between groups over time. Possible lack of blinding in the outcome assessors, however, could have influenced these results. No between-group differences in growth, bone mineral density, and sexual maturation were reported.[93]

Metformin. Trials were limited in their ability to detect adverse effects due to small sample size and limited duration. No trials reported any serious adverse events. One trial specifically reported that no episodes of vomiting or lactic acidosis occurred. Serum lactate, liver, and renal function parameters were reported as remaining normal or not different between groups in two trials.[98,98,99,99] The largest of the three trials reported gastrointestinal side effects among 29 percent of patients on metformin compared to 19 percent of those on placebo.[100] In the other two trials, some patients were reported to have nausea which, in three cases, required a 25 to 50 percent dose reduction in order to continue in the trial.

Chapter 4. Discussion

Summary of Review Findings

We evaluated 13 behavioral intervention trials conducted in 1258 overweight or obese children and adolescents aged 4 to 18 years. We also evaluated seven trials that combined pharmacological treatments (sibutramine or orlistat) with behavioral interventions in a total of 1294 very obese adolescents aged 12 to 18 years (plus an additional three trials of metformin in 145 very obese adolescents at increased risk for diabetes) (See Summary of Evidence Table 9). With the exception of four behavioral intervention trials[83,84,103,104] and one pharmacological trial each for sibutramine[91] and metformin,[98] all of the trials reviewed for this report were newly available since our previous USPSTF review. Given the increased volume of new, relevant trials, we were able to focus on trials addressing the USPSTF's primary question about whether there are treatments accessible by primary care that are effective (i.e., work better than no or minimal treatment). As such, we did not re-address the comparative effectiveness trials considered in the previous report. These comparative effectiveness trials provided little data that would elucidate the absolute effectiveness of obesity treatment programs since they largely compared unique intervention components that were not repeated by other studies.[2]

Behavioral Interventions

Our report found that comprehensive medium- to high-intensity behavioral interventions for obese children and adolescents aged 6 years and older can effectively produce short-term improvements in weight and perhaps in adiposity. The amount of absolute or relative weight change associated with these interventions is generally modest (1.9 to 3.3 kg/m^2 difference in mean BMI change 6 to 12 months after starting treatment, compared with controls). For an 8-year-old boy or girl, the largest BMI difference (3.3 kg/m^2) would translate to about 13 pounds (based on 50^{th} percentile for height for ages 8 and 9, approximately 2 inches of growth). For a 12-year-old boy or girl, this would translate to 17 to 18 pounds difference under the similar growth assumptions (50^{th} percentile for height at ages 12 and 13). In girls aged 16 years this BMI difference would translate to about 19 pounds, while for boys aged 16 years the difference would be between 22 and 23 pounds using the growth assumptions based on the 50^{th} percentile for ages 16 and 17. Very limited evidence suggests that these improvements can be maintained over the 12 months following treatment. The intervention effects possible with behavioral interventions, particularly medium- to high-intensity comprehensive interventions, appear adequate to improve adiposity. Limited evidence suggests that reductions in cardiovascular risk factors (e.g., blood pressure, lipids, blood glucose, or insulin resistance) do not routinely occur, but are possible particularly for insulin resistance measures in the setting of medium- to high-intensity comprehensive interventions. Firm conclusions are difficult to draw since these outcomes were not consistently reported in the behavioral intervention literature, with no more than four studies reporting any one risk factor. Since children and adolescents included in behavioral interventions tended to be less obese than those in pharmacological treatment trials, they might also be less likely to have elevated cardiovascular or diabetes risk factors, and thus these difference would be difficult to detect.

Medium-to-high interventions were conducted in specialty health care (such as pediatric obesity referral clinics) or similar settings. While the interventions would likely not be feasible for implementation in a primary care setting, they would are feasible for a health plan to offer, thus making them potentially available for referral from primary care. Lower intensity comprehensive (or focused) interventions that might be feasible for primary care had a more modest, less consistent benefit on BMI. Further research on these less intensive, more feasible interventions is greatly needed.

Behavioral weight management interventions also have few harms. Based on 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 one that followed 158 children for 10 years and found that weight loss was not related to growth in height in a multivariate model controlling for child age, sex, baseline height, baseline percent overweight, and midparental height.[108] We also found little risk of exercise-induced injuries from behavioral interventions. Although these findings are reassuring, they are limited by incomplete reporting, given that fewer than half of the behavioral intervention trials specifically reported on any potential adverse effects.

While available trials did allow us to judge the effects of these interventions had on weight loss, it is still unclear what the important elements of effective behavioral weight management programs are, beyond the apparent benefit of more intensive interventions that had more hours of participant contact. Most treatment programs focused on supporting healthy lifestyle. While some trials in adolescents had the explicit goal of weight reduction, most trials generally aimed at reducing participants' relative level of overweight through limiting weight gain as the child grew. Many trials utilized behavioral management techniques such as teaching parents and/or children about goal-setting, problem-solving, relapse prevention, and managing their environment to encourage healthy lifestyle.

Physical activity is clearly an important factor in altering the balance between caloric intake and expenditure, and therefore has in important role to play in weight loss interventions. All but three of the interventions included exercise sessions or instruction in behavioral management principles targeting exercise. It appears that organized exercise sessions increase the likelihood of treatment success, but this could not be determined conclusively since programs with organized exercise also tended to be more intensive programs with more hours of contact. Regardless of whether children and adolescents exercise under the supervision of interventionists or on their own time, improved physical fitness is likely beneficial even if it does not increase weight loss.[109,110]

All programs targeting younger children involved their parents or guardians, since adults usually control most of younger children's food intake. Since all of the trials in younger children included responsible adults, however, we have no empirical basis for quantifying the importance of parental involvement in this age group. The one trial in adolescents that included parental involvement was effective. Since these interventions included many components, however, it was impossible to isolate the specific effect of parental involvement in interventions targeting adolescents.

Combined Pharmacological and Behavioral Interventions

Pharmacological adjuncts to behavioral interventions have been studied only in obese adolescents aged 12 to 18 years who meet adult criteria for class II obesity (mean BMI of 35 to 40 kg/m^2 at trial entry). These trials study the additional effect of the pharmacological agent to behavioral therapy alone, in contrast to the purely behavioral trials that compare the effects of behavioral interventions to outcomes among untreated or minimally treated controls. Treatments with pharmacological agents (sibutramine and orlistat) delivered in combination with behavioral interventions over 6 to 12 months have been studied, but longer term results after treatment discontinuation were not available for any of the pharmacological treatment trials. This is an important limitation in our overall knowledge about their beneficial effects. Three small trials in a small number of very obese adolescents (n=145) at high risk for type 2 diabetes mellitus examined the impact of metformin on glucose tolerance, insulin sensitivity, and BMI. These results are preliminary, however, and are not directly applicable to the general population of obese adolescents.

Combined pharmacological (sibutramine or orlistat) and behavioral interventions significantly reduced BMI (compared with placebo combined with the same behavioral interventions) with limited data suggested greater impact with longer treatment (6 vs. 12 months). Additionally, these trials found a greater impact from sibutramine compared with orlistat. In the largest single study, orlistat treatment appeared to primarily attenuate weight gain, but this could be due to the behavioral intervention component of the orlistat trial being ineffective. In this multi-center trial, all 32 centers had the freedom to use their own approach to the trial's behavioral intervention, with no assessment of delivery.[93] Therefore, the quality or intensity of the behavioral interventions across the entire trial is impossible to gauge. Sibutramine treatment for 12 months achieved the largest weight impact of any combined pharmacological and behavioral intervention tests. After 12 months of sibutramine plus a behavioral intervention, trial participants receiving 10 to15 mg per day of sibutramine treatment plus a behavioral intervention decreased their BMI 2.9 kg/m^2, corresponding to an average weight reduction of 6.5 kg (14 pounds). This is compared with a BMI reduction of 0.3 kg/m^2, corresponding to a weight gain of 1.9 kg (4.2 pounds), among trial participants receiving a behavioral intervention plus placebo. The difference between the sibutramine and placebo groups in this trial is similar in magnitude to that found by the behavioral intervention described as a best-case example in a specialty care setting.[77] Direct head-to-head comparisons of pharmacological agents in combination with the same, proven behavioral interventions would allow us to confirm our impressions based on indirect comparisons across different studies. Studies comparing these combined treatments with effective medium-to-high intensity behavioral interventions would also be very valuable.

Combined pharmacological and behavioral interventions generally measured their impact on cardiovascular risk factors (e.g., blood pressure, lipids, insulin resistance, glucose) and waist circumference, but did not generally test their impact on adiposity in addition to BMI. Waist circumference in those receiving sibutramine was reduced in most of the sibutramine trials, 7 to 8 cm compared with 2 to 3 cm reductions in controls. Participants receiving orlistat reduced their waist and hip circumference (2.7 and 1.5 cm respectively), compared with controls (0.9 and 0.1 cm reductions). Improvements in HDL cholesterol, *triglycerides*, and glucose tolerance measures (serum insulin and HOMA) were reported in the sibutramine treatment group in the largest multicenter trial (n=498), but not in smaller studies or in the orlistat studies. While trial

participants receiving sibutramine were consistently more likely to develop elevated heart rates than placebo-treated participants, they had similar rates of discontinuation due to this side effect. Systolic or diastolic blood pressure (or both) were elevated in about half of the trials. These differences, however, were small in magnitude and are of unknown clinical significance. Mild-moderate gastrointestinal side effects (most commonly oily spotting, evacuation, abdominal pain, fecal urgency, or flatus with discharge) occurred in 20 to 30 percent of patients taking orlistat and 9 percent reported fecal incontinence. Few participants (2 percent) discontinued treatment due to these side effects, although 35 percent dropped out before the trial ended. The impact 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. Although sibutramine appears to have a larger effect on weight than orlistat, based on indirect comparisons, the FDA has only approved orlistat for use in pediatric populations (aged 12 years or older). Both drugs have side effects that must be taken into account when considering treatment for an individual patient. While orlistat has a higher rate of adverse effects, the nature of these effects may be less clinically significant than those seen with sibutramine. These risks should also be weighed against the fact that both drugs lack evidence of persistence of weight reduction after active treatment ends.

Long-Term Maintenance

Evidence of treatment maintenance is quite limited in behavioral intervention trials, and nonexistent in trials of pharmacological treatments. Although this review focused on controlled trials, additional observational evidence sheds some light on long-term effectiveness of behavioral intervention program and on the natural history of obesity in children. An observational study of a behavioral intervention by Epstein and colleagues, for example, reported on 10-year followup of four comparative effectiveness treatment trials in children 6 to 12 years of age that were conducted between 1981 and 1986 in an academic multi-disciplinary specialty obesity treatment setting.[111] This study did not meet our inclusion criteria because it had no control group for comparison purposes. While this study did report that 30 percent of their participants were not obese at 10-year followup, it is difficult to determine if this is a higher rate of change than would be seen in a general population of obese children. Freedman and colleagues' large scale observational study of children in Bogalusa, Louisiana[43] found that 22.8 percent of 9 to 11 year olds who were at or above the 95th percentile were no longer obese an average of 16 years later, which is lower than the 30 percent found by Epstein and colleagues and may be a reflection of both natural history and treatment. Another retrospective observational study from the UK found that 39.3 percent of obese 16-year-olds were no longer obese at age 30, which is a higher rate of remission than that reported by the Epstein study. Several differences between the populations and settings, as well as uncertainty about what proportion were treated in these naturalistic studies, limit drawing definitive conclusions about whether children undergoing treatment programs are more or less likely to be obese at long-term followup. Limited as it is, the results from trials comparing treated and control participants are still our best evidence. Thus, longer-term followup of participants from existing (and future) trials could be extremely informative.

Applicability to Real-World Settings

Two of the behavioral intervention programs specifically addressed the use of very low-intensity interventions (approximately 4 hours of total intervention time) that could be integrated into primary care.[81,83] One of these improved short-term weight loss[83] and could be feasible for implementation in some primary care practices. This program relied on support staff to provide adjunctive care through mail and phone counseling, thus relieving the primary care provider of some of the burden of conducting the intervention. Dissemination research would be needed to truly determine wide-spread 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. For example, the comprehensive and effective Bright Bodies weight management program developed by Savoye and colleagues[77] 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.

Considering the BMI levels and ages of study participants, currently studied treatments cannot be clearly applied to the entire population of overweight and obese children and adolescents. We found no evidence addressing weight management approaches in overweight or obese children under 4 years old. Additionally, while overweight and obesity are about equally prevalent among older children and adolescents in the general population,[23] behavioral intervention trials were conducted wholly or mostly in obese children and adolescents. Combined pharmacological and behavioral interventions were applied only to very obese adolescents. As recommended by others,[11] behavioral interventions should be the appropriate first-line approach for overweight children and adolescents, although current studies do not clarify their use or impact in non-obese children and adolescents. Available evidence does not illuminate whether those who are overweight (but not obese) have as high a need for treatment or if they would respond similarly to weight management interventions.

The adolescents in whom effective pharmacological treatments have been studied are in the upper percentiles of the BMI range or meet criteria for Class II or III obesity in adults, and thus represent a small fraction of the 16 percent of girls and 18 percent of boys aged 12 to 19 who are obese. Recent data estimates that only 1 to 3 percent of 13- to 17-year-old girls and 3 to 5 percent of 13- to 17-year-old boys have BMIs that are at or above the 99th percentile for their age and sex.[22] Based on evidence, the use of pharmacological treatment would be primarily limited to this small group adolescents.

While pharmacological treatments have been studied in multi-site clinical trials, which enhances their applicability, treatment adherence outside of the trial setting and longer term weight impacts remain unclear. Adolescents choosing to participate in either behavioral or combined behavioral-pharmacologic treatment trials may also be more or less likely than the average overweight or obese adolescent to respond to the intervention provided. They may have higher levels of motivation to lose weight, for example, and therefore do better than the average adolescent. Conversely, they may also have a greater number of failed weight loss attempts, which may make them less likely to succeed than the typical overweight or obese teen in the

community. The supports provided in a typical trial may also exceed those provided in a usual treatment setting.

Applicability to Vulnerable Populations

Research on treating obesity must be considered in terms of its applicability to the general population of obese children and adolescents and, in particular, those bearing the greatest burden due to higher prevalence of obesity. These vulnerable groups include racial and ethnic minorities[23,26] and those within lowest income groups,[29] both of whom disproportionately bear the brunt of the obesity epidemic.

Minority involvement in addressing the obesity epidemic will be essential, and as such, their involvement in obesity research is critical. Among the behavioral trials, only a few reported that at least 10 percent of their sample was Hispanic[77,83,86] or Black.[77,88] One of these trials, whose sample was 24.7 percent Hispanic and 38.5 percent Black, reported that there were no differences in any outcome measure between ethnic groups.[77]

We found no evidence to suggest that medication treatment is more or less effective in Black or Hispanic than in White youth. Black and Hispanic youth were present in the samples of most of the medication trials, although only three[92,93,98] examined differential impact of treatment by ethnicity: a large-scale trial of sibutramine,[92] a large-scale trial of orlistat,[93] and a small trial of metformin.[98] None of these trials found that race had an effect on response to treatment. None of these trials, however, was designed to detect differences among race and ethnic groups and thus further studies among racial and ethnic minority groups are warranted.

Little was reported about the socioeconomic status of participants in any of the studies. Given the lack of universal access to health care, however, programs delivered through health care settings could be out of reach of many. Obesity prevention programs conducted in places such as schools[3] could ostensibly reach those without access through healthcare systems.

Review Limitations

Limitations in the Body of Evidence

The quality of research on treating child and adolescent obesity has improved substantially our previous USPSTF review that enumerated concerns about the childhood obesity treatment literature, specifically regarding behavioral interventions. These concerns were echoed by others and included small sample sizes, high attrition (among other quality issues), less than ideal outcome measures, and highly heterogeneous treatment approaches.[10] While several of the newly published trials have over 100 participants, retention remains somewhat problematic, with most reported retention below 90 percent. However, several trials reporting retention lower than 90 percent used statistical methods to attenuate or examine the effects of missing data. Outcome measurement has improved—almost all of the newer trials reported raw BMI scores or BMI SDS and all directly measured their participants rather than relying on self-report. A lingering quality issue is that the blinding procedures for treatment allocation and outcomes assessment were often not described. Research would also be improved with more explicit reporting on intervention fidelity and how the outcomes affected other outcomes (both harms and benefits, such as comorbidities). Finally, while treatment trials remain quite heterogeneous, it is hoped that better

reporting and growth in the research base, including replication of effective intervention studies, will eventually allow determination of effective components of behavioral interventions.

While methods and reporting have improved and the number of studies has increased, providing summary measures of expected treatment effects is still very difficult due to the heterogeneity in the behavioral intervention literature (e.g., populations, intervention intensity, settings, treatment components, types of outcomes assessed). Thus, our findings and meta-analysis should be interpreted with caution. While it appears that treatment comprehensiveness and intensity are important, other factors, such as treatment setting and age, also appear to be important and may not have been fairly considered in our analyses, since we did not have enough data to conduct analyses stratified by these factors.

While larger trials of pharmacological treatments are quite new (2005 and 2006), the available treatment data for these approaches remains limited. There are only two weight-loss medications studied (sibutramine and orlistat), with few randomized trials overall, and only one large-scale trial of each of the medications. No trials were conducted among children age 11 years or younger, so no conclusions can be drawn regarding efficacy or safety for that age group. We found no data on maintenance of treatment effect or safety after the 6 to 12 months of active treatment ended. Additionally, these medication's long-term effects have not been sufficiently documented, so longer follow up remains very important. Medication use may have either a positive or negative effect on long-term maintenance of weight changes, compared with exclusively behavioral approaches, so longer follow-up is very important. While we found sibutramine and orlistat each had one large-sample trial, these trials were not large enough to detect rare, but serious, adverse effects. The high variability across trials in intensity and possible variability in intervention fidelity for behavioral interventions hampered our ability to determine both the combined and independent effect of the medication.

Limitations in Our Approach

A limitation to our meta-analysis is that we combined different measures of weight change that have different underlying assumptions and distributions. We attempted to minimize the effects of this by analyzing BMI change whenever it was available, so the majority of the trials did use a common metric. 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 with the meta-analysis was limited to studies the reported BMI or BMI change. Because change in BMI has a different meaning for children of different ages, it might have been preferable to analyze change in BMI SDS, which is adjusted for age and sex. However, many authors did not report BMI SDS. Given that this requires special software or look-up data to calculate BMI SDS, it was not feasible to expect authors to provide this data upon request. Further, experts still have not determined if there is a single best measure for weight management studies in children and adolescent.[15]

We did not include comparative effectiveness trials in this updated review, as our primary goal was to determine whether treatment worked and the size of the effects compared with no treatment. As such, our review did not include all studies that others might consider relevant. Future reviews may consider comparative effectiveness for populations and interventions viewed to be established as efficacious.

Our examination of other beneficial outcomes was limited to studies that met our general inclusion criteria, including reporting some measure of weight change 6 months or more after the baseline assessment. Given the primary purpose of this review (focus on weight management), we did not include trials that reported other beneficial outcomes without some measure of weight change, and therefore might have missed some reports of other beneficial outcomes.

We did not address the impact of population-based prevention programs on weight reduction in overweight or obese children. These programs are primarily targeted at preventing obesity, but since some children participating in these programs are already overweight or obese when they begin, it would be useful to know the degree to which overweight and obese children benefit. It would also be useful to know whether overweight and obese children suffer deleterious effects of such programs, such as increased dieting, increased teasing, poorer self-esteem, or other quality of life detriments.

Contextual Issues/Next Steps

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.[11,40] This stepped-care model, which has been recommended by the Expert Committee (which was convened by the American Medical Association [AMA] and co-funded in collaboration with the Department of Health and Human Services' Health Resources and Services Administration [HRSA] and the CDC), delineates approaches that range from simple preventive messages aimed at younger children and those who are not overweight, to weight management approaches that increase in intensity as the child becomes more obese or has more weight-related health problems. Behavioral interventions are seen as a best first-line treatment, and our review found that they can be effective and safe when delivered to obese children aged 4 years and older.

A broader approach to obesity care may be required to have a definite impact on childhood obesity within the health care system. These efforts should include connecting the health care system with efforts in the broader community. Dietz and colleagues[112] have proposed a model of care in which self-management by the patient or parent is considered central. In order to support self-management, the health care system should make decision support tools available to office-based providers, teach providers to help children and adolescents with excess weight and their families to make changes and access helpful resources, and help increase patient confidence in their ability to make changes. The Expert Committee has recommended a complementary office-based system that relies on a network of health system resources (such as pediatric dietitians or behavioralists) and referral resources (including community resources and specialty treatment settings with access to a multidisciplinary team experienced with childhood obesity).[11] Both groups recognize that health plans also have a role to play in changing the environment, particularly to support obesity prevention, through partnerships with schools and community organizations.[8,112]

While this report focuses on the effectiveness and benefits of treatments in children and adolescents who are already overweight or obese, the challenge of achieving significant weight loss (and the uncertainty as to how well any weight reduction can be maintained) reaffirms the importance of obesity prevention. Obesity prevention is a critical component of the full breadth

of a public health approach to overweight and obesity among American children and adolescents. Preventive approaches emphasize helping children and adolescents develop lifelong healthy habits to prevent the development of overweight or obesity during childhood and into adulthood. Obesity prevention should be conceptualized broadly to include environmental modifications to encourage healthier lifestyles, as well as health promotion campaigns in schools, communities, and health care settings. Given the relatively small effects seen in most behavioral interventions, and the fact that more invasive interventions are only appropriate for a small portion of the population, prevention programs are likely to be the most effective agents in slowing the growth of childhood obesity.

Calling for public health action at its broadest and most inclusive level, the Institute of Medicine (IOM) created a set of 10 integrated recommendations for families, schools, communities, the public sector, and the private sector to prevent the development of obesity in the majority of children and adolescents in the United States.[12] The IOM recommendation for the healthcare system is that clinicians engage in the prevention of childhood obesity, with support from professional organizations, insurers, and accrediting groups, for both individual and population-based prevention. Given this emphasis, but a lack of evidence for effective healthcare system-based prevention approaches in the past,[7] it will be important for the next USPSTF update to consider whether there is sufficient evidence to evaluate primary care's role in primary prevention.

Given the importance of child and adolescent obesity worldwide, this is an extremely active area for ongoing research, guideline development, and implementation of policies that affect all aspects of society. Federal agencies and private foundations, such as the Robert Wood Johnson Foundation,[113] have put very high priority on funding obesity research and disseminating findings. We identified over 20 ongoing clinical studies that investigate the broad spectrum of issues related to obesity in children and adolescents.[114] Thus, this issue will require frequent revisiting for those intending to make policy and clinical decisions based on the most up-to-date thinking and evidence available.

Future Research

Based on this review, we have several recommendations for funding additional research in obesity treatment. These recommendations also reflect input from our expert reviewers. The relative importance of funding treatment studies (as compared to prevention studies) is beyond the scope of this report, but bears consideration.

Childhood overweight has been the focus of considerable research in recent years, and certainty in the short-term effectiveness of medium- to high-intensity behavioral intervention programs is emerging. Replication of behavioral intervention trials (particularly given their heterogeneity of treatment components) is needed to confirm the benefits of these programs, to estimate their likely effects in real-world settings, to determine their feasibility and sustainability, and to report on cost-effectiveness. Understanding important components of behavioral interventions is also an ongoing need, including determining whether specific diet or physical activity approaches or general skills training in making and sustaining behavior change are critical. To help clarify which components of these programs are most important, and for which age groups, researchers should provide consistent and detailed descriptions of treatment components, including information on intensity and duration of treatment components. In

addition, trials should report on program adherence, including receipt of treatment, quality of delivery, participant responsiveness, and whether any of these factors varied by subgroups. This would enable reviewers to distinguish small group differences due to difficulty in adhering to the treatment program from ineffectiveness of the program as designed for that subgroup. Consistency in reporting of weight-related outcomes is also crucial for analyzing the literature as a body and to allow statistical pooling, as well as potentially exploring the importance of treatment components statistically. Future meta-analyses would be improved if all studies consistently reported at least the means and standard deviations for these weight-related measures: BMI, change in BMI, BMI SDS, and change in BMI SDS. Similarly, all studies and trials of weight management treatments should systematically assess and report on possible harms, on changes in weight-related co-morbidities, on changes in psychosocial and related outcomes, and should monitor and report other unanticipated effects, particularly associated with non-behavioral treatments. Additionally, once it becomes clear to what degree multi-factorial treatments can resolve weight-related co-morbidities, it will be important to investigate whether certain intervention components (e.g., increased physical activity, fat-mass reduction, and modification of dietary macronutrient or micronutrient intakes) are the key drivers of health benefits.

Longer-term followup is needed to confirm maintenance of treatment and to assess longer term risks or harms, preferably with outcomes measured at the end of treatment and at fixed follow-up points, such as 1, 2, and 5 years from baseline. As further research elucidates both short- and long-term health benefits, more appropriate clinical treatment planning will be possible, particularly for children and adolescents who are not experiencing immediate weight-related health consequences. There is a particular need for more information on the maintenance of treatment effect in youth taking sibutramine and orlistat for weight loss. Followup data at least 1 year, and ideally up to 3 years, after pharmaceutical treatment has ended is sorely needed. Given our limited certainty about the quality of the behavioral interventions delivered within current pharmaceutical trials, exploring whether greater treatment effects are possible when pharmacotherapies are combined with proven, effectively delivered behavioral interventions could be important. As effective treatment data accrue, it would also be useful to explore whether different subgroups of patients respond better to different types of treatments within a single modality (e.g., different medications or behavioral approaches), different treatment modalities, (behavioral interventions as opposed to pharmacotherapies), or different treatment combinations (e.g., behavioral only vs. behavioral with pharmacotherapy).

More studies are needed in understudied populations: in minority children and adolescents; of behavioral interventions in younger children (5 years and under); and of behavioral interventions in children who are overweight but not obese. Future studies should also evaluate specific approaches that have been advocated by experts for treating excess weight in childhood and adolescence. For example, the Expert Committee's recommendation[11] of a stepped care approach, which is pragmatic and evidence-informed, but has never been tested through formal research. We also found no controlled trials on more aggressive dietary treatments, such as protein-modified fasts, which may be of use in very obese children for whom more invasive treatments would be considered. It could be beneficial to compare aggressive dietary treatments to both standard weight management approaches and pharmacological approaches.

The health effects of childhood obesity (particularly independent of the long-term increased risk of adult obesity and its attendant morbidity) are still not sufficiently understood. Researchers and clinicians are left with the question, "What are the best ways to improve the current and future health of obese, as well as overweight, children and adolescents?" In addition, a broader understanding of the prevalence and implications of obesity-related disorders in childhood, and of the natural history of overweight and obesity, are needed to answer this question. Documenting changes in BMI (growth trajectories) and their determinants—in those who are underweight, normal weight, overweight, and obese, beginning at various time points in childhood and adolescence, and considering males and females and different racial/ethnic subgroups separately—would be very useful. A better understanding of the natural history of this condition will be important to complement prevention and intervention efforts.

Finally, just as the portability of research-tested interventions into the real world must be tested in dissemination trials, it is also important for researchers to make efforts to describe results and implications in real-world terms that can be understand and used by policy makers and the general public. Being clear about how much weight loss a child may be expected to experience, or how much weight gain is prevented, is crucial. It is very useful to lay readers if researchers provide illustrative examples and ranges of outcomes in terms that the public understands, such as pounds (in the United States) or kilograms. To the extent possible, it is important for researchers to translate clinical outcomes such as changes in blood pressure and fitness levels into terms that demonstrate whether these changes are likely to have any real impact on a child's health. Ongoing epidemiologic research within children and adolescents who have made favorable weight-related changes to help establish the health impact of various degrees of weight change on short-term and longer term health outcomes will be critical in this regard.

Conclusions

Considerable headway has been made in the past several years in determining the effectiveness of treatments for obese children and adolescents. Behavioral interventions have been studied in children and adolescents aged 4 to 18 years, while adjunctive pharmacological treatments have been studied only in highly obese adolescents. Behavioral interventions have demonstrated beneficial effects on weight compared with no or minimal treatment. Effects are small to moderate after 6 to 12 months of treatment. Some evidence supports more robust effects on weight from medium- to high-intensity comprehensive interventions, with weight changes in some instances similar to those achieved through pharmacological treatments combined with behavioral interventions. Limited evidence supports maintenance of behavioral treatment effects for at least 12 months after treatment ends. Effective behavioral interventions address healthy lifestyle, utilize behavioral management techniques, provide physical activity as part of treatment, and, in children under aged 12 years, involve parents. Sibutramine plus a behavioral intervention can lead to moderate weight loss over 12 months of treatment in very obese adolescents, with smaller treatment effects from orlistat treatment. The evidence base for pharmacological treatments is limited to one large multicenter study for each type of medication, along with a small number of other trials. No trials provide follow-up after treatment has been discontinued.

Clarifying the contribution of various treatment approaches in achieving short-term and long-term health benefits (as well as weight loss) is imperative in all ages of children and

adolescents and across all levels of overweight and obesity. Since most children and adolescents who are overweight or obese will likely be best served by behavioral interventions, further research in this area is imperative. Thoughtful planning by funding agencies to support studies that elucidate the role of common behavioral treatment components across a range of overweight subjects and settings would be very beneficial. Given the limited role that treatment can play in the obesity epidemic, research to further our understanding of obesity prevention programs in children and adolescents must also be a high priority.

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Acronyms

Code or Abbreviation	Definition
AE	Adverse Effects
B	Black
BT	Behavioral Treatment
BIA	Bio-electrical impedance analysis
BMI	Body mass index
BP	Blood pressure
BT	Behavioral therapy
calc	Calculated from given data
CI	95% Confidence interval
CDC	Center for Disease Control
CHD	Coronary Heart Disease
CVD	Cardiovascular disease
CV	Cardiovascular
D	Dietary
DBP	Diastolic blood pressure
DEXA	Dual x-ray absorptiometry
DM	Diabetes mellitus, Type 2
EST	Estimated from given data
F	Female
FC	Family Counseling
FFM	Fat free mass
FM	Fat mass
FPG	Fasting plasma glucose
GP	General Practitioner
H	Height
HDL	High-density lipoprotein cholesterol
HOMA	Homeostasis model assessment of insulin sensitivity
HMO	Health Maintenance Organization
HR	Hazards ratio
IGT	Impaired Glucose Tolerance
ITT	Intention-to-treat
Kcal	Kilocalorie
Kg	Kilogram
Kg/m^2	Kilograms divided by meters squared (formula for BMI)
KQ	Key question
LDL	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
M	Male
MA	Mexican American
MM	Millimeters
MRI	Magnetic resonance imaging
N	Number
NA	Not applicable
NHANES	National Health and Nutrition Examination Survey
NHB	Non-Hispanic blacks
NHW	Non-Hispanic whites
NIH	National Institute of Health
NR	Not reported
OGTT	Oral Glucose Tolerance Test
OR	Odds ratio
OW	Overweight
P	P-value
PA	Physical Activity
PCP	Primary care provider
PT	Parent Training
RYGB	Roux-en-Y Gastric Bypass

Code or Abbreviation	Definition
SA	Sedentary Activity
SBP	Systolic blood pressure
SD	Standard Deviation
SDS	Standard Deviation Score
SE	Standard error
SKF	Skin fold thickness
SSF	Subscapular skinfold thickness

Code or Abbreviation	Definition
TC	Total cholesterol
TG	Triglycerides
TSF	Triceps skinfold
W	White
WHO	World Health Organization
WT	Weight

Glossary

Adipose tissue: Fat tissue in the body.

Behavioral treatment: Behavioral treatment (or behavior therapy) draws on the principles of learning theory (stimulus–behavior contingencies or behavior–reward contingencies). Consists of assessment (identifying and specifying problem behaviors and the circumstances in which they are elicited), treatment (including setting specific, measurable and modest goals that are continually revised) and monitoring. Behavior change processes include stimulus control, graded exposure, extinction and reward.

Behavioral management interventions: Interventions that include at least some behavioral management principles, such as those used in behavioral treatment. May be less intensive than behavioral treatment.

Behavioral interventions: A generic term encompassing brief behaviorally-based counseling, behavioral management interventions, and behavioral treatment.

Behaviorally-based counseling interventions: Brief counseling in which the primary goal is usually to provide information and make recommendations, with minimal discussion of behavioral management principles. May be delivered in primary care or other settings and primarily involve office staff. Is analogous to the Prevention Plus activities recommended as the first step for those that are overweight in the Expert Panel.

Bio-electrical impendence (BIA): A way to estimate the amount of body weight that is fat and nonfat. Nonfat weight comes from bone, muscle, body water, organs and other tissues. BIA works by measuring how difficult it is for a harmless electrical current to move through the body. The more fat a person has the harder it is for electricity to flow through the body. The less fat a person has, the easier it is for electricity to flow through the body. By measuring the flow of electricity, one can estimate body fat percent.

Body Mass Index (BMI): A measure of body weight relative to height. BMI is a tool that is often used to determine if a person is at a healthy weight, overweight, or obese, and whether a persons' health is at risk due to his or her weight. To calculate BMI, use the following formula: weight in kilograms/ height in meters^2

Body Mass Index Standard Deviation Score (BMI SDS): This is also known as a BMI z-score. A standard deviation score quantifies the distance of a BMI from the average BMI of a population or sample. In a normally distributed population, 84% of the population has a BMI SDS at or below 1.0 and 97.5% of the population have a BMI SDS at or below 2.0. The Center for Disease Control and Prevention provides a computer program that converts BMI scores (combined with age and sex of the child) to BMI SDSs. They also provide tables for select BMI scores.

Body Mass Index Z-score (BMI z-score): See Body Mass Index Standard Deviation Score.

Dual Energy X-ray Absorptiometry (DEXA)[†]: An enhanced form of x-ray technology that is used to measure bone loss. DEXA is today's established standard for measuring bone mineral density (BMD).An x-ray (radiograph) is a painless medical test that helps physicians diagnose and treat medical conditions. Radiography involves exposing a part of the body to a small dose of ionizing radiation to produce pictures of the inside of the body. X-rays are the oldest and most frequently used form of medical imaging. DEXA is most often performed on the lower spine and hips. Portable DEXA devices, including some that use ultrasound waves rather than x-rays, measure the wrist, fingers or heel and are sometimes used for screening purposes.

Dyslipidemia: An abnormal profile of blood lipids. The characteristic dyslipidemia associated with insulin resistance and poorly controlled diabetes includes high levels of triglycerides, low levels of HDL-C, and partitioning of LDL-C into relatively small and dense particles.

Fasting Plasma Glucose (FPG): Also known as fasting blood sugar, the measurement of plasma glucose generally taken after an overnight fast.

Glucose: A building block for most carbohydrates. Digestion causes some carbohydrates to break down into glucose. After digestion, glucose is carried in the blood and goes to the body cells where it is used for energy or stored.

References

[†] http://www.radiologyinfo.org/en/info.cfm?pg=dexa&bhcp=1

High-density Lipoprotein (HDL): A unit made up of proteins and fats that carry cholesterol to the liver. The liver removes cholesterol from the body. HDL is commonly called "good " cholesterol. High levels of HDL cholesterol lower the risk of heart disease. An HDL level of 60 mg/dl or greater is considered high and is protective against heart disease. An HDL level less than 40 mg/dl is considered low and increases the risk for developing heart disease.

Homeostasis Model Assessment of insulin resistance (HOMA)[‡]: An empirical mathematical formula based on fasting plasma glucose and fasting plasma insulin levels that was developed as a surrogate measurement of in vivo insulin sensitivity

$$\text{HOMA-IR} = \frac{\text{fasting plasma insulin (μIU/mL) x fasting plasma glucose (mmol/L)}}{22.5}$$

Hypertension/High blood pressure: Blood pressure rises and falls throughout the day. An optimal blood pressure is less than 120/80 mmHg. When blood pressure stays high—greater than or equal to 140/90 mmHg—you have high blood pressure. With high blood pressure, the heart works harder, arteries can be damaged, and your chances of a stroke, heart attack and kidney problems are greater.

Insulin resistance: Reduced effectiveness of insulin to mediate its metabolic effects. Insulin resistance generally refers to glucose metabolism, but can be used to describe reductions in other aspects of insulin action. Insulin resistance is a primary abnormality that places people at risk for type 2 diabetes. Additional conditions may be associated with insulin resistance, including cardiovascular disease, hyperinsulinemia, dyslipidemia, hypertension, abdominal obesity, and clotting abnormalities, among others.

Insulin: A hormone made by the pancreas that helps moves glucose (sugar) from the blood to muscles and other tissues. Insulin controls blood sugar levels.

Intention-to-treat: A strategy for analyzing data from a randomized controlled trial. All participants are included in the arm to which they were allocated, whether or not they received (or completed) the intervention given to that arm. Intention-to-treat analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by randomization and which may reflect non-adherence to the protocol. The term is often misused in trial publications when some participants were excluded.[3]

Last Observation Carried Forward (LOCF): An imputation that substitutes the last data collected for a time point with missing data.

Low-Density Lipoprotein (LDL): A unit made up of proteins and fats that carry cholesterol in the body. High levels of LDL cholesterol cause a buildup of cholesterol in the arteries. Commonly called "bad" cholesterol, high levels of LDL increase the risk of heart disease.

Metformin: is an oral anti-diabetic drug from the biguanide class.

Obese/Obesity: In children aged 2-17, overweight is defined as having a BMI at or above the 95th percentile, compared with other children of the same age and sex, *or* having a BMI of 30 or more, whichever is lower.

Overweight: In children aged 2-17, overweight is defined as having a BMI in the 85th to 94th percentile, compared with other children of the same age and sex.

Percentile: The percentile indicates the relative position of the child's BMI among children of the same sex and age. Specifically, a percentile tells the proportion of a population or sample that are at or below a given percentile value. For example, 95% of the population is at or below the 95th percentile. To determine a child's BMI percentile score, his or her BMI is compared with published BMI percentile scores based on large, representative samples of children. In the U.S., norms developed by the Center for Disease Control and Prevention are most widely use. Several other countries have developed their own BMI norms.

Physical activity: Any form of exercise or movement. Physical activity may include planned activities such as walking, running, strength training, basketball, or other sports. Physical activity may also include daily activities such as household chores, yard work, walking the dog, etc. It is recommended that adults get at least 30 minutes of moderate-intensity physical activity most days for general health benefits. Adults who wish to lose weight or maintain weight loss may require 60 to 90 minutes of physical activity. Children should get at least 60 minutes of moderate-intensity physical activity most days of the week. Moderate-intensity physical activity is any activity that requires about as much energy as walking 2 miles in 30 minutes.

Skinfold thickness: A measure of the amount of fat under the skin; the measurement is made with a caliper. Measurements at several sites are normally required as the percent of fat at each site varies with age, sex and ethnicity. Skinfold measurements are usually taken at the triceps, subscapular and supra-iliac sites.

[‡] http://www.ndei.org/v2/website/Glossary

Subcutaneous adipose tissue: The body fat located under the skin; evaluated by skinfold calipers.

Triglycerides: Triglycerides are the chemical form in which most fat exists in food as well as in the body. They're also present in blood plasma and, in association with cholesterol, form the plasma lipids.

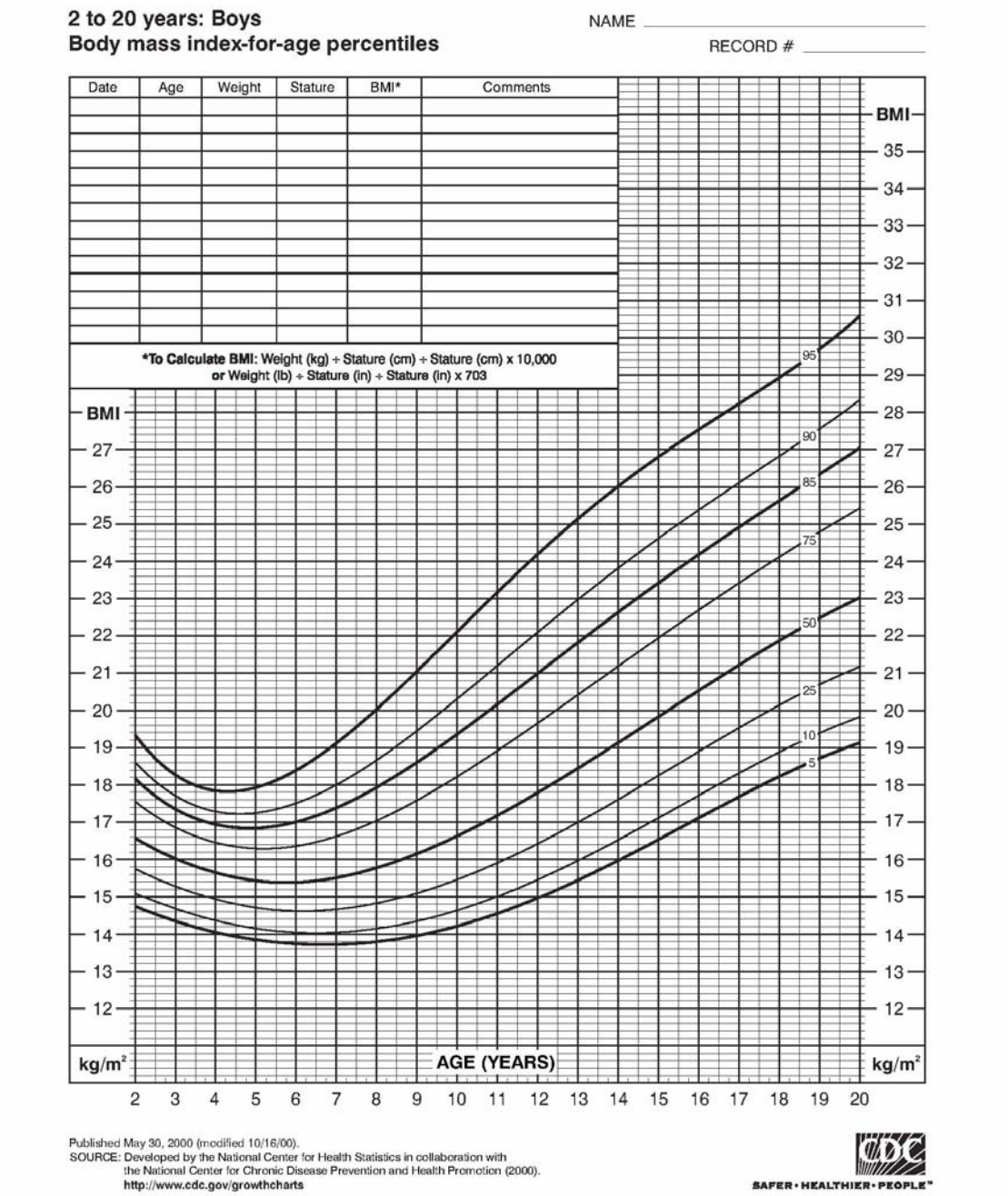
Type 2 diabetes: Diabetes that results from insulin resistance and inadequate insulin secretion (formerly known as non–insulin-dependent diabetes mellitus or NIDDM). Insulin resistance is generally present before diabetes develops and insulin secretion declines progressively, leading to progressive hyperglycemia. Patients require treatments to reduce insulin resistance and/or increase insulin levels to regulate blood glucose levels.

Visceral abdominal adipose tissue: The body fat located inside the peritoneal cavity.

Waist circumference: A measurement of the waist. Fat around the waist increases the risk of obesity related health problems. Women with a waist measurement of more than 35 inches or men with a waist measurement of more than 40 inches have a higher risk of developing obesity-related health problems, such as diabetes, high blood pressure, and heart disease.

Tables and Figures

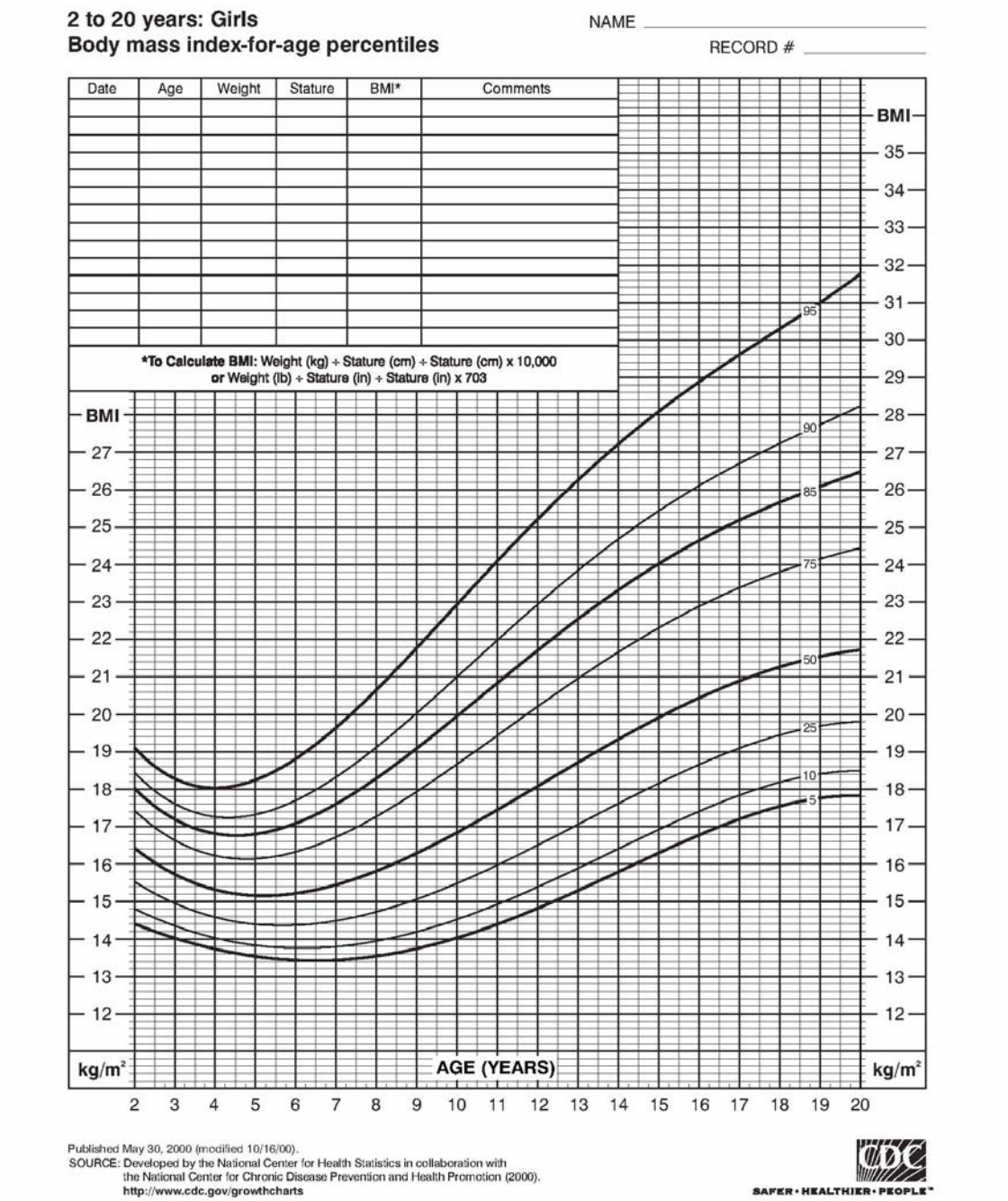
Figure 1. Illustrative BMI percentile chart with table of weight and BMI standard deviation score for selected percentiles: Boys



Age	Height		50th percentile Weight		BMI	BMI	85th percentile Weight		BMI	BMI	95th percentile Weight		BMI	BMI
Yrs	in	cm	lbs	kg		SDS	lb	kg		SDS	lbs	kg		SDS
8	50.5	128.3	57.2	26.0	15.8	0.0	64.8	29.5	17.9	1.0	72.4	32.9	20.0	1.6
12	58.5	148.6	86.5	39.3	17.8	0.0	102.0	46.4	21.0	1.0	117.6	53.4	24.2	1.6
16	68.5	174.0	136.5	62.1	20.5	0.0	161.2	73.3	24.2	1.0	183.2	83.3	27.5	1.6

BMI-body mass index; SDS-standard deviation score

Figure 2. Illustrative BMI percentile chart with table of weight and BMI standard deviation score for selected percentiles: Girls



Age	Height		50th percentile Weight		BMI	BMI	85th percentile Weight		BMI	BMI	95th percentile Weight		BMI	BMI
	in	cm	lbs	kg		SDS	lb	kg		SDS	lbs	kg		SDS
8	50.5	128.3	57.2	26.0	15.8	0.0	66.3	30.1	18.3	1.0	75.0	34.0	20.7	1.7
12	59.5	151.1	90.9	41.3	18.1	0.0	109.0	49.5	21.7	1.0	126.6	57.5	25.2	1.6
16	64	162.6	118.7	53.9	20.4	0.0	143.1	65.0	24.6	1.0	168.1	76.4	28.9	1.6

BMI-body mass index; SDS-standard deviation score

Table 1. Definition of overweight and obesity terms for children and adolescents and adults

Current Terminology	Terminology Used in Previous Report	Definition in Children and Adolescents[11]	Definition in Adults [115]
Overweight	At risk for overweight	85th – 94th percentile BMI (age-sex specific)	25 – 29 BMI (kg/m^2)
Obese	Overweight	≥ 95th percentile BMI (age-sex specific) or BMI ≥ 30 kg/m^2	Class I: 30 – 34.9 BMI (kg/m^2) Class II: 35.0 – 39.9 BMI (kg/m^2) Class III: ≥ 40 BMI (kg/m^2)
Severe obesity	Not used	> 99th percentile BMI (age-sex specific)	NIH criteria for bariatric surgery:[116] >40 BMI (kg/m^2) or >35 BMI (kg/m^2) with co-morbidities

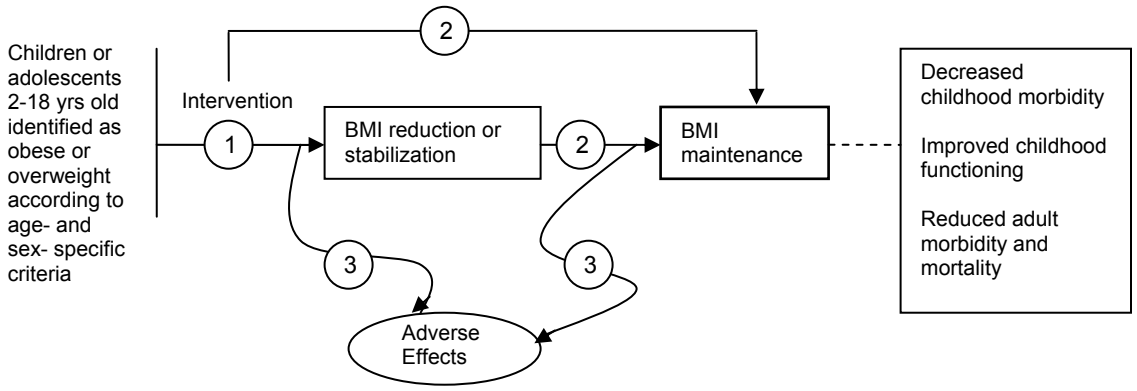
Table 2. BMI (kg/m^2) at 50th, 85th, 95th, and 99th percentiles and weight in pounds for BMI (kg/m^2) of 25, 30, 35, and 40 at ages 8, 12, and 16 years

		BMI (kg/m^2) at percentiles* Children and adolescents				Weight (lbs) at Adult BMI cut-points**			
	50th Percentile for Height		Over-weight	Obesity	Severe Obesity	Over-weight	Obesity Class I	Obesity Class II	Obesity Class III
Age (Sex)	**inches**	**50th**	**85th**	**95th**	**99th**	**25**	**30**	**35**	**40**
8 (Male)	50.5	15.8	17.9	20.0	25.6	91	109	127	145
8 (Female)	50.5	15.8	18.3	20.7	26.4	91	109	127	145
12 (Male)	58.5	17.8	21.0	24.2	31.8	122	146	170	195
12 (Female)	59.5	18.1	21.7	25.2	33.1	126	151	176	201
16 (Male)	68.5	20.5	24.2	27.5	33.9	167	200	234	267
16 (Female)	64	20.4	24.6	28.9	39.1	146	174	204	233

*Estimated average height for age from 50th percentile on CDC Growth Chart "Stature-for-age percentiles: Boy (or Girls), 2 to 20 years".

**Pounds = (BMI x inches^2) /703 was used to convert from BMI to pounds.

Figure 3. Analytic framework and key questions



Key Questions (KQ)

KQ1. Do weight management programs (behavioral, pharmacological) lead to BMI, weight, or adiposity stabilization or reduction in children and adolescents who are obese (≥ 95th BMI percentile) or overweight (85th–94th percentile)?

KQ1a. Do these programs lead to other positive outcomes (e.g., 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, pharmacological) 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 (e.g., 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, pharmacological) attempting to stabilize, reduce, or maintain BMI?

Figure 4. Pooled analysis: Short-term effect size of behavioral interventions (KQ1)

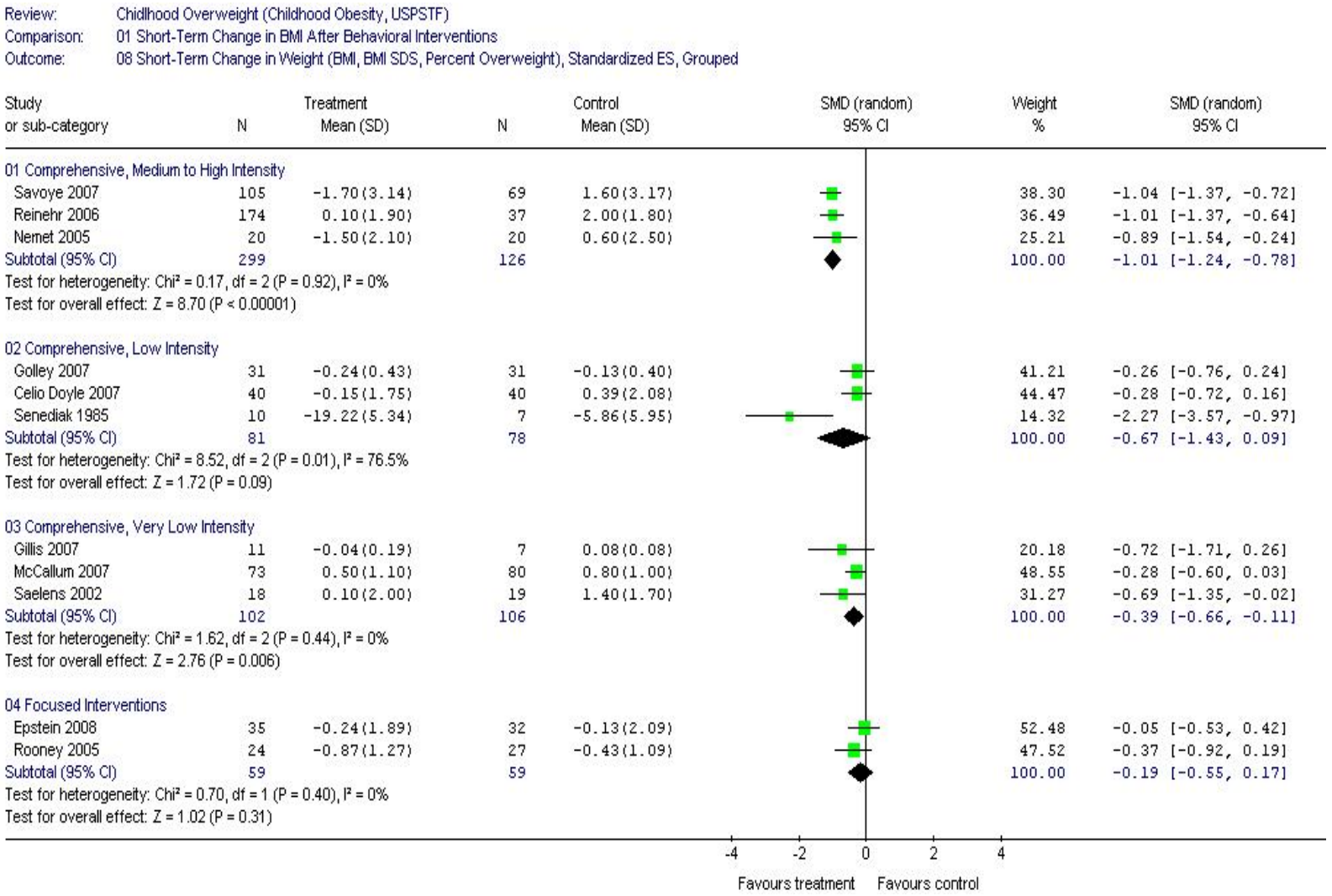


Figure 5. Pooled analysis: Maintenance effect size of behavioral interventions (KQ2)

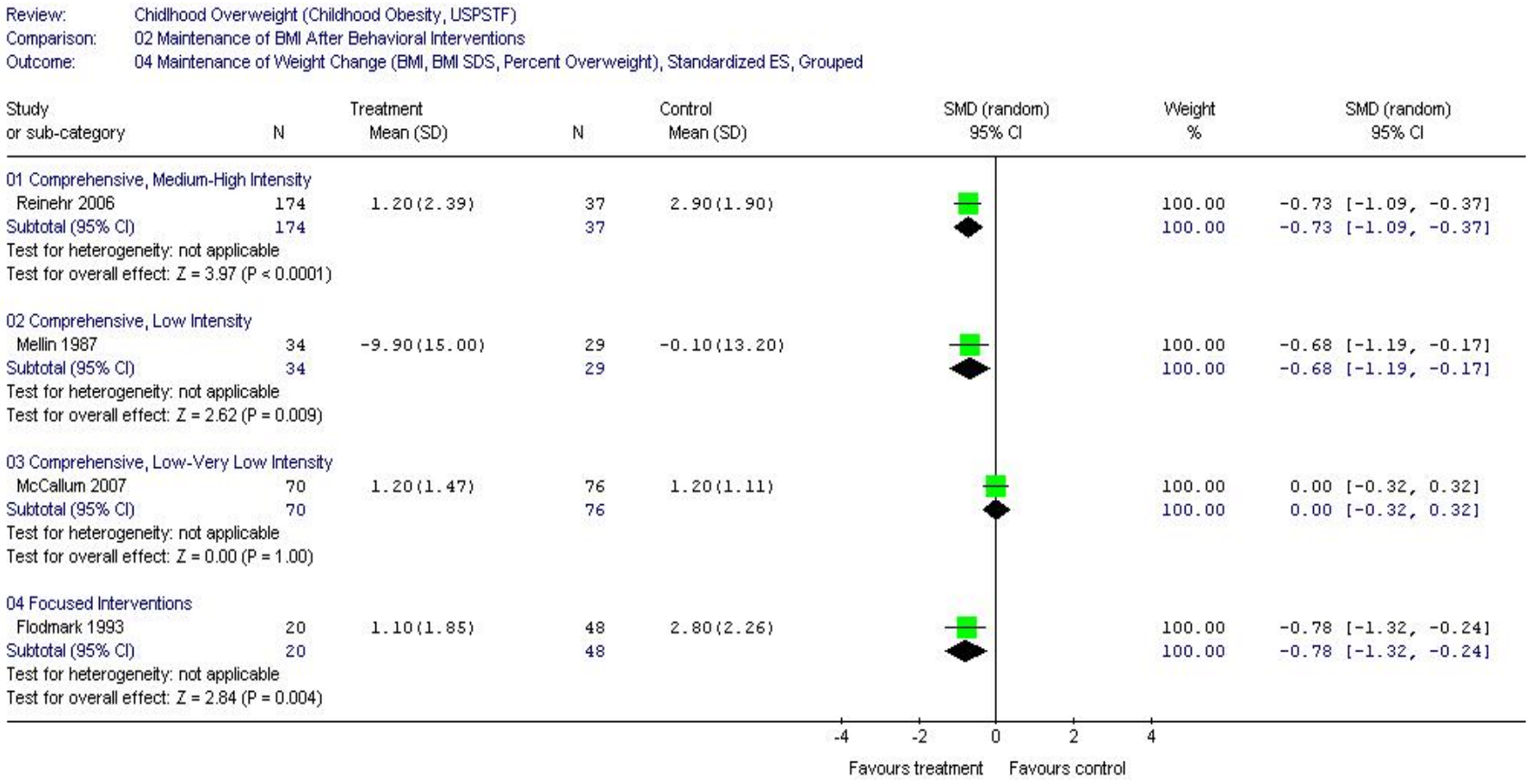


Table 3. Short-term and maintenance outcomes of behavioral interventions

Study Reference Setting	N Randomized Age Baseline BMI	Intervention Hours (I-C) Intervention Components	Short-Term BMI Change: Mean Change (SD of Change)	Maintenance of BMI Change: Mean Change (SD of Change)
Comprehensive Programs, Medium (26-75 hrs) to High (76+ hrs) Intensity				
Savoye et al 2007[77] Health Care	N: 174 Age 8-16 BMI: I: 35.8 ± 7.6 C: 36.2 ± 6.2	97.5 hrs I: D,PA+, BehMod, Fam C: Brief semi-annual counseling	**12-mo (post-tx)**** I: -1.7 ± 3.1 (c) C: +1.6 ± 3.2 (c)	(Not Reported)
Reinehr et al 2006[79,89] Health Care	N: 240 Age 6-14 BMI: I: 27.0 ± 4.4 (c) C: 26.1 ± 4.0 (c)	76 hrs I: D,PA+, BehMod,Fam,MHTx C: No treatment due to distance from clinic	**12-mo (post-tx)**** I: +0.1 ± 1.9 (c) C: +2.0 ± 1.8 (c)	**24-mo (12-mos post-tx)**** I: +1.2 ± 2.4 (c) C: +2.9 ± 1.9 (c)
Nemet et al 2005[85] Child Health and Sports Center	N=54 Average age 11.1 BMI: I: 27.7 ± 3.6 C: 28.0 ± 5.2	35.75 hrs I: D, PA+, BehMod, Fam C Nutritional counseling	**12-mo (9-mo post-tx)*** I: -1.5 ± 2.1 (c) C: +0.6 ± 2.5 (c)	(Not Reported)
Comprehensive Programs, Low-Intensity (11-25 hrs)				
Mellin et al 1987[104] Health Care	N=66 Age 12-18 (15.6) BMI:NR †Percent Overweight: I: 36.5% (SD NR) C: 29.5% (SD NR)	24 hrs I: D, PA+, BehMod C: No treatment	(Not Reported)	**15-mo (12-mo post-tx):** †Percent Overweight: I: -9.9 ± 15.0 (p<0.01)** C: -0.1 ± 13.2 (n.s.)**
Golley 2007[80] Health Care	N=111 Age 6-9 BMI: 24.3 ± 2.6 (overall)	10.3 hrs (I1), 22 hrs (I2) I1: D, PA, Fam, MHTx I2: D, PA+, BehMod, Fam, MHTx C: Wait List	12-mo (7-mos post-tx): †BMI SDS: I1: -0.15 ± 0.47 I2: -0.24 ± 0.43 C: -0.13 ± 0.40	(Not Reported)
Doyle et al 2008;[86] Celio et al 2006[88] E-mail, Internet	N=83 Age 12-18 BMI: I: 34.6 ± 7.8 C: 33.9 ± 6.9	16 hrs I: D, PA, BehMod C: Information only	8-mo (4-mo post-tx):‡ I: -0.2 ± 1.8 C: +0.4 ± 2.1	(Not Reported)
Senediak et al 1985[84] Setting NR	N=35 Age 6-12 BMI:NR †Percent Overweight: I1: 32.9% ± 14.0 I2: 35.9% ± 12.2 C: 36.7% ± 5.5	12 hrs (I1, I2, C) I1: D, PA, BehMod, Fam I2: D, PA, BehMod, Fam C: Social support, relaxation, mood monitoring	**6-mo (3-5 mo post-tx)*:** †Percent Overweight: I1: -13.0% ± 6.3 (c) I2: -19.2% ± 5.4 (c) C: -5.9% ± 6.0 (c)	(Not Reported)

Table 3. Short-term and maintenance outcomes of behavioral interventions (cont.)

Study Reference Setting	N Randomized Age Baseline BMI	Intervention Hours (I-C) Intervention Components	Short-Term BMI Change: Mean Change (SD of Change)	Maintenance of BMI Change: Mean Change (SD of Change)
Comprehensive Programs, Very Low-Intensity (<10 hrs)				
Gillis 2007[78] Health Care	N: 27 Age 7-16 BMI SDS I: 1.98 ± 0.21 C: 2.16 ± 0.34	8 hrs I: D, PA, BehMod C: 1 counseling session	6-mo (post-tx): †BMI SDS: I: -0.045 ± 0.19 C: +0.075 ± 0.08	(Not Reported)
McCallum et al, 2007[81,90] Primary Care	N=163 Age 5-9 BMI: I: 20.5 ± 2.2 C: 20.0 ± 1.8	4 hrs I: D, PA, BehMod, Fam C: Usual primary care	9-mo (6-mo post-tx): I: +0.5 ± 1.1 (c) C: +0.8 ± 1.0 (c)	15-mo (12-mo post-tx): I: +1.2 ± 1.5 (c) C: +1.2 ± 1.1 (c)
Saelens et al 2002[83] Primary Care	N=44 Age 12-16 BMI: I: 31.0 ± 3.5 C: 30.7 ± 3.1	3.8 hrs I: D, PA, BehMod C: Usual primary care	**7-mo (3-mo post-tx)*:** I: +0.1 ± 2.0 (c) C: +1.4 ± 1.7 (c)	(Not Reported)
Focused Interventions, Very Low- to Low-Intensity				
Flodmark 1993[103] Health Care	N=93 Age 10-11 BMI: I1: 25.5 ± 2.3 (c) I2: 24.7 ± 1.8 (c) C: 25.1 ± 2.5 (c)	12 hrs (I1), 24 hrs (I2) I1:D, PA, Fam I2:D, PA, Fam, MHTx C: Matched controls, no treatment	(Not Reported)	**~48-mo (30-34 mo post-tx)*:** I1: +1.6 ± 2.0 (c) I2: +1.1 ± 1.8 (c) C: +2.8 ± 2.3 (c)
Rooney 2005[82] Community	N=98 families, 353 people Age 5-12 BMI: I1: 21.1 ± 6.2 I2: 22.2 ± 6.2 C: 21.9 ± 6.0	3 hrs (I1), 21 hrs (I2) I1: PA, Fam, Pedometer I2: D, PA, Fam, Pedometer C: No Treatment	9-mo (6 mo post-tx):‡ I1 -0.4 ± 1.0 (c) I2: -0.9 ± 1.3 (c) C: -0.4 ± 1.1 (c)	(Not Reported)
Epstein et al 2008[87] Health Care	N=70 Age 4-7 BMI: I: 19.3 ± 2.5 C: 19.1 ± 3.5	Hours NA, likely Very Low I: PA, Fam, Use of device to limit TV & computer time C: Fam, No device	**24-mo (post-intervention)**§ †BMI SDS: I: -0.24 ± 1.9 C: -0.13 ± 2.1	(Not Reported)

Note: Interventions ordered first by setting and second by intensity.
Abbreviations: I- Intervention group; C- Control group; (c)-calculated; NR-Not Reported; D-dietary counseling; PA-physical activity counseling; PA+-organized physical activity sessions; BehMod-behavioral modification principles used to address diet and physical activity changes; Fam-family or parent was a target of the intervention; MHTx-mental health treatment beyond behavior modification for diet and physical activity; post-tx- post treatment; SD-standard deviation
* p<0.05; **p<0.01, **bold** if p<0.05
†BMI not reported, so other outcome listed
‡Unpublished data supplied by author
§Data were not provided for the 12-month mid-treatment 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.

Table 4. Effective behavioral interventions for overweight or obesity

Study Reference	Age Range, N, Intervention Hours (Intensity)	Description of Intervention
Short-Term Outcomes		
Savoye et al 2007[77] Health Care	8-16 n=174 97.5 hrs (High)	***Diet:*** Non-dieting approach emphasizing low-fat, nutrient-dense foods of moderate portion sizes. ***PA:*** Two 50-min sessions/wk for first 6 months, then 1 session every 2 weeks. Each session included warm-up, high-intensity aerobic exercise, and cool-down. Goal to sustain 65% to 80% of age-adjusted max heart rate for duration of aerobic exercise. Also encouraged to exercise 3 additional days/week at home and to decrease sedentary behaviors. ***Beh Tx***: One 50-min session/wk for first 6 months, then 1 session every 2 weeks. Topics included self-awareness, goal-setting, stimulus control, coping skills training, cognitive behavior strategies, contingency management. ***Family:*** Parents attended separate group during children's behavioral treatment groups. Emphasized parents' role modeling health behavior, coping skills training.
Reinehr et al 2006[79] Health Care	6-14 n=240 76 hrs (High)	***Diet:*** Recommended diet of 30% fat, 15% protein, 55% carb (only 5% sugar). Categorized foods using Traffic Light system: red="stop", yellow="consider the amount", green="OK when hungry or thirsty. Total kcal went from 1459 ± 379 pre-treatment to 1250 ± 299 kcal post-treatment ***PA:*** Once per week for 12 months, consisted of ballgames, jogging, trampoline, instruction in physical activity as part of everyday life, and encouragement to reduce amount of time spend watching TV ***Beh Tx***: In first 3 months, 6-session nutrition course and 6-session behavior therapy groups for children. Family therapy provided for the next 3 months, with up to 3-month extension as needed. Lifestyle modification approach, details of topic covered not reported. ***Family:*** 6-session parents' course for parents, 3 "Talk rounds for parents", plus family therapy described above.
Gillis 2007[78] Health Care	7-16 n=27 8 hrs (Very low)	***Diet:*** Two discussions of healthy diet; asked to record food intake once/week. No details of recommended diet reported. ***PA:*** Two sessions discussing exercise; asked to record exercise once/week. No details of exercise recommendations reported. ***Beh Tx***: Self-monitor food and physical activity one day per week ***Family:*** None
Nemet et al 2005[85] Health Care ("Child Health and Sports Center")	Avg age 11.1 n=54 35.75 hrs (Medium)	***Diet:*** 6 one-on-one meetings with a dietitian plus four group lectures, covering reasons for childhood obesity, nutrition information such as the food pyramid, food labels, food preparation, eating habits, regular meals. Recommend balanced diet of 5,021 to 8,368 KJ, a deficit of ~30% from baseline intake, or 15% less than estimated daily required intake. ***PA:*** Two 1-hour sessions/week for 14 weeks designed to mimic the type and intensity of exercise that children normally perform. Activities varied in duration and intensity, but usually included activities promoting endurance. Attention given to improving flexibility and coordination. Instructed to exercise at home for additional 30-45 minutes/week and to reduce sedentary activities. ***Beh Tx***: Information on controlling the environment to minimize over-eating, coping with situations that encourage overeating. ***Family:*** Varied with child's age. Ages 6-8: parents only for first 2 meetings, children joined thereafter. Ages 8 years-puberty: parents and children invited to all sessions. Puberty onward: Parents and youth attend first meeting, then alternate parents and child.

Table 4. Effective behavioral interventions for overweight or obesity (cont.)

Study Reference	Age Range, N, Intervention Hours (Intensity)	*Description of Intervention*
Short-Term Outcomes		
Saelens et al 2002[83] Primary Care	12-16 n=44 3.8 hrs (Very low)	***Diet:*** Adaptation of Traffic Light diet, goal to reduce to ~1200-1500 kcal/day. Focus on reduction in overall quantity of food and increasing healthy eating, with no prohibition of any particular foods. Computer-based assessment used to identify eating habits, develop initial recommendation/plan. Meeting with pediatrician to confirm/modify plan, 11 10-20 minute follow-up phone calls with support staff to discuss food diaries and other behavior change issues. ***PA:*** PA also assessed via computer, goals set with pediatrician, encouraged by phone counselors. Monitored PA starting with 5th phone call, goal minimum of 60 minutes of at least moderate intensity PA 5 days/week. ***Beh Tx***: Behavioral skills covered include self-monitoring, goal setting, problem solving, stimulus control, self-reward, and preplanning. ***Family:*** Parents sent information sheets corresponding to materials received by youth, highlighting ways in which parents can be most helpful. Recommended parental skills included stimulus/environmental control, positive reinforcement, and preplanning.
Senediak et al 1985[84] Setting NR	6-12 n=45 12 hrs (Low)	***Diet:*** Covered variety of nutritional and dietary topics, recommended diet based on Food Exchange System and Traffic Light System. ***PA:*** Children instructed to engage in at least four 30-minute aerobic exercise sessions per week. Basic conditioning exercises introduced initially, then more strenuous aerobic exercise. Also recommended other lifestyle changes (such as walking instead of riding in the car) to encourage physical activity. ***Beh Tx***: Utilized self-monitoring, self-reinforcement and parental reinforcement, stimulus control techniques (e.g., restricting food consumption to specific times and places), attempted to modify negative cognitions that may contribute to obesity. ***Family:*** Both parents and children involved in all sessions, given materials and homework.
Epstein et al 2008[87] Health Care	4-7 N=70 Hours NA (Very low)	***Diet:*** None described ***PA:*** Installed devices on all computer and television screens to monitor screen time and limit their use, following a gradual reducing schedule. ***Beh Tx:*** None described ***Family:*** Separate codes were entered for each person in the household, so screen time was monitored and limited separately for each person.
Maintenance Outcomes		
Mellin et al1987[104] Health Care	12-18 n=66 24 hrs (Low)	***Diet:*** Sustainable, small changes in diet; very-low-calorie or restrictive diets discouraged. No specific details on recommended diet. ***PA:*** Encouraged to make sustainable, small changes in exercise habits. No further details provided. ***Beh Tx***: 14 weekly sessions; self-directed change format, encourage small, sustainable changes in relationships, lifestyle, communication, and attitudes. Details of encouraged change process not described. ***Family:*** Two parent meetings; instructed on strategies for supporting their child's weight-loss efforts, including altering family dietary and activity habits, and improving parenting and communication skills.
Flodmark et al, 1993[103] Health Care	10-11 n=93 I1: 12 hrs I2: 24 hrs (Low)	***Diet:*** Counseling by pediatrician and/or dietitian; recommend 1500 to 1700 kcal, with 30% of calories from fat. ***PA:*** No recommendations described ***Beh Tx***: None described. ***Family:*** Family therapy focused on reinforcing the resources of the family and creating and optimal emotional climate for helping the obese child. Adjustments to family hierarchy/structure, plus solution-focused therapeutic techniques.

Abbreviations: PA- physical activity; Beh TX – behavioral treatment

Table 5. Results of randomized controlled trials of pharmacological anti-obesity treatments among adolescents, by drug type

Source	N	Baseline BMI (kg/m^2)	Treatment months	Change BMI (kg/m^2) p value	Physiological Outcomes		Adverse Events
Sibutramine							
Berkowitz et al, 2003[91]	43 39	I: 37.5 ± 4.0 C: 38.0 ± 3.6	6	-3.2[a] -1.5[a] p=0.001[b]	WC: SD LDL: NS HDL: NS TG: NS FPG: NS	Insulin: NS HOMA: NS Heart Rate: SD[e] Systolic BP: SD[e] Diastolic BP: NS	Adverse Events: NS
Berkowitz et al, 2006[92]	368 130	I: 36.1 ± 3.8 C: 35.9 ± 4.1	12	-2.9 -0.3 p < 0.001	WC: SD LDL: NS HDL: SD TG: SD FPG: NS	Insulin: SD HOMA: SD Heart Rate: SD[e] Systolic BP: SD[e] Diastolic BP: SD[e]	Adverse Events: NS SAE: NS d/c med: NS Growth: NS Maturation: NS
Garcia-Morales et al, 2006[94]	26 25	I: 35.1± 5.3 C: 36.6 ± 5.2	6	-3.4 (-2.5, -4.2) -1.8 (-0.9, -2.6) P< 0.005*	WC: NS LDL: NS HDL: NS TG: NS	FPG NS Heart Rate: SD[e] Systolic BP: NS Diastolic BP: SD[e]	Adverse Events: NS d/c med: NS Maturation: NS Growth: NS
Godoy-Matos et al, 2005[95]	30 30	I: 37.5 ± 3.8 (f) 37.6 ± 4.3 (m) C: 35.8 ± 4.2 (f) 37.4 ± 1.9 (m)	6	-3.6 ± 2.5 -0.9 ± 0.9 p < 0.001	WC: SD LDL: NS HDL: NS TG: NS FPG: NS	Insulin: NS Heart Rate: NS Systolic BP: NS Diastolic BP: NS	SAE: NS d/c med: NS Other: SD
Van Mil et al, 2007[97]	12 12	I: 30.1 ± 4.5 C: 33.3 ± 5.0	3 + 3 mos f/u[c]	-0.8[d] -1.4[d] NR	% Fat Mass: NS Heart Rate: NS	Systolic BP: NS Diastolic BP: NS	Adverse Event: NS d/c med: NS Other: SD

Table 5. Results of randomized controlled trials of pharmacological anti-obesity treatments among adolescents, by drug type (cont.)

Source	N	Baseline BMI (kg/m^2)	Treatment months	Change BMI (kg/m^2) p value	Physiological Outcomes		Adverse Events
Orlistat							
Chanoine et al, 2005[93]	357 182	I: 35.7 ± 4.2 C: 35.4 ± 4.1	12	-0.55 +0.3 p < 0.001	WC: SD Other Adiposity: SD LDL: NS HDL: NS TG: NS	FPG: NS Insulin: NS Heart Rate: NS Systolic BP: NS Diastolic BP: SD[f]	Growth: NS Maturation: NS Other: SD
Maahs et al, 2006[96]	20 20	I: 39.2 ± 1.2 C: 41.7 ± 2.6	6	-1.3 ± 1.6 -0.8 ± 3.0 NS	% Fat Mass: NS LDL: NS HDL: NS	TG: NS FPG: NS Insulin: NS	Other: SD

a: Calculated based on average BMI at baseline and average percentage change in BMI for each group (I: -8.5% ± 6.8%, C: -4.0% ± 5.4%).
b: Based on comparison of percent change in BMI between groups
*result of ANOVA testing interaction between treatment group and time
c: Patients were treated with BT + sibutramine or placebo for 3 mos and then BT alone for 3 mos.
d: calculated based on differences reported baseline to 3 mos and 3 mos to 6 mos.
e: Relative increased rate over time in sibutramine group compared to placebo group
f: Relative reduction in rate over time in orlistat group compared to placebo group
Abbreviations: IG - Intervention group; CG - Control group; BT - Behavioral Treatment, NS - not significant; NR - not reported; WC - Waist circumference; LDL - Low-density Lipoprotein; HDL- High-density Lipoprotein; TG - triglyceride; FPG - Fasting plasma glucose; BP - Blood pressure; SD - statistically significant difference; SAE - Serious adverse events; HOMA - Homeostasis model assessment of insulin sensitivity; d/c - discontinue.

Table 6. Randomized, placebo-controlled, clinical trials evaluating pharmacological agents among special populations of obese children and adolescents and reporting weight outcomes

Source	N randomized Study design Country	Population Length of study	Intervention Drug dose	Baseline BMI	BMI Results
Srinivasan et al, 2006[99]	N = 28 Cross-over RCT Australia	Obese children and adolescents ages 9-18 years with clinical suspicion of insulin resistance (fasting insulin: glucose > 4.5 or acanthosis nigricans) 12 months	A: Metformin for 6 months, then placebo for 6 months B: Placebo for 6 months, then metformin for 6 months Metformin dose: gradually increased (over 3 wks) up to 2 g/day vs. placebo	Total sample: 35.2 ± 5.1 kg/m^2 (not reported by study group)	ΔΔ BMI SDS* -0.12 p=0.005 ΔΔ BMI -1.26 kg/m^2 p=0.002
Freemark et al., 2001[98]	N =32 RCT USA	Obese adolescents ages 12 to 19 years with fasting insulin concentration > 15 μU/mL; and ≥ 1 first- or second-degree relative with type 2 DM 6 months	IG: Metformin CG: Placebo Metformin dose: 500 mg, twice per day	IG: 41.5 ± 0.9 CG: 38.7 ± 1.3 (p < 0.05)	Δ BMI SDS IG: -0.12 CG: 0.23 p< 0.02 Δ BMI IG: -0.5 kg/m^2 CG: 0.9 kg/m^2 p-value NR
Love-Osborne et al, 2008[100]	N = 85 RCT USA	Adolescents 12 - 19 with fasting insulin level > 25μU/mL or homeostasis model assessment > 3.5 and 2 of 3 risk factors (presence of acanthosis nigricans, obesity (BMI>95%ile), or family history of T2DM) 6 months	IG: Metformin + behavioral intervention (personal goal-setting) CG: Placebo + behavioral intervention (personal goal-setting) Metformin dose: increased over 2 months to 850 mg twice per day, (if tolerated)	IG:39.4 ± 6.5 CG:39.3 ± 7.2	Δ BMI IG: -0.16 ± 1.89 CG: 0.63 ± 1.29 p-value 0.11 >5% BMI decrease: IG: 11 (22.9%) CG: 0 (0%) p = 0.001

Abbreviations: BMI - Body mass index; DM - Diabetes mellitus; IG - intervention group; CG - control group; RCT - randomized controlled trial
*ΔΔ BMI = Δ BMI$_{IG}$ - Δ BMI$_{CG}$

Table 7. Other positive medical outcomes reported in behavioral intervention trials

Study Reference	Increase in High-density lipids (HDL)	Decrease in Low-density lipids (LDL) †	Decrease in Triglycerides	Decrease in systolic BP	Decrease in diastolic BP	Decrease in Fasting Glucose	Decrease in Fasting Insulin	Decrease in HOMA-IR	Adiposity (Measure)
Flodmark 1993[103]	--	--	--	--	--	--	--	--	IG: Triceps, subscapular, suprailiac skinfold; decrease in thickness
Gillis 2007[78]	N	N	N	--	--	--	--	--	--
Golley 2007[80]	N	--	N	N	N	N	N	--	IG: decrease in Waist circumference
Nemet et al 2005[85]	--	--	--	--	--	--	--	--	IG: Triceps, subscapular skinfold; decrease in thickness
Reinehr et al 2006[79]	N	IG	N	IG	N	N	IG	IG	--
Savoye et al 2007[77]	N	N	N	--	--	N	IG	IG	IG: Bioelectric impedance; decrease in body fat percentage
Senediak et al 1985[84]	--	--	--	--	--	--	--	--	IG: Subscapular skinfold; decrease in thickness

N - No group differences, IG - Result favors intervention group
†HDL and LDL differences are reported separately; trials do not report on the ratio of HDL to LDL
BP- blood pressure; DEXA - Dual-energy x-ray absorptiometry; HOMA - homeostasis model assessment of insulin resistance

Table 8. Potentially harmful effects of behavioral interventions for childhood overweight

Study Reference	Outcomes of All Potential Harmful Effects Examined
Height	
Savoye et al 2007[77]	No group difference in changes in height at 6 months or 12 months
Golley 2007[80]	No group difference in changes in height at 12 months
Eating Pathology and Body Image	
Saelens et al 2002[83]	Problematic eating/eating disorder psychopathology did not differ between groups
Doyle et al, unpub;[86]	Control group showed greater decline in Shape Concern than Intervention group; no other differences in eating disorder pathology
McCallum et al 2007[81]	No differences on child-reported ratings of body satisfaction or appearance/self-worth
Other	
Mellin et al 1987[104]	Depression improved in treatment group, did not change in control group.
Supplementary Trials, Injuries Related to Physical Activity	
Sung et al 2002[107]	No training-related injuries. (Ages 8-11, Baseline BMI 25.5)
Davis et al 2006[106]	1 bone fracture in exercising group (11 and I2 combined) (Ages 7-11, Baseline BMI 26.5)

Table 9. Overall summary of evidence

No. of studies	Design	Limitations	Consistency	Applicability	Overall Quality	Summary of Findings
KQ1. Short-Term (6- to 12-month) Weight Outcomes						
Behavioral Interventions						
11	10 RCTs, 1 CCT	Heterogeneity along many dimensions, including age of participants, baseline degree of excess weight, intervention approach, setting, country, treatment intensity, time to followup; high attrition in many trials	Fair: All medium- or high-intensity, comprehensive programs were consistently effective; some low- and very low-intensity trials were effective, but are so heterogeneous that patterns cannot be identified to explain the inconsistencies.	Fair: Two trials conducted in primary care with primary care samples, and a third was conducted in primary care but used a sample referred for help with obesity. Higher intensity treatments could be feasible for health care systems to offer, but may not be broadly available.	Fair to Good: 5 rated fair quality and 6 rated good quality	Comprehensive moderate- to high-intensity interventions resulted in a 1.9 to 3.3 kg/m^2 difference in mean BMI change in children aged 6 and older, 6-12 months after starting treatment, compared with controls. For a 16-year-old girl, the largest BMI difference (3.3 kg/m^2) would translate into a 20 pound difference at the end of treatment. Low and very low-intensity programs showed inconsistent results and generally had smaller effects.
Phamacological + Behavioral Interventions						
Sibutramine: 5 Orlistat: 2 Metformin: 3	RCTs	Only one large-scale trial for each of sibutramine and orlistat; fairly high attrition in large trials; only studies in very obese (adult class II obesity) 12 to 18-year-olds; metformin has been studied only among selected populations at high risk for diabetes in small, fair-quality trials	Good for sibutramine, Fair for orlistat, fair to poor for metformin	Fair: Most trials conducted in settings feasible for primary care-referral (specialty weight loss or research clinics); metformin results are applicable only to selected populations and were a secondary outcome of treatment aimed at blood sugar regulation.	Good for sibutramine and orlistat; Fair for metformin	*Sibutramine:* 12 to 18-year-olds receiving 12 months of sibutramine plus a behavioral intervention showed an average BMI difference of 2.6 $kg/m^{2,}$ compared with those receiving a placebo, and a weight difference of 19 pounds. *Orlistat:* Mean BMI was 0.85 kg/m^2 less in orlistat users after treatment, compared with those receiving the behavioral intervention only in large, good-quality trial. *Metformin:* Metformin users showed greater reductions in BMI and BMI SDS after 6 months of treatment in two small trials but no significant BMI difference in the third trial

Table 9. Overall summary of evidence (cont.)

No. of studies	Design	Limitations	Consistency	Applicability	Overall Quality	Summary of Findings
KQ2. Maintenance of Weight Outcomes						
Behavioral Interventions						
4	2 RCTs, 2 CCTs	Only four trials, all different from each other on dimensions listed above;	Fair	Fair: one was conducted in primary care, but only one of four conducted in the US and two of four were older trials (1993 and 1987)	Fair: 3 trials rated fair quality, 1 trial rated good quality.	Three of four trials found that improvements in weight were maintained 12 months or more after treatment ended. Two trials reported 1.7 kg/m^2 greater weight loss in treatment than control groups, and one very low-intensity primary care-based trial reported no group differences in BMI. A trial reporting change in percent overweight found that it declined by 9.8 percentage points more in the intervention than control group.
Pharmacological + Behavioral Interventions						
No evidence						
KQ1a & KQ2a: Other beneficial outcomes of weight management interventions						
Behavioral Interventions						
13	11 RCTs, 2 CCTs	Other beneficial outcomes inconsistently reported; some outcomes reported in only one or a few trials; same outcomes measured differently in different trials.	Fair to poor	Fair: Two trials conducted in primary care with primary care samples, and a third was conducted in primary care but used a sample referred for help with obesity	Fair to Good: 8 rated fair quality, 5 good quality	Other outcomes reported included adiposity, cardiovascular risk factors, physical fitness, behavioral outcomes, and psychosocial outcomes. Results in all areas were mixed, but the outcomes that were most likely to show greater improvement in the intervention group were measures of adiposity (5 of 5 found group differences), insulin-related measures (2 of 3 found group differences), and measures of physical fitness (2 of 3 found group differences).

Table 9. Overall summary of evidence (cont.)

No. of studies	Design	Limitations	Consistency	Applicability	Overall Quality	Summary of Findings
Pharmacological + Behavioral Interventions						
Sibutramine: 5 Orlistat: 2 Metformin: 3	RCTs	Only one large-scale trial for each of sibutramine and orlistat; fairly high attrition in large trials; only studies in very obese (adult class II obesity) 12 to 18-year-olds; metformin has been studied only among special populations in small, fair-quality trials	Good for sibutramine, Fair for orlistat, metformin	Fair: Most trials conducted in settings feasible for primary care-referral (specialty weight loss or research clinics); metformin results are applicable only to selected populations	Good for sibutramine and orlistat; Fair for metformin	*Sibutramine:* In three of four trials, the sibutramine groups reduced the waist circumference on average by 7-8 cm, compared with 2-3 cm in the control groups. One good quality trial also found greater reductions in HDL cholesterol, triglycerides, serum insulin, and HOMA, compared to the placebo group, but no differences in LDL or fasting serum glucose. *Orlistat:* Groups differed on fat mass in large, good quality trial, but not in the smaller trial; no differences in either trial on LDL, HDL, TG, FPG, insulin, or systolic blood pressure. The good-quality trial found small reduction in diastolic blood pressure. *Metformin*: One trial reported improved subcutaneous adiposity; two of three found improvements in fasting glucose and insulin. One trial found improvements in lipid parameters.
KQ1b & KQ2b: Effective components of weight management interventions						
Behavioral Interventions						
13	11 RCTs, 2 CCTs	Heterogeneity along many dimensions, making it impossible to isolate the effects of individual components of treatment	Poor	Fair to poor since interventions are so hetergeneous	Fair to Good—but not directly applicable to this question	We examined the use of organized physical activity sessions, parental involvement, and the use of behavior management techniques. None of the components clearly improved the chance of showing a positive weight management effect. Organized physical activity sessions did increase the likelihood of treatment success, but it was confounded with treatment intensity, and it was therefore impossible to determine whether it was the exercise sessions or the overall intensity of the treatment program that improved the chances of success.
Pharmacological + Behavioral Interventions						
Data were insufficient to explore the importance of specific treatment components.						

Table 9. Overall summary of evidence (cont.)

No. of studies	Design	Limitations	Consistency	Applicability	Overall Quality	Summary of Findings
KQ1c & KQ2c: Population or environmental factors that affect weight management interventions						
Behavioral Interventions						
Data were insufficient to explore the importance of population or environmental factors.						
Pharmacological + Behavioral Interventions						
Data were insufficient to explore the importance of population or environmental factors.						
KQ3. Harms of weight management interventions						
Behavioral Interventions						
11 (9 + 2 supplementary)	RCTs	Harms inconsistently reported, specific harm outcomes reported in only 1 to 3 trials, and outcomes were measured differently	Fair: outcomes consistently show no harms, but little consistency in what and how harms were measured.	Fair: Both of the primary care-based trials reported one of more harms outcomes, but most studies didn't provide this data	Fair to poor—given reporting limitations for harms	Trials reported potential harms of impact on height, eating pathology or body image, depression, and injury. We found no evidence that behavioral intervention programs may be harmful
Pharmacological + Behavioral Interventions						
Sibutramine: 5 Orlistat: 2 Metformin: 3	RCTs	Only one large-scale trial for each of sibutramine and orlistat and limited to 12 months f/u. Metformin studied only in small, fair-quality studies	Good for sibutramine, orlistat and metformin	Fair: Most trials conducted in settings feasible for primary care-referral (specialty weight loss or research clinics); metformin results are applicable only to very selected populations	Good for sibutramine and orlistat; Fair for metformin	*Sibutramine:* Serious adverse effects: 2.7% (sibutramine) vs. 1% (placebo); sibutramine had increased heart rate, systolic blood pressure, abdominal complaints, and constipation; no effects on growth *Orlistat:* Serious adverse effects 3% in both drug and placebo; greater gastrointestinal side effects (>30% in drug); no effects on growth *Metformin:* No serious adverse effects; serum lactate and renal function remained normal; gastrointestinal side effects in 29% of metformin patients.

Abbreviations: BMI-body mass index; BMI SDS- Body Mass Index Standard Deviation Score; LDL-Low-density lipoprotein cholesterol, HDL- High-density lipoprotein cholesterol, TG-triglycerides, FPG-fasting plasma glucose; HOMA- Homeostasis model assessment of insulin sensitivity

Appendix A. Detailed Methods

Key Questions and Analytic Framework

Using the methods of the USPSTF,[70] we developed three key questions (KQ) (with six sub-key questions) and an analytic frame work (Figure 3) in conjunction with members of the USPSTF to update its 2005 recommendation on Screening for Childhood Overweight and Obesity[2]. These KQs were designed to evaluate the effectiveness and safety of behavioral and pharmacological 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 using short-term (6-12 months since enrolling in treatment), while KQ2 focuses on the maintenance of BMI improvements through medium-term (between 1 to 5 years since enrollment and at least 12 months since treatment ended). KQ3 assesses adverse effects of behavioral and pharmacological interventions. KQ1a and KQ2a consider other beneficial outcomes arising from the interventions. KQ1b, KQ2b, KQ1c, and KQ2c consider 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, Database of Abstracts of Reviews of Effects (DARE), the Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CCRCT), and Education Resources Information Center (ERIC) 2004 to 2007. We selected relevant, good quality systematic reviews where available to assist in conducting our literature search. Quality criteria were based on USPSTF methods,[70] supplemented by NICE methodology[9](see Appendix A Table 3). 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.[9] 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 pharmacological treatments[54] as the basis for our search for pharmacological treatments. We conducted update searches in Ovid MEDLINE®, PsycINFO, Database of Abstracts of Reviews of Effects, the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Education Resources Information Center from 2005 (2003 for pharmacological treatments) to June 10, 2008, to identify literature that was published after the search dates of these reports (Appendix A Table 1). The literature search and reports[9,54] were supplemented by hand-searching the reference lists of other good-quality reviews of childhood obesity treatment,[2,7,117-119] 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 key question. Discrepancies were resolved

by consensus. Detailed inclusion/exclusion criteria can be found in Appendix A Table 2. Briefly, the study population included overweight or obese 2 to 18 year-olds. We excluded studies of children with idiosyncratic weight management issues due to 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 these were also reported. Interventions using mazindol were excluded because it is no longer used in current practice. Trials were required to have a minimal intervention or control group and randomize at least 10 participants in each arm. Only controlled trials (RCTs and CCTs) were included for efficacy (short-term and maintenance) of behavioral and pharmacological treatments. Weight management programs reporting pre-specified adverse events resulting in death, hospitalization, or need for urgent medical or psychiatric treatment were included to assess harms (KQ3) for all treatment modalities, even if they did not report one of our specified weight outcomes or did not meet the minimum 6-month followup required for the other key questions. 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 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 (e.g., 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 & KQ2a), important components of care (KQ1b & KQ2b) and population or environmental factors (KQ1c & KQ3c) using trials that were included for KQ1 (short-term efficacy) or KQ2 (maintenance efficacy). When reported, we abstracted data on beneficial outcomes, including impact on co-morbidities.

We used a two-step process to determine which specific intervention components we examined for KQ1b and KQ2b. First, we examined prior literature and identified several factors that may affect weight outcomes in behavioral interventions. These include whether or not studies included organized physical activity sessions,[73] behavioral management techniques[2,10] (for dietary and physical activity), or involved parents or families in addition to the child (clarifying extent to which parental involvement is important, for what ages).[10,74,119] 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 and under); A=Adolescents only (only included those aged 10 and older); B=Both age groups (age range included both younger children and adolescents)). We coded the three 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) used of behavioral modification principles (0=no or minimal use of behavioral modification principles,1=applied behavioral modification principles in treatment); (3) family involvement (0=no parental involvement beyond

consent/receiving materials; 1=parent attended 1 to 3 sessions, less intensive involvement than child; 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 using established design-specific criteria (Appendix A Table 3). Discrepancies were resolved by consensus or consultation with a third investigator. Poor-quality studies were excluded. Eight trials of behavioral interventions[120-127] and one of pharmacological treatment[128] were excluded because they did not meet our quality criteria.

Treatment intensity was categorized by hours of contact as follows: very low intensity (less than 10 hours); low (10 to 25 hours); medium (26 to 75 hours), high (over 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 next 6 months, assuming no more than 2 sessions are 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 to 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 followup reported in any of the included trials was 4 years. Maintenance was evaluated where possible using multiple measurements in the same individuals at least 12 months after an active intervention ended, or by using single post-baseline-measurements in the medium term. Weight outcomes were abstracted as reported, and included many different measures: endpoint BMI, absolute change in BMI from baseline, percent change in BMI from baseline, absolute change in BMI SDS from baseline, endpoint weight, and absolute change in weight from baseline.

In addition, we evaluated whether or not 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 were considered comprehensive. 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 appear to serve as cues leading to inappropriate eating, such as while watching television); eating management (techniques specifically aimed at modifying the act of eating, such as eating slowly); contingency management (contingency contracting, where 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 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 pharmacological agents. We address each type of intervention for each of the six key questions listed in our analytic framework. We discuss each pharmacological agent as a separate intervention.

Where possible, data were synthesized using quantitative methods. For most questions, however, we relied on qualitative synthesis due to 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 Centers for Disease Control and Prevention (CDC)[14] 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 employed on-line calculators provided at the CDC web site[75,76] 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 = (BMI*inches^2)/703.

Studies reported a variety of weight outcomes including BMI, BMI percentile scores, BMI standard deviation or z-scores, and percent overweight. All of these measures have strengths and limitations. While BMI is reliably measured and widely used, it can be problematic when averaging BMI change over a wide age range where 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 (above the 99th percentile).

To avoid the difficulties with an limited upper range of BMI percentile scores, many researchers report BMI standard deviation scores (SDS, 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 standard deviation units above or below the median, based on statistically derived curves.[129] BMI SDS requires the use of published computer programs that access reference data and formulae, such as that published by the CDC[130] Percent overweight is calculated by the simple formula:

100*(child's BMI/50th percentile BMI for child's age and sex).

This method was used chiefly in earlier studies, 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 post-intervention BMI or changes in BMI from baseline and compared these changes between intervention and control groups. Among trials that did not report BMI or change in BMI, three trials reported weight outcomes as changes in BMI standard deviation scores (SDS),[78,80,87] and one trial reported changes in percent overweight.[84] Three[79,80,87] of the trials that reported BMI or related measures between groups at followup statistically tested only whether shape and slope of the curves from baseline through followup were significantly different. For one of these trials[87] we used 24-month outcomes as an estimate for 12-month outcomes, which were shown graphically, but did not report means and standard deviations. 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 since the graphical display in the article indicated non-overlapping confidence intervals at 12-month followup

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 examining only those reporting BMI change and found that that pattern of results and magnitude of effects were very 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 the number randomized, or the number with complete data, for example) was used as the n in the meta-analysis. If both intention-to-treat (ITT) and completers-only analyses were reported, we selected the ITT analysis for inclusion in the meta-analysis. If a trial involved two active treatment arms, the arm with a 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 post-baseline. No trials reported maintenance outcomes at more than one time point for both intervention and control groups. We used random effects models because the trials varied considerably along many dimensions that would impact both baseline BMI (e.g., age, minimum overweight inclusion criteria) and change in BMI (e.g., intensity of intervention, comprehensiveness of treatment program). All meta-analyses were conducted using RevMan 4.2.

Trials were grouped according to comprehensiveness and intensity into the following categories: (1) comprehensive, medium (26-75 hours of contact) to high (76 or more hours) intensity; (2) comprehensive, low intensity (11-25 hours); (3) comprehensive, very low intensity (fewer than 10 hours); (4) focused interventions. Interventions were considered to be comprehensive if they provided dietary counseling,

physical activity counseling, and employed behavior modification principles to assist with behavior change. Trials were only statistically combined within category. All trials reporting maintenance outcomes (KQ2) fell into different categories, and were therefore not statistically combined, though the forest plot is presented to facilitate comparison with across trials.

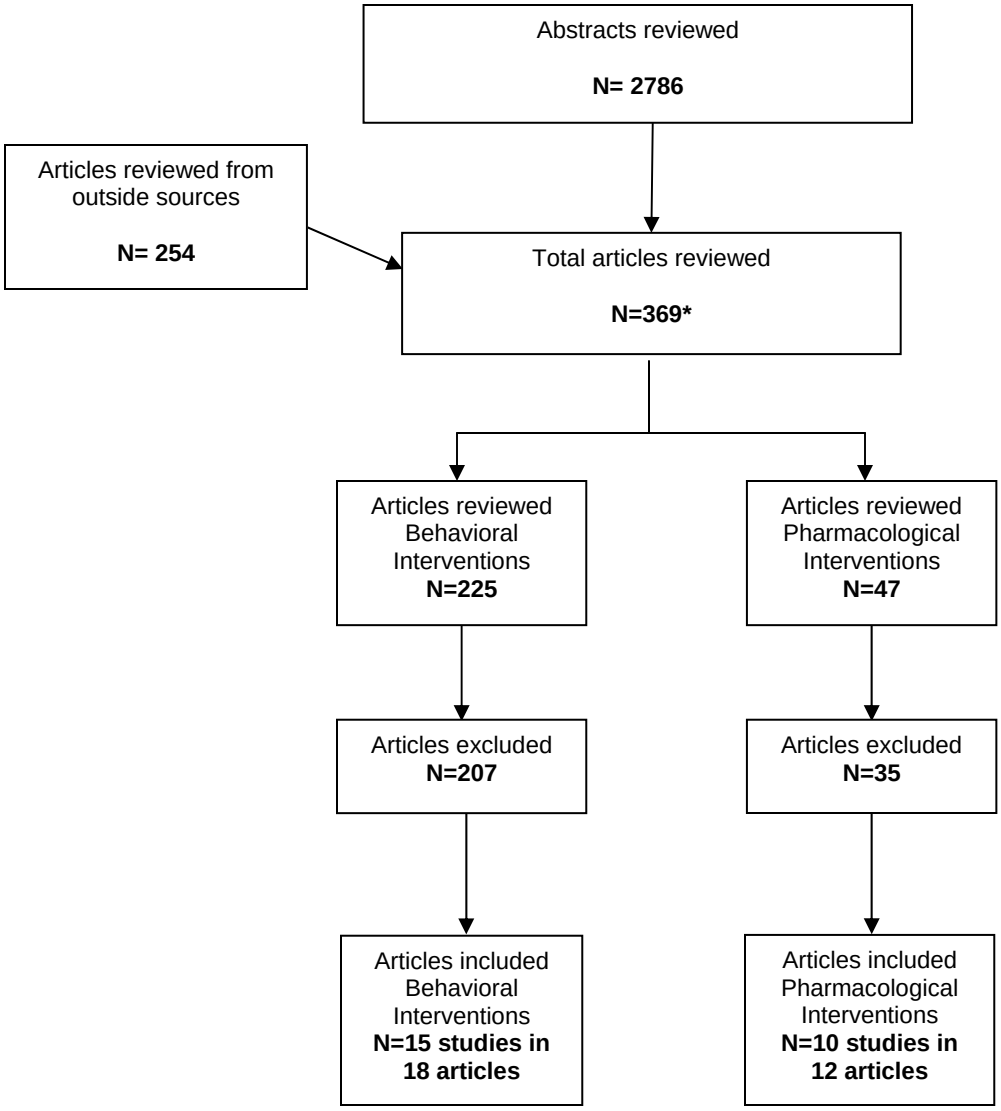
If mean change scores from baseline for each group were not reported, we calculated an unadjusted difference between the mean baseline and mean followup scores for each group using simple subtraction. Standard deviations (SDs) of the change scores were reported in five trials with post-treatment outcomes and one trial with followup outcome. In addition, two authors who did not report them in published articles provided us with these unpublished data.[82,88] We calculated standard deviations for trials that did not report them. Baseline BMI is highly correlated with post-treatment and follow-up BMI, and we had to take this correlation into account when calculating the standard deviations of the change scores. In order to estimate the degree of correlation, we examined data from a recently published trial in a school setting[131] that reported both the SDs of the change scores (which we were attempting to calculate) and the SDs of the baseline and post-treatment BMIs (which we would use to calculate of the SDs of the change scores). Although this trial was excluded from the current review due to 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 post-treatment BMI was approximately 0.90. Therefore, we assumed a correlation of 0.90 for the remaining trials and calculated SDs of BMI change using the following formula:

$$SD_{baseline\text{-}followup} = sqrt(SD^2_{baseline} + SD^2_{followup} - 2*0.90*SD_{baseline}*SD_{followup}).$$

When given standard errors rather than standard deviations, we calculated standard deviations by multiplying the standard error by the square root of n. When given symmetric confidence limits rather than standard deviations, we determined the standard deviation using the following formula:

$$\text{Std Dev} = \frac{(\text{CI width})(sqrt(n))}{2*(1.96)}$$

Appendix A Figure 1. Search results and article flow



*Includes bariatric surgery articles.

Appendix A Table 1. Exact search strings

Database: MEDLINE, Database of Abstracts of Reviews of Effectiveness, Education Resource Information Center, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, NICE, PsycInfo <2003 to June 2008>
Search Strategy:

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.
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]

Appendix A Table 1. Exact search strings

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.

Appendix A Table 1. Exact search strings

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

Appendix A Table 1. Exact search strings

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

Appendix A Table 2. Study eligibility criteria

1. Populations. The following apply to all Key Questions:
    a. Age 2-18. If study substantially overlaps our age range (e.g., 14-65), include article if results for younger participants reported separately. For study of "young adult" or "college-aged", exclude unless average age is <19 or "college freshmen" is specified.
    b. Either (a) entire sample is ≥overweight or obese (85th percentile for age and sex-specific BMI, or who meet previously accepted criteria for overweight based on ideal body weight) or (b) ≥50% of the sample are overweight or obese AND ≥80% of the sample have one 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. Exclude trials in which the sample is limited to youth: (1) with eating disorders, (2) pregnant/ post-partum, (3) overweight/obesity secondary to genetic or medical condition, including Polycystic ovarian syndrome, hypothyroid, Cushings, GH deficiency, insulinoma, hypothalamic disorders (e.g. Froehlich's syndrome), Laurence-Moon-Biedl syndrome, Prader-Willi syndrome, weight gain secondary to medications (e.g., antipsychotics), or (4) other idiosyncratic weight-loss issues.

2. Study Design.
    a. All studies for KQ1 and KQ2 (including sub-KQ) must have an outcomes assessment at 6 months or later post-baseline. No minimum follow-up is required for serious (i.e., requiring urgent medical care) adverse events, KQ3.
    b. Behavioral interventions: limit to RCT or CCT with minimal intervention or placebo control, with a minimum of 10 subjects per treatment arm
    c. Pharmacological interventions: RCT with placebo pill control, with a minimum of 10 subjects per treatment arm

3. Setting.
    a. For Behavioral interventions: all KQ except *serious* (i.e., requiring urgent medical care) adverse effects (KQ3): limit to countries listed as "high" human development on Human Development Index (over .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, 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. Include behavioral (published ≥1985), pharmacological, 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 (e.g., physical activity).
    b. Intevention must be either 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. Exclude trials in which intervention focuses primary prevention, changes in the build environment, mazindol.

5. Outcomes.
    a. KQ1 and KQ2 (and sub-KQs): Must provide acceptable adiposity outcome (2-C, 3-C or 4-C models, except 2-C models not using Lohman's age and sex-specific equation or using the measurement of total bady fat K+) or weight outcome (e.g., baseline and post-intervention 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 & KQ2 trials will be included. For trials that are not included for KQ1 or KQ2, outcomes are limited to serious adverse events, such as death, need for medical or psychiatric treatment, or growth retardation

Appendix A Table 3. Quality rating criteria

Design	U.S. Preventive Services Task Force quality rating criteria[70]	National Institute for Health and Clinical Excellence methodology checklists[132]
Systematic reviews and meta-analyses	• Comprehensiveness of sources considered/search strategy used • Standard appraisal of included studies • Validity of conclusions • Recency and relevance are especially important for systematic reviews	• The study addresses an appropriate and clearly focused question • A description of the methodology used is included • The literature search is sufficiently rigorous to identify all the relevant studies • 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 • Nonbiased selection of cases/controls with exclusion criteria applied equally to both • Response rate • Diagnostic testing procedures applied equally to each group • Measurement of exposure accurate and applied equally to each group • Appropriate attention to potential confounding variables	• The study addresses an appropriate and clearly focused question • The cases and controls are taken from comparable populations • The same exclusion criteria are used for both cases and controls • What percentage of each group (cases and controls) participated in the study? • Comparison is made between participants and non-participants to establish their similarities or differences • Cases are clearly defined and differentiated from controls • Is it clearly established that controls are non-cases? • 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 confidence intervals been provided?

Appendix A Table 3. Quality rating criteria

Design	U.S. Preventive Services Task Force quality rating criteria[70]	National Institute for Health and Clinical Excellence methodology checklists[132]
Randomized controlled trials (RCTs)	• Initial assembly of comparable groups employs adequate randomization, including first concealment and whether potential confounders were distributed equally among groups. • Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination) • Important differential loss to follow-up or overall high loss to follow-up • Measurements: equal, reliable, and valid (includes masking of outcome assessment) • Clear definition of the interventions • All important outcomes considered	• The study addresses an appropriate and clearly focused question • The assignment of subjects to treatment groups is randomized • An adequate concealment method is used • Subjects and investigators are kept 'blind' about treatment allocation • The treatment and control groups are similar at the start of the trial • 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 more than one site, results are comparable for all sites

Appendix A Table 3. Quality rating criteria

Design	U.S. Preventive Services Task Force quality rating criteria[70]	National Institute for Health and Clinical Excellence methodology checklists[132]
Cohort studies	• Initial assembly of comparable groups employs consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts • Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination) • Important differential loss to follow-up or overall high loss to follow-up • Measurements: equal, reliable, and valid (includes masking of outcome assessment) • Clear definition of the interventions • All important outcomes considered	• The study addresses an appropriate and clearly focused question • The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation • The study indicates how many of the people asked to take part did so, in each of the groups being studied • The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis • What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed? • 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 • Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome • 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 confidence intervals been provided?
Diagnostic accuracy studies	• Screening test relevant, available for primary care, adequately described • Study uses a credible reference standard, performed regardless of test results • Reference standard interpreted independently of screening test • Handles indeterminate result in a reasonable manner • Spectrum of patients included in study • Sample size • Administration of reliable screening test	• The nature of the test being studied is clearly specified • The test is compared with an appropriate gold standard • Where no gold standard exists, a validated reference standard is used as a comparator • Patients for testing are selected either as a consecutive series or randomly, from a clearly defined study population • The test and gold standard are measured independently (blind) of each other • The test and gold standard are applied as close together in time as possible • Results are reported for all patients that are entered into the study • A pre-diagnosis is made and reported

Appendix A Table 3. Quality rating criteria

Hierarchy of research design

I	Properly conducted randomized controlled trial (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
III:	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Study characteristics	Patient characteristics	CONSORT Numbers, Retention	Inclusion/Exclusion Criteria	Description of Intervention Groups	Intervention Components
Doyle et al, 2008[86] Celio et al 2006[88] Good	RCT 83 adolescents Setting for enrollment/assessment NR, Internet-based intervention USA (CA and MO) Media adverstisements; flyers in schools, medical facilities, and weight-loss organizations; referrals from pediatricians and school nurses Weight Loss and improved eating disorders attitudes/behaviors	Age: 12-18 (Mean 14.5) 62.5% Female 50% White 12.5% Hispanic 26.3% Black 11.3% Other SES: 43.1% parent college graduate or higher Co-morb: NR	155 assessed for eligibility 72 excluded: 14 did not meet criteria 25 not interested 33 did not attend/complete screening 83 randomized I: 42 C: 41 <u>Retention, in-person outcome assessment (personal communication):</u> I: 28/42 (66.7%) C: 29/41 (70.3%) Retention, incl self-report (published): I: 33/42 (78.6%) C: 33/41 (80.5%) Intention-to-treat/baseline substitution analysis (published): I: 40/42 (92.2%) C: 40/41 (97.6%)	<u>Incl:</u> Age 12-18; ≥85th %ile for age and sex per CDC 2000 growth charts; Internet access at home or where regular use was possible <u>Excl:</u> Medical condition (e.g. endocrinologic diseases); use of prescription medication assoc with significant weight changes; complications of overweight that contraindicated moderate physical activity (e.g. orthopedic disorders); reading ability <6th grade; curr/past eating disorder diagnosis	I: Student Bodies 2 (SB2), Internet-delivered moderated cognitive-behavioral program; basic educational material; guided behavioral modification for wt loss; cognitive exercises for body image issues; gender-specific interfaces and content; on-line journal for recording food intake, physical activity, weight, triggers for body dissatisfaction; individual e-mail contact with moderator; discussion group; monthly newletter to parents C: Basic information on nutrition and physical activity	I: Diet, Physical Activity, Behavior Modification C: Diet, Physical Activity (Information only)

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Treatment Target: Individual/Family vs. Group Treatment	Treatment Intensity	Mean Entry Wt (Mean ± SD)	Interv phase 2-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo
Doyle et al, 2008[86] Celio et al 2006[88] Good	Child Individual and on-line Group	I: # sessions varied 60-120 min/wk encouraged 16-wks (est 1 hr/wk*16wks=16 hrs) (est 1 hr rather than 1.5 because partic read avg of 30% of material, and 35% of partic read <10% of material) C: 0 sessions (0 hrs)	Of those with complete data (from Table 3): BMI SDS: I: 2.19 ± 0.50 C: 2.19 ± 0.44 per CDC 2000 Growth Charts BMI: I: 34.6 ± 7.8 C: 33.9 ± 6.9 (est exceeds 97th %ile on average)	4-mo, BMI SDS: I: 2.11 ± 0.51 C: 2.20 ± 0.43 p=0.03 BMI: I: 34.0 ± 7.6 C: 34.1 ± 6.6 n.s.		

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Follow-up (≥ 3 mo post-intervention)	Data used for Meta-analysis (BMI Change (Mean ± SD), if available)	Physiological Outcomes	Other anthropo-morphic Outcomes (list)	Other Beneficial Outcomes	Adverse Effects (report findings)
Doyle et al, 2008[86] Celio et al 2006[88] Good	8-mo (4-mo post-intervention), BMI SDS: I: 2.10 ± 0.51 C: 2.15 ± 0.48 p=0.29 BMI: I: 34.4 ± 7.6 C: 34.3 ± 6.9 n.s. Personal communication, ITT (n=40): Change in BMI: I: -0.15 ± 1.75 C: 0.39 ± 2.08	Change in BMI: I: -0.15 ± 1.75 C: 0.39 ± 2.08	Lipids: No Glucose tol: No BP: No Phys fitness: No	None	Self-image (Shape Concern)	C group showed greater decline in Shape Concern than I group; no other differences in eating disorder pathology

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Study characteristics	Patient characteristics	CONSORT Numbers, Retention	Inclusion/Exclusion Criteria	Description of Intervention Groups	Intervention Components
Epstein et al 2008[87] Good	RCT 70 children University Children's hospital USA Media ads, flyers, direct mailings Determine effects of reducing television viewing and computer use on zBMI	Age: 4-7 (Mean 5.9 (c)) 47% Female (c) 24% minority (c) Mean SES 43.2 (c) Comorb: NR	185 assessed for eligibility 115 did not partic (77 did not meet incl crit, 30 withdrew, 8 lost to fup) 70 randomized: I: 36 C: 34 Retention: I: 35/36 (97%) C: 32/34 (94%)	Incl: Age 4-7; BMI ≥75th percentile for age and sex; ≥14 hrs/week TV or computer viewing; unlimited access to TV; family agreement to have TV monitoring devices attached to every TV and computer in house Excl: Medical conditions that prevented regular physical activity	I: Device attached to all TVs and computers to monitor and control viewing time, financial incentives to children for being under their screen time budget, star charts, parents encouraged to praise children for alternate activities; newletters and encouragement for parents C: Newsletter of parenting tips, activities, and recipes for kids; kids given $2.00/wk; no restrictions on access to TV/computers	I: Physical Activity, Family (Target), screen device C: None

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Treatment Target: Individual/Family vs. Group Treatment	Treatment Intensity	Mean Entry Wt (Mean ± SD)	Interv phase 2-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo
Epstein et al 2008[87] Good	Each family member Family	Not applicable	BMI: (Mean ± SD) I: 19.3 ± 2.5 C: 19.1 ± 3.5 BMI SDS: (Mean ± SD) I: 1.69 ± 0.58 C: 1.51 ± 0.57 (est ≥ 95th %ile on average)	6-mo(mid-treatment):Change in BMI SDS from baseline (est from graph for I group): I: -0.15 (SD NR) C:+0.05 (0.29) p=0.02	12-mo (mid-treatment): change in BMI SDS from baseline (est from graph): I: -0.16 (SD NR) C:-0.02 (SD NR) p=0.03	24-mo (post-intervention) change in BMI SDS from baseline (Mean ± SE): I: -0.24 ± 0.32* C:-0.13 ± 0.37* group*time effect p<.05 SD calculations: I: 0.32*sqrt(35)= 1.89 C: 0.37*sqrt(32)= 2.09

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Follow-up (≥ 3 mo post-intervention)	Data used for Meta-analysis (BMI Change (Mean ± SD), if available)	Physiological Outcomes	Other anthropo-morphic Outcomes (list)	Other Beneficial Outcomes	Adverse Effects (report findings)
Epstein et al 2008[87] Good		BMI SDS I: -0.24 ± 1.89 C:-0.13 ± 2.09	Lipids: No Glucose tol: No BP: No Phys fitness: No	None	Energy intake, physical activity, sedentary behavior	NR

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Study characteristics	Patient characteristics	CONSORT Numbers, Retention	Inclusion/Exclusion Criteria	Description of Intervention Groups	Intervention Components
Flodmark et al 1993[103] Fair	CCT 43 children (plus 50 matched controls) Outpatient referral clinical setting Sweden Screening program in schools Prevention of progression to severe obesity	Age: 10-11 (Mean NR) 52% Female (c) Race/Eth: NR SES: NR Comorb: clinically euthyroid, blood pressures less than 140/90, none with signs of endocrine d/o	Treatment groups: 1,906 screened 1,774 parents consent to study participate 49 BMI >23.0 44 randomized: I1 (conventional treatment): 19 I2 (I1 + family therapy): 24 C (matched controls): 50 (excluded 1 patient who was a pilot case) Unclear if controls pulled from same screening population as randomized <u>Retention:</u> I1: 19/19 (100%) I2: 20/24 (83%) C: 48/50 (96%)	<u>Incl:</u> BMI > 23.0 kg/m^2	I1: Conventional treatment: dietary counseling with dietitian, monthly visits to experienced pediatrician w interest in wt problems, low fat, 1500-1700 kcal diet prescribed, exercise encouraged I2: Same as above + family therapy C: Matched controls, no treatment	I1: Diet, Physical Activity, Family (Target) I2: Diet, Physical Activity, Family (Target), Mental Health Treatment C: None

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Treatment Target: Individual/Family vs. Group Treatment	Treatment Intensity	Mean Entry Wt (Mean ± SD)	Interv phase 2-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo
Flodmark et al 1993[103] Fair	I1: Child, parent Individual I2: Family Individual	I1: 0-1 session w dietitian, 5 sessions w/ pediatrician minutes NR 14-18 mos (est 6 * 1 hr *2 family member= 12 hrs) I2: 0-1 session w dietitian, 5 sessions w/ pediatrician, 6 family therapy sessions minutes NR 14-18 mos (est 12 * 1 hr *2 family member = 24 hrs) C: None (0 hrs)	BMI: (Mean ± SE) I1: 25.5 ± 0.53* I2: 24.7 ± 0.36* C: 25.1 ± 0.35* *calculated SD (SE*sqrt(n)): I1: 0.53*sqrt(19)=2.31 I2: 0.36*sqrt(24)=1.76 C: 0.35*sqrt(50)=2.47 (est >95th %ile on average)	NA	<u>Post-treatment (14-18 mos):</u> BMI (Mean ± SE) I1=26.1 ± 0.72 I2=25.0 ± 0.53 C: (data not collected)	

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Follow-up (≥ 3 mo post-intervention)	Data used for Meta-analysis (BMI Change (Mean ± SD), if available)	Physiological Outcomes	Other anthropo-morphic Outcomes (list)	Other Beneficial Outcomes	Adverse Effects (report findings)
Flodmark et al 1993[103] Fair	~48-mo (30-34 mos post-intervention) BMI: (Mean ± SE) I1=27.1 ± 0.88* I2: 25.8 ± 0.73* C: 27.9 ± 0.61* p=.15 *calculated SD (SE*sqrt(n)): I1: 0.88*sqrt(19)=3.84 I2: 0.73*sqrt(20)=3.26 C: 0.61*sqrt(48)=4.23	BMI change: Post-tx (14-18 mos): NA Follow-up (30-34 mo post-tx): I1: (not used in meta-analysis) I2: +1.1 ± 1.85 C: +2.8 ± 2.32 (SDs calc)	Lipids: No Glucose tol: No BP: No Phys fitness: Yes	Triceps, Subscapular, Suprailiac skinfolds	None	NR

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Study characteristics	Patient characteristics	CONSORT Numbers, Retention	Inclusion/Exclusion Criteria	Description of Intervention Groups	Intervention Components
Gillis et al 2007[78] Fair	RCT 27 children Primary care clinics in urban Jewish ultra-orthodox neighborhoods Israel 2 primary care clinics Weight loss, improvement in adverse metabolic consequences of obesity and obesity-related attitudes	Age: 7-16 (10.6 (calc)) %Male NR Race/Eth: 100% Jewish SES: NR Co-morb: NR	27 recruited 27 randomized I: 14 C: 13 <u>Retention:</u> 18/27 (66.7%) overall I: 11/14 (78.6%) C: 7/13 (53.8%)	<u>Incl:</u> Age 7-16; BMI>90th %ile; refered to author (endocrinologist) for evaluation of obesity	I: Basic discussion on health diet and exercise (at baseline and 3-months); asked to record food/exercise one day/week; weekly phone call to review food/exercise diary and encourage adherence to prescribed plan C: Basic discussion on health diet and exercise (at baseline and 3-months)	I: Diet, Physical Activity, Behavior Modification, Family (Not target) C: Diet, Physical Activity (brief counseling)

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Treatment Target: Individual/Family vs. Group Treatment	Treatment Intensity	Mean Entry Wt (Mean ± SD)	Interv phase 2-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo
Gillis et al 2007[78] Fair	Child Individual	I: 2 1/2 hr clinic visits + 24 weekly calls (est) # Min/session NR 26 weeks (est) (est 2*.5*hr*2(parent+child) + 24*.25 hr = 8 hrs) C: 2 clinic visits # minutes NR (est 2 hrs)	BMI SDS: I: 1.98 ± 0.21 C: 2.16 ± 0.34 (est >95th %ile on average)	6-mo BMI SDS: I: 1.93 ± 0.37 C: 2.23 ± 0.29 p=0.40 BMI SDS change: I: -0.045 ± 0.19 C: 0.075 ± 0.08 p=0.10	NA	NA

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Follow-up (≥ 3 mo post-intervention)	Data used for Meta-analysis (BMI Change (Mean ± SD), if available)	Physiological Outcomes	Other anthropo-morphic Outcomes (list)	Other Beneficial Outcomes	Adverse Effects (report findings)
Gillis et al 2007[78] Fair	NA	<u>BMI SDS change:</u> I: -0.045 ± 0.19 C: 0.075 ± 0.08	Lipids: Yes Glucose tol: Yes BP: No Phys fitness: Yes	None	Diet (self-report of change), Physical Activity (self-report of change)	NR

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Study characteristics	Patient characteristics	CONSORT Numbers, Retention	Inclusion/Exclusion Criteria	Description of Intervention Groups	Intervention Components
Golley et al 2007[80] Good	RCT 111 children teaching hospitals Australia media publicity and school newsletters Weight management in prepubertal children	Age: 6-9 (Mean 8.2) 64% Female (calc) 98% White SES: Index of relative socioeconomic advantage slightly above South Australian average Co-morb: NR	262 Initial phone screening completed 126 eligibility confirmed at medical screening 115 consented 111 completed baseline assessment 111 randomized: I1 (Parenting group): 37 I2 (Parenting + lifestyle): 38 C:(Wait list): 36 Retention: I1: 29/37 (78.4%) I2: 31/38 (81.6%) C: 31/36 (86.1%)	Incl: Age 6-9; Overweight, per International Obesity Task Force definition); Tanner Stage 1; caregiver willing to attend sessions and able to read and understand English Excl: BMI z-score >3.5; syndromal cause of obesity; medication use that may influence weight; diagnosis of physical or developmental disability; sibling enrolled in study	I1 Parenting skills training, aims to promote parental competence to manage child's behavior with emphasis on dietary and activity behaviors in program examples, pamphlet covering eating and activity behaviors, I2: Parenting + Intensive lifestyle education covering wide variety of topics related to healthy eating, activity, and emotional sequalae of overweight such as self-esteem and teasing. C: Wait-list Control, 3-4 brief phone calls for encourage retention in study	I1: Diet, Physical Activity, Family (Target), Mental Health Treatment I2: Diet, Physical Activity+, Behavior Modification, Family (Target), Mental Health Treatment C: Diet, Physical Activity (pamphlets only)

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Treatment Target: Individual/Family vs. Group Treatment	Treatment Intensity	Mean Entry Wt (Mean ± SD)	Interv phase 2-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo
Golley et al 2007[80] Good	Parent Group and Individual	I1: 4 group, 7 individual group=120 min indiv=15-20 min 21 wks (calc) (4*2 hrs + 7*.33 hrs =10.33 hrs) I2: 11 group 120 min # wks NR (22 hrs) C: 3-4 5-minute phone calls (0.33 hrs)	BMI: 24.3 ± 2.6 (overall) BMI z-score: I1: 2.76 ± 0.58 I2: 2.74 ± 0.58 C: 2.75 ± 0.39 (est >97th %ile on average)	<u>6-mo (1-mo post-intervention):</u> BMI z-score: I1: 2.63 ± 0.53 I2: 2.52 ± 0.53 C: (NR)		NA

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Follow-up (≥ 3 mo post-intervention)	Data used for Meta-analysis (BMI Change (Mean ± SD), if available)	Physiological Outcomes	Other anthropo-morphic Outcomes (list)	Other Beneficial Outcomes	Adverse Effects (report findings)
Golley et al 2007[80] Good	12-mo (7-mos post-intervention): BMI SDS: I1: 2.56 ± 0.79 I2: 2.43 ± 0.68 C: 2.60 ± 0.57 group*time effect p=0.76 Change in BMI SDS: I1: -0.15 ± 0.47 I2: -0.24 ± 0.43 C: -0.13 ± 0.40 group*time effect p=0.76 % who increased BMI SDS: I1: 24% I2: 19% C: 45% p<0.03	Change in BMI SDS: I1 (not used in MA) I2: -0.24 ± 0.43 C: -0.13 ± 0.40	Lipids: Yes Glucose tol: Yes BP: Yes Phys fitness: No	Waist circumference	None	Height change did not differ between treatment and control conditions

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Study characteristics	Patient characteristics	CONSORT Numbers, Retention	Inclusion/Exclusion Criteria	Description of Intervention Groups	Intervention Components
McCallum et al, 2007[81] McCallum et al, 2005[90] Good	RCT 163 children Oupatient medical clinic Australia GPs recruited from sociodemographically diverse practices Weight loss in moderately overweight children	Age: 5-9 (Mean 7.4) 52% Female Race/Eth: NR SES: practices range from <10th to >90th %ile; median practice close to 50th %ile Comorb: NR	2112 screened 505 overweight or mildly obese 342 excluded or refused, 163 randomized: I: 82 C: 81 Retention: 9-mo fup I: 73/82 (89%) C: 80/81 (99%) 12-mo fup I: 70/82 (85%) C: 76/81 (94%)	Incl: Age 5-9; attending participating medical practice; classified as overweight or mildly obese per International Obesity Task Force definition; not receiving ongoing weight management in secondary or tertiary care program Excl: SDS ≥ 3.0, chromosomal, endocrine, or medical condition/ disability/ medication which could have an impact on wt or growth	I: General practitioner given folder prior to appointment containing child's individualized intervention materials, BMI, and 2-page summary of parent responses from baseline questionnaire. Brief solution-focused intervention to set and record appropriate, healthy lifestyle goals with the family; personalized 20-page "Family Folder" containing topic sheets targeting different areas of behavior change C: Usual care	I: Diet, Physical Activity, Behavior Modification, Family (Target) C: Usual care

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Treatment Target: Individual/Family vs. Group Treatment	Treatment Intensity	Mean Entry Wt (Mean ± SD)	Interv phase 2-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo
McCallum et al, 2007[81] McCallum et al, 2005[90] Good	Child, parent Individual	I: 4 sessions minutes NR 12-weeks (assume .5 hrs appointments, 4*.5 hrs*2 fam members=4 hrs total) C: NR (0 hrs)	BMI I: 20.5 ± 2.2 C: 20.0 ± 1.8 BMI SDS I: 2.0 ± 0.5 C: 1.9 ± 0.5 (per UK 1990 Growth Reference) (est >95th %ile on average)	NA	NA	NA

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Follow-up (≥ 3 mo post-intervention)	Data used for Meta-analysis (BMI Change (Mean ± SD), if available)	Physiological Outcomes	Other anthropo-morphic Outcomes (list)	Other Beneficial Outcomes	Adverse Effects (report findings)
McCallum et al, 2007[81] McCallum et al, 2005[90] Good	<u>9-mo (6-mo post-intervention)</u> BMI: I: 21.0 ± 2.6 C: 20.8 ± 2.2 adjusted p=0.25 BMI SDS: I: 1.96 ± 0.64 C: 1.93 ± 0.57 adjusted p=0.12 (per CDC 2000 Growth Charts) <u>15-mo (12-mo post-intervention)</u> BMI: I: 21.7 ± 3.1 C: 21.2 ± 2.4 adjusted p=1.0 BMI SDS: I: 2.0 ± 0.68 C: 1.92 ± 0.59 adjusted p=0.62 (per CDC 2000 Growth Charts)	<u>BMI change</u> Post-treatment: NR Follow-up (9 mo post-treatment) I: +0.5 ± 1.1 C: +0.8 ± 1.0 Follow-up (12 mo post-treatment) I: +1.2 ± 1.5 C: +1.2 ± 1.1 (calc)	Lipids: No Glucose tol: No BP: No Phys fitness: No	None	Diet (4-day food diary) Physical Activity (4-day activity diary)	"Little evidence of either harm or benefit of the intervention with respect to parent- and child-reported child health status and child-reported body satisfaction and appearance/self-worth."

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Study characteristics	Patient characteristics	CONSORT Numbers, Retention	Inclusion/Exclusion Criteria	Description of Intervention Groups	Intervention Components
Mellin et al 1987[104] Fair	RCT 66 adolescents Rural health dept; rural nutrition private practice, suburban medical clinic; urban outpatient clinic USA Newspaper announcements, notices to physicians and school personnel Weight loss	Age 12-18 (Mean 15.6) 79% Female 87.9% White 7.6% Hispanic 4.5% Asian or Black (calc) SES: NR Co-morb: NR	66 responded to recruitment 66 randomized I: 37 C: 29 Retention: I: 34/37 (92%) C: 29/29 (100%)	NR	I: SHAPEDOWN program; cognitive, behavioral, affective treatment encouraging successive, sustainable, small modification in diet, exercies, relationship, lifestyle, communicatins, and attitudes. C: no treatment controls	I: Diet, Physical Activity+, Behavior Modification, Family (Not target) C: No treatment

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Treatment Target: Individual/Family vs. Group Treatment	Treatment Intensity	Mean Entry Wt (Mean ± SD)	Interv phase 2-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo
Mellin et al 1987[104] Fair	Child, Parent Group	I: 14 sessions with adolescents 2 parent sessions 90 min/session 14 weeks (16*1.5 hrs =24 hrs) C: None (0 hrs)	% Overweight I: 36.5% (SD NR) C: 29.5% (SD NR) per 1973 US National Center for Health Statistics Wt, kg I: 79.2 (SD NR) C: 77.0 (SD NR) (est >95th %ile on average)	3-mo change in % overweight I: -5.9 ± 6.8 C: -0.3 ± 6.6 dependent t-test I: p<0.001 C: n.s.	NA	NA

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Follow-up (≥ 3 mo post-intervention)	Data used for Meta-analysis (BMI Change (Mean ± SD), if available)	Physiological Outcomes	Other anthropo-morphic Outcomes (list)	Other Beneficial Outcomes	Adverse Effects (report findings)
Mellin et al 1987[104] Fair	15-mo (12-mo post-intervention) change in % overweight I: -9.9 ± 15.0 C: -0.1 ± 13.2 dependent t-test I: p<0.01 C: n.s.	15-mo (12-mo post-intervention) change in % overweight I: -9.9 ± 15.0 C: -0.1 ± 13.2	Lipids: No Glucose tol: No BP: No Phys fitness: No	None	Weight-related behaviors; depressive symptoms; self-esteem	Depression symptoms improved in treatment group, did not change in control group; self-esteem improved in both groups

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Study characteristics	Patient characteristics	CONSORT Numbers, Retention	Inclusion/Exclusion Criteria	Description of Intervention Groups	Intervention Components
Nemet et al 2005[85] Fair	RCT 54 children Child Health and Sports Center Isreal Self-referral Weight Loss	Age: range 6-16 (Mean 11.1) 43.5% Female Race/Eth: NR (Isreali) SES: NR Co-morb: NR	54 self-referred to center, randomized: I: 30 C: 24 Retention: 3-mo: I: 24/30 (80.0%) C: 22/24 (91.7%) 12-mo: I:20/30 (66.7%) C: 20/24 (83.3%)	NR, but reported that none of the children had an organic cause for obesity, none received any medication that might interfere with growth or weight control. Unclear if these were exclusion criteria.	I: Twice weekly exercise sessions plus expectation of at least one exercise session at home, 6 semi-monthly parent and/or child meetings with dietician primarily for nutritional counseling, 4 general interest lectures for parents and children on topics related to childhood obesity. C: At least one nutritional counseling session, encouraged to exercise 3 times/week on their own.	I: Diet, Physical Activity+, Behavior Modification, Family (Target) C: Usual Care

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Treatment Target: Individual/Family vs. Group Treatment	Treatment Intensity	Mean Entry Wt (Mean ± SD)	Interv phase 2-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo
Nemet et al 2005[85] Fair	I: Child, Parent Individual C: Child, Parent Individual	I: 28 1-hr exercise sessions 6 30-45 min nutrition counseling 4 lecture, minutes NR 14 wks (calc) (28*1 + 1 hr + .75hr + 4*.75*2)=28+1.75 +6=35.75 hrs C: 1 or more nutrition counseling sessions, minute NR (Est 1 hr)	BMI: I: 27.7 ± 3.6 C: 28.0 ± 5.2 BMI percentile: I: 98.2 ± 0.3 C: 97.2 ± 0.7 Weight, kg: I: 59.1 ± 15.7 C: 63.4 ± 23.6 (all among those with followup, n=40)	<u>3-mo</u> BMI: I: 26.8 ± 3.9 C: 27.6 ± 5.6 p<0.05 Weight, kg: I: 61.0 ± 18.3 C: 64.5 ± 24.1 p<0.05		

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Follow-up (≥ 3 mo post-intervention)	Data used for Meta-analysis (BMI Change (Mean ± SD), if available)	Physiological Outcomes	Other anthropo-morphic Outcomes (list)	Other Beneficial Outcomes	Adverse Effects (report findings)
Nemet et al 2005[85] Fair	12-mo (9-mos post-intervention): BMI: I: 26.1 ± 4.7 C: 28.6 ± 5.8 p<0.05 BMI percentile: I: 92.3 ± 3.0 C: 96.1 ± 1.4 p<0.05 Weight, kg: I: 59.7 ± 17.7 C: 68.6 ± 24.8 p<0.05	<u>BMI change:</u> Follow-up (12-mo post-tx): I: -1.5 ± 2.1 C: +0.6 ± 2.5 (calc)	Lipids: Yes Glucose tol: No BP: No Phys fitness: Yes	triceps, Subscapular skinfolds	Diet, Physical activity, Sedentary behavior	"No adverse events were noted during the intervention"

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Study characteristics	Patient characteristics	CONSORT Numbers, Retention	Inclusion/Exclusion Criteria	Description of Intervention Groups	Intervention Components
Reinehr et al 2006[79] Reinehr et al 2007[89] Fair	CCT 240 children Overweight specialty treatment unit in medical facility Germany Recruitment NR Weight loss and cardiovascular disease risk profile improvement	Age: 6-14 (Mean 10.4) 46.7% Female Race/Eth: NR SES: NR Co-morb: 0% endocrine disorders	240 analyzed: I: 203 C: 37 Retention: 12 & 24-mo: I: 174/203 (86%) C: 37/37 (100%) 4-yr*: I: 142/170 (84%) *from Reinehr 2007	Incl: Age 6-14; BMI >97th %ile per 2001 German norms; participate in local exercise group for ≥ 8 wks to prove motivation Excl: Endocrine disorders, familial hyperlipidemia, or syndromal obesity	I: Multidisciplinary treatment team, program includes physical exercise, nutrition education, behavioral therapy, individual and/or family therapy C: No treatment; Comprised of children who met all criteria but did not participate due to travel distance to the treatment facility	I: Diet, Physical Activity+, Behavior Modification, Family (Target), Mental Health Treatment C: No Treatment

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Treatment Target: Individual/Family vs. Group Treatment	Treatment Target: Treatment Intensity	Mean Entry Wt (Mean ± SD)	Interv phase 2-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo
Reinehr et al 2006[79] Reinehr et al 2007[89] Fair	I: Child, parent, family Individual, group C: None	I: 6 1.5-hr parent group sessions 6 1.5-hr child group sessions 3 1-hr parent sessions 52 exercise session (minutes NR) variable number (est 6) 30-minute individual and/or family therapy sessions (12*1.5hr + 3 + 52*1 hr + 6*.5hr = 76.0 hrs) 1 yr C: None (0 hrs)	BMI: I: 27.0 (26.4, 27.6) C: 26.1 (25.2, 27.8) *SD calc: I: (1.2*sqrt(203))/3.92= 4.36 C: (2.2*sqrt(37)))/3.92=4.03 BMI SDS: I: 2.4 (2.3, 2.4) C: 2.3 (2.2, 2.4) (est >97th %ile on average)	NA	<u>12-mo</u> BMI: I: 27.1 (26.4, 27.6)* C: 28.1 (27.0, 29.2)* p=0.013 (treatment x time effect) *SD calc: I: (1.2*sqrt(174))/3.92= 4.04 C: (2.2*sqrt(37)))/3.92=3.41 BMI SDS: I: 2.1 (2.1, 2.2) C: 2.3 (2.1, 2.4) p=0.007 (treatment x time effect)	

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Follow-up (≥ 3 mo post-intervention)	Data used for Meta-analysis (BMI Change (Mean ± SD), if available)	Physiological Outcomes	Other anthropo-morphic Outcomes (list)	Other Beneficial Outcomes	Adverse Effects (report findings)
Reinehr et al 2006[79] Reinehr et al 2007[89] Fair	<u>24-mo (12-mos post-intervention)</u> BMI: I: 28.2 (27.4, 29.0)* C: 29.0 (28.0, 30.8)* p=0.013 (treatment x time effect) *SD calc: I: (1.6*sqrt(174))/3.92= 5.38 C: (2.8*sqrt(37))/3.92=4.34 BMI SDS: I: 2.1 (2.1, 2.2)* C: 2.3 (2.1, 2.4)* p=0.007 (treatment x time effect) *SD calc: I: (0.1*sqrt(174))/3.92=0.34 C: (0.3*sqrt(37))/3.92=0.46 48-mo (36-mo post-intervention) I group only: BMI SDS reduced in first 3 months (p<.001), then did not change in the rest of the observation period.	<u>BMI change</u> Post-treatment (12-mo) I: +0.1 ± 1.9 C: +2.0 ± 1.8 24-mo (12-mo post-treatment): I: +1.2 ± 2.4 C: +2.9 ± 1.9 (calc)	Lipids: Yes Glucose tol: Yes BP: Yes Phys fitness: No	None	None	NR

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Study characteristics	Patient characteristics	CONSORT Numbers, Retention	Inclusion/Exclusion Criteria	Description of Intervention Groups	Intervention Components
Rooney et al 2005[82] Fair	RCT 98 families (353 people, adults and children combined) NR USA NR Increased physical activity	Age: 5-12 (Mean 9.7) 51% Female Race/Eth: NR SES: NR Co-morb: NR	98 families (n=353) randomized 87 families (n=316) analyzed: I1: 28 families/n=104 I2: 30 families/n=112 C: 29 families/n=100 Retention: 87/98 families (88.8%) 316/353 people (89.5%) Individual children (personal communication): I1: 21 I2: 24 C: 27 (denominators unknown, and unclear of this includes only overweight children or siblings also)	Incl: At least one child aged 5-12 with BMI over 84th %ile; at least one adult willing to participate. (Siblings also invited to participate)	I1: Pedometer group given a pedometer, instructed in its use and told to walk 10,000 steps daily for 12 weeks; biweekly newsletters containing informative articles and fun activity tips. I2: Pedometer + education group; above, plus education sessions covering nutrition, physical activity, other parenting issues. C: Not described	I1: Physical Activity, Family (Target), Pedometer I2: Diet, Physical Activity, Family (Target), Pedometer C: No treatment

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Treatment Target: Individual/Family vs. Group Treatment	Treatment Intensity	Mean Entry Wt (Mean ± SD)	Interv phase 2-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo
Rooney et al 2005[82] Fair	Family NR	I1: #session, min NR 12 wks (est 1 hr pedometer instruction*3 fam members=3 hrs) I2: 1 session pedometer instruction (est 1 hr) 6 1-hr wt loss education sessions (est (1hr+7 hrs)*3 family members=21 hrs) 12 wks C: NR (est 0 hrs)	BMI: I1: 21.1 ± 6.24 I2: 22.25 ± 6.23 C: 21.9 ± 5.95 (personal communication) BMI %ile: I1&I2: 80.8 C: 85.6 (per CDC growth charts, year not specified)	3-mo BMI %ile: I1&I2: 82.3 C: 85.0 p=0.42	NA	NA

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Follow-up (≥ 3 mo post-intervention)	Data used for Meta-analysis (BMI Change (Mean ± SD), if available)	Physiological Outcomes	Other anthropo-morphic Outcomes (list)	Other Beneficial Outcomes	Adverse Effects (report findings)
Rooney et al 2005[82] Fair	9-mo (6 mos post-intervention) adjusted BMI ± SE: I1: 21.61 ± 1.19 I2: 23.11 ± 0.82 C: 22.45 ± 1.04 (personal communication) adjusted BMI change ± SE: I1: -0.38 ± 0.22* I2: -0.87 ± 0.26* C: -0.43 ± 0.21* (personal communication) *SDs calc from SE: I1: 0.22*sqrt(21)=1.01 I2: 0.26*sqrt(24) =1.27 C: 0.21*sqrt(27)=1.09 unadjusted BMI %ile: I1&I2: 80.9 (SD NR) C: 84.3 (SD NR) p=0.33 unadjusted change in BMI %ile: I1&I2: +0.31 (SD NR) C: -1.32 (SD NR) p=0.28	BMI change I1: (not used in MA) I2: -0.87 ± 1.27 C: -0.43 ± 1.09	Lipids: No Glucose tol: No BP: No Phys fitness: No	None	sedentary activity	NR

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Study characteristics	Patient characteristics	CONSORT Numbers, Retention	Inclusion/Exclusion Criteria	Description of Intervention Groups	Intervention Components
Saelens et al 2002[83] Good	RCT 44 adolescents Primary care clinical setting USA Flyers in pediatric clinic waiting room, pediatrician encouragement to participate Weight loss	Age: 12-16 Mean 14.2 ± 1.2 40.9% Female 70.5% White 15.9% Hispanic 4.5% Black 2.3% Asian 6.8% Multi-ethnic SES: Median household income $60K-69K Co-morb: NR	59 scheduled baseline assmt 47 complete baseline assmt 44 met weight criteria and were randomized I: 23 C: 21 Retention: I: 18/23 (78%) complete followup C: 19/21 (90%) fup Conducted Intention-to-treat analysis on full sample (n=44), replacing missing values with group change values	Incl: Age 12-16; 20-100% above median (50%ile) for BMI for sex and age per CDC 2000 growth charts; interested in weight control, but not currently engaged in another wt control program; otherwise healthy as determined by pediatrician	I: Healthy habits intervention: computerized assessment; meeting with pediatritian to discuss results of assessment, develop action plan; 10-20 minutes counseling calls; mailed participant manual in three different mailings (part of manual mailed each time); encouraged self-monitoring of food intake and physical activity C: Typical care intervention: 5-10 minute meeting with pediatrician assessing motivation and providing (non-tailored) information on healthy eating and physical activity	I: Diet, Physical Activity, Behavior Modification C: Diet, Physical Activity (Information only)

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Treatment Target: Individual/Family vs. Group Treatment	Treatment Intensity	Mean Entry Wt (Mean ± SD)	Interv phase 2-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo
Saelens et al 2002[83] Good	Child Individual	I: 1 pediatrician session, 11 phone calls Pediatrician visit 5-10 minutes, phone calls 10-20 minutes 14-16 wks total (10 min + 11*20 min = 230 min = 3.8 hrs) C: 1 pediatrician session 5-10 minutes 1 day (0.2 hrs)	BMI I: 31.0 ± 3.5 C: 30.7 ± 3.1 % OW I: 62.0 ± 20.5 C: 62.3 ± 17.4 (per 2000 CDC growth charts) (est >97th %ile on average)	4-mo BMI z-score: I: 2.15 (SD NR) C: 2.02 (SD NR) (est from graph) p=0.04 (Intention-to-treat analysis) and p=0.03 (completers) for overall time*treatment effect in repeated measures ANOVA model BMI: I: 30.9 ± 3.8 C: 31.8 ± 3.4 p=NR % Overweight: I: 59.8 ± 21.8 C: 66.2 ± 18.6 p=NR	NA	NA

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Follow-up (≥ 3 mo post-intervention)	Data used for Meta-analysis (BMI Change (Mean ± SD), if available)	Physiological Outcomes	Other anthropo-morphic Outcomes (list)	Other Beneficial Outcomes	Adverse Effects (report findings)
Saelens et al 2002[83] Good	7-mo (3-mo post intervention) BMI z-score: I: 2.15 (SD NR) C: 2.01 (SD NR) (est from graph) p=0.04 (ITT analysis) and p=0.03 (completers) for overall time*treatment effect in repeated measures ANOVA model BMI: I: 31.1 ± 4.5 C: 32.1 ± 3.8 p=NR % Overweight: I: 59.6 ± 24.6 C: 66.4 ± 20.1 p=NR	BMI change 7-mo (3 mo post-tx): I: +0.1 ± 2.0 C: +1.4 ± 1.7 (SDs calc)	Lipids: No Glucose tol: No BP: No Phys fitness: No	None	Diet, Physical activity, Sedentary behavior, problematic eating/eating disorder psychopathology	Problematic eating/eating disorder psychopathology did not differ between treatment and control groups

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Study characteristics	Patient characteristics	CONSORT Numbers, Retention	Inclusion/Exclusion Criteria	Description of Intervention Groups	Intervention Components
Savoye et al 2007[77] Good	RCT 174 children and adolescents Pediatric obesity clinic USA NR Changes in BMI, body composition, insulin sensitivity, blood pressure, and lipid profiles	Age: 8-16 (Mean 12.1 (calc)) 60.9% Female (calc) 36.8% White 24.7% Hispanic 38.5% Black (all calc) SES: NR Co-morb: 0% Diabetes	284 assessed 271 met inclusion criteria 209 consented and randomized I: 105 C: 69 (n=35 in 3rd tx arm which was dropped) <u>Retention:</u> I: 86/105 (81.9%) 6-mo intervtn/assessmt C: 49/69 (71.0%) 6-mo intervtn/assessment I: 75/105 (71.4%) 12-mo intervtn/assessment C: 44/69 (63.8%) 12-mo intervention/assessment All observations (n=174) used in analysis (conducted MI to fill in missing data)	<u>Incl</u>: BMI >95th %ile; age 8-16; English-speaking; caregiver willing to participate. <u>Excl</u>: Diabetes; severe psychiatric disorder or cognitive deficits; serious medical condition that would preclude them from participation; taking medications that could cause significant weight gain; using medications for weight loss; involved in weight management program	I: Bright Bodies Weight Management, twice weekly exercise program; weekly nutrition education and behavior modification class. C: pediatric obesity clinic visit every 6 months for diet and exercise counseling and brief pschosocial counseling with social worker.	I: Diet, Physical Activity+, Behavior Modification, Family (Target) C: Diet, Physical Activity, Mental Health Treatment (brief counseling)

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Individual/Family vs. Group Treatment	Treatment Intensity	Mean Entry Wt (Mean ± SD)	Interv phase 2-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo
Savoye et al 2007[77] Good	Child, Parent Group	I: 65 sessions (calc) 90 min/session 52 weeks (65*1.5=97.5 hrs) C: 2 sessions (calc) min/sessin NR 52 weeks (est) (2*1 hr=2 hrs)	BMI I: 35.8 ± 7.6 C: 36.2 ± 6.2 Wt, kg I: 87.0 ± 25.1 C: 91.2 ± 23.3 (est >97th %ile on average)	6-mo Change in BMI I: -2.1 (-2.6, -1.5)* C: 1.1 (0.4, 1.8)* p<0.001 *SD calc: I: 1.1*sqrt(105)/3.92=2.88 C: 1.4*sqrt(69)/3.92=2.97 Change in weight, kg I: -2.6 (-4.2, -0.9) C: 5.0 (2.9, 7.2) p<0.001	12-mo Change in BMI I: -1.7 (-2.3, -1.1)* C: 1.6 (0.8, 2.3)* p<0.001 *SD calculated: I: 1.2*sqrt(105)/(2*1.96)]=3.14 C: 1.5*sqrt(69)/(2*1.96) =3.17 Change in weight, kg I: 0.3 (-1.4, 2.0) C: 7.7 (5.3, 10.0) p<0.001	NA

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Follow-up (≥ 3 mo post-intervention)	Data used for Meta-analysis (BMI Change (Mean ± SD), if available)	Physiological Outcomes	Other anthropo-morphic Outcomes (list)	Other Beneficial Outcomes	Adverse Effects (report findings)
Savoye et al 2007[77] Good	NA	BMI change Post-tx (12-mo): I: -1.7 ± 3.14 C: +1.6 ± 3.17 Follow-up: NR	Lipids: Yes Glucose tol: Yes BP: Yes Phys fitness: No	% Body fat, Body fat mass		Found no difference between treatment and control group in changes in height at 6 months or 12 months

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Study characteristics	Patient characteristics	CONSORT Numbers, Retention	Inclusion/Exclusion Criteria	Description of Intervention Groups	Intervention Components
Senediak et al 1985[84] Fair	35 children Setting NR USA Media ads + publicity to medical professionals Weight loss	Age: 6-12 (calc) (Mean 10.3) 34% Female (est) Race/Eth: NR SES: NR Co-morb: NR	45 randomized: I1 (rapid schedule): 12 I2 (standard schedule): 12 C1 (attention control): 11 C2 (wait-list): 10 (not reported here) Retention: I1: 8/12 (66.7%) I2: 10/12 (83.3%) C1: 7/11 (63.6%)	Incl: At least 20% overweight for height, age, and sex Excl: Height not below 20th %ile for age; no history of psychiatric contact; no history of endocrine or metabolic disorders; not in special education	I1: Rapid schedule Behavioral therapy I2: Gradually decreasing schedule Behavioral therapy C1: Relaxaion, mood management control C2: Wait list (not reported here)	I1&I2: Diet, Physical Activity+, Behavior Modification, Family (Target) C: Mental Health Treatment, Family (Target)

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Treatment Target: Individual/Family vs. Group Treatment	Treatment Intensity	Mean Entry Wt (Mean ± SD)	Interv phase 2-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo
Senediak et al 1985[84] Fair	Child, parent Group	All: 8 90-minute sessions (12 hrs) I1&C1: 4 wks I2: 15 wks	Weight, kg (of those with 26-wk outcomes data) I1: 50.6 ± 6.8 I2: 51.4 ± 10.5 C: 44.5 ± 5.3 %Overweight (of those with 26-wk outcomes data) I1: 32.9 ± 14.0 I2: 35.9 ± 12.2 C: 36.7 ± 5.5 (est >95th %ile on average)	NA (report post-treatment, but since post-tx point different (1 mo vs 3.5-mo), will only report post-intervention follow-up		

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Evidence Table 1. Behavioral intervention trials

Study Reference Study Quality	Follow-up (≥ 3 mo post-intervention)	Data used for Meta-analysis (BMI Change (Mean ± SD), if available)	Physiological Outcomes	Other anthropo-morphic Outcomes (list)	Other Beneficial Outcomes	Adverse Effects (report findings)
Senediak et al 1985[84] Fair	6-mo (3-5 mo post-intervention) Weight, kg I1: 49.5 ± 7.4 I2: 48.6 ± 11.1 C1: 44.8 ± 4.9 p<0.05 (I1 & I2 vs. C1) %Overweight I1: 19.9 ± 14.2 I2: 16.6 ± 11.5 C1: 30.8 ± 10.4 p<0.05 (I1 & I2 vs. C1)	%OW change I1: (not used in MA) I2: -19.22 ± 5.3 C: -5.86 ± 6.0 (calc)	Lipids: No Glucose tol: No BP: No Phys fitness: No	Subscapular skinfold	NR	NR

Abbreviations: I: Intervention; NR: Not reported; DM: Diabetes Mellitus; C: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation; (c): calculated

Appendix B Table 2. Summary table of pharmacological study characteristics

Source	Intervention	No. of months of drug treatment	No. of behavioral intervention sessions	Characteristics	No of study sites	Country	% Attrition	Quality[a]	Placebo Run-in Period	Funding Source
Sibutramine										
Berkowitz et al, 2003[91]	Sibutramine (5 mg/d for 1 wk, 10 mg/d for 4 wks, then 15 mg) + BI or placebo + BI	6	19	N randomized: 82 Age: 13-17 Female: 67%	1	USA	10%	Good	Yes	NIH, hospital, pharm
Berkowitz et al, 2006[92]	Sibutramine (10 mg/day for 6 mos, then 10-15 mg/d) + BI or placebo + BI	12	10	N randomized: 498 Age: 12-16 Female: 66%	33	USA	28%[b]	Good	No	Pharm
Garcia-Morales et al, 2006[94]	Sibutramine (10 mg/d) + BI or placebo + BI	6	8	N randomized: 51 Age: 14-18 Female: 56%	1	Mexico	22%	Fair	Yes	Pharm
Godoy-Matos et al, 2005[95]	Sibutramine (10 mg/d) or placebo	6	1	N randomized: 60 Age: 14-17 Female: 82%	1	Brazil	17%[b]	Fair	Yes	Pharm
Van Mil et al, 2007[97]	Sibutramine (5 mg/d for 2 wks, then 10 mg/d) + BI or placebo + BI	3[c]	16	N randomized: 24 Age: 12-17 Female: 54%	1	Nether-lands	17%[b]	Fair	No	NR
Orlistat										
Chanoine et al, 2005[93]	Orlistat (120 mg, TID) + BI or placebo + BI	12	18	N: 539 Age: 12-16 Female: 67%	32	USA & Canada	35%	Good	Yes	Pharm
Maahs et al, 2006[96]	Orlistat (120 mg, TID) + BI or placebo + BI	6	7	N: 40 Age: 14-18 Female: 67%	1	USA	15%	Fair	No	University supported

Abbreviations: BI - behavioral intervention (with or without a behavioral management program); TID - three times daily; NR - not reported; Pharm-pharmaceutical; NIH-National Institute of Health.

[a] Quality criteria are described in Appendix B Table 1.

[b] Attrition rate was different between the intervention and control groups.

[c] Patients were treated with BT + sibutramine or placebo for 3 mos. and then BT alone for 3 mos.

Appendix B Evidence Table 3. Pharmacological intervention trials

Study Reference Study Quality	Study Characteristics	Patient Characteristics	CONSORT Numbers Retention	Inclusion/Exclusion	Description of Intervention Groups	Dose/ Duration	Mean Entry Wt
Sibutramine							
Berkowitz et al 2003[91] Budd et al 2007[101] Good	RCT 82 adolescents University-based specialty research clinic USA Source NR Weight loss March 1999- August 2002 Funding: NIH; Hospital; Pharmaceutical	Age: 13-17 (Mean 14.1) 67.1% Female 54.9% White 41.5% Black 3.6% Other SES: NR Co-Morb: 0% DM	146 Evaluated 64 Excluded due to: psychiatric condition (24), not interested (21) Unable to attend group meetings (12), medical conditions (2), other (7) 82 randomized: I: 43 C: 39 Retention: I: 93% follow-up C:87.2% follow-up	Inclusion: Age 13-17; BMI 32-44 Exclusion: cardiovascular disease; Type 1 or 2 diabetes; major psychiatric disorder; pregnancy; use of wt-loss medication; weight loss of ≥ 5kg in past 6 mos; use of medication associated with weight gain; use of medication contraindicated with use of sibutramine; cigarette smoking	I: Sibutramine + Behavior Therapy C: Placebo + Behavior Therapy	Week 1: placebo Week 2: 5 mg/day Wks 3-6: 10 mg/day Wks 7-6 mos: 15 mg/day (decreased dose if systolic or diastolic BP increased by ≥10 mm Hg or pulse rate increased by ≥15% from baseline for 2 consecutive visits	BMI: I: 37.5 ± 4.0 C: 38.0 ± 3.6 BMI SDS: I: 2.4 ± 0.2 C: 2.5 ± 0.2

Abbreviations: IG: Intervention; NR: Not reported; DM: Diabetes Mellitus; CG: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation

Appendix B Evidence Table 3. Pharmacological intervention trials

Study Reference Study Quality	Interv phase 6-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo	Post-Intervention	Physiological Outcomes Reported	Other anthropo-morphic Outcomes	Adverse Effects
Sibutramine							
Berkowitz et al 2003[91] Budd et al 2007[101] Good	6-mo % change in BMI: IG: -8.5% ± 6.8% CG: -4.0% ± 5.4% p=0.001 Change in BMI SDS: IG: -0.2 ± 0.2 CG: -0.1 ± 0.1 p=0.003	NA	NA	NA	Lipids: Yes Glucose tol: Yes BP: Yes Phys fitness: No Pulse: pulse rate higher in IG compared to CG by 5-6 bpm at 3 mos (P < 0.001) and 6 mos (p=0.007) Systolic blood pressure: at 3 mos, mean was increased in IG (1.8 (10.7) mmHG) and decreased in CG (-3.6(8.6); ES 0.55 (95% CI 0.10-1.00);p=0.02) at 6 mos, IG: 0.4 (9.0) mmHg CG: -4.0 (8.9) mmHg ES: 0.45 (-0.02, 0.92) p=0.06 Diastolic blood pressure: no differences between groups Elevated Blood Pressure: IG: 3/43 (7.0%) CG: 0/39 (0%) p=0.06 No statistically significant difference between groups at 6 mos for lipids, triglycerides, serum insulin, serum glucose, HOMA	Waist Circumference Waist Circ(cm) IG: -8.2(6.9) CG: -2.8 (5.6) p<0.001	Any A.E.: IG: 6/43 (13.9%) CG: 3/39 (7.8%) NS See cardiovascular effects reported in physiological outcomes column Total rate of discontinuation due to A.E. among those taking sibutramine (I group in months 0-6 and 7-12, C group in months 7-12): 10/82 (12.2%); due to increased BP or HR 5/82 (6%), ecchymoses, VPCs or rash of unclear etiology Sexual maturity: NR Height change: NR

Abbreviations: IG: Intervention; NR: Not reported; DM: Diabetes Mellitus; CG: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation

Appendix B Evidence Table 3. Pharmacological intervention trials

Study Reference Study Quality	Study Characteristics	Patient Characteristics	CONSORT Numbers Retention	Inclusion/Exclusion	Description of Intervention Groups	Dose/ Duration	Mean Entry Wt
Berkowitz et al 2006[92] Daniels et al 2007[102] Good	RCT 498 adolescents 33 weight-loss clinics USA Databases of weight-loss clinics; advertisements Weight loss July 2000-February 2002 Funding: Pharmaceutical	Age: 12-16 (Mean 13.7) 65.7% Female White: 56.6% Black: 21.1% Hispanic: 15.7% Other: 6.6% SES: NR Co-morb: 0% DM BP > 130/85 I: 5 (1.4%) C: 3 (2.3%)	498 randomized I: 368 C: 130 Retention: I: 281 (76%) follow-up C: 80 (62%) follow-up	Inclusion: Age 12-16; BMI ≥ 2 SD more than U.S. weighted mean of the 95th %ile based on age/sex per 1998 Rosner norms (ref 17); BMI ≤ 44 Exclusion: cardiovascular disease; Type 1 or 2 diabetes; major psychiatric disorder; pregnancy; use of wt-loss medication or participation in weight loss program for >2 wks; use of medication associated with weight gain; use of medication contraindicated with use of sibutramine; cigarette smoking; Systolic blood pressure >130 mm HG; Diastolic blood pressure >85 mm Hg; pulse rate > 95 beats/min	I: Sibutramine + Behavior Therapy C: Placebo + Behavior Therapy	10 mg daily, increase to 15 mg daily at 6 mos if have not lost 10% of initial BMI or more. Total of 12 mos. At 6 mos increased to 15 mg dose N=174 (47.9%) of the Sibutramine group	BMI: I: 36.1 ± 3.8 C: 35.9 ± 4.1 NS

Abbreviations: IG: Intervention; NR: Not reported; DM: Diabetes Mellitus; CG: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation

Appendix B Evidence Table 3. Pharmacological intervention trials

Study Reference Study Quality	Interv phase 6-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo	Post-Intervention	Physiological Outcomes Reported	Other anthropo-morphic Outcomes	Adverse Effects
Berkowitz et al 2006[92] Daniels et al 2007[102] Good	NA	<u>12-mo</u> % change in BMI: IG: -9.4 ± 0.51 CG: -1.2 ± 0.90 p<0.001 Absolute change in BMI: IG: -2.9 CG:-0.3 p<0.001 (using last observation carried forward)	NA	NA	Lipids: Yes Glucose tol: Yes BP: Yes Phys fitness: No <u>Mean difference between groups:</u> Systolic BP: 1.0 mm HG (95% CI 0.1 – 1.9) p=0.03 Diastolic BP: 1.7 mmHG (95% CI 1.0-2.5) p<0.001 Pulse rate: 2.5 beats per minute (95%CI 1.6-3.3) p<0.001 (For the BP parameters, the differences between groups were a reflection of a reduction in BP in the control group and slight (or no) reduction on average in the sibutramine group.)	Waist circumference WC (cm): IG: -8.2 ± 0.49 CG: -1.8 ± 0.86 p<0.001	Any A.E.: IG: 327/368 (89%) CG: 111/130 (85%) NS Serious A.E.: IG: 2.7% (10/368) 0.8% (1/130) p=0.30 Discontinuation due to A.E. IG: 23/368 (6%) CG: 7/130 (5%) p=0.83 Tachycardia: IG: 46/368 (13%) CG: 8/130 (6%) p=0.05 Suicide attempt 1/368 (0.3%) 1/130 (0.8%) Depression/depressed state 5/368 (1.4%) 1/130 (0.8%) ECG: No clinically significant QTc prolongation or other mean changes from baseline. Also see additional relevant results in physiological

Abbreviations: IG: Intervention; NR: Not reported; DM: Diabetes Mellitus; CG: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation

Appendix B Evidence Table 3. Pharmacological intervention trials

Study Reference Study Quality	Study Characteristics	Patient Characteristics	CONSORT Numbers Retention	Inclusion/Exclusion	Description of Intervention Groups	Dose/ Duration	Mean Entry Wt
Van Mil et al, 2007[97] Fair	RCT 24 adolescents Obesity research center The Netherlands Regional public health department, pediatric outpatient clinic of teaching hospital Weight Loss Time period NR Funding NR	Age: 12-17 yrs (Mean 14.0 (calc)) 54.2% Female Race/Eth: NR SES: NR Co-morb: NR	24 randomized Retention: I: 11/12 (91.7%) C: 9/12 (75.0%)	Inclusion: Age 12-18; BMI ≥ 97th %ile for age and sex; triceps skinfold thickness ≥ 97th %ile for age and sex per 1996 Dutch norms (ref 9); persisting obesity despite professionally supervised wt loss attempts. Exclusion: Endocrine or other secondary causes of overweight; significant physical or medical illness.	I: Sibutramine + Behavior Therapy C: Placebo + Behavior Therapy	Wks 1-2: 5 mg/day Wks 3-12: 10 mg/day	BMI: I: 30.1 ± 4.5 C: 33.3 ± 5.0 BMI SDS: I: 2.60 ± 0.55 C: 2.97 ± 0.47

Abbreviations: IG: Intervention; NR: Not reported; DM: Diabetes Mellitus; CG: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation

Appendix B Evidence Table 3. Pharmacological intervention trials

Study Reference Study Quality	Interv phase 6-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo	Post-Intervention	Physiological Outcomes Reported	Other anthropo-morphic Outcomes	Adverse Effects
Van Mil et al, 2007[97] Fair	NA	NA	NA	6-mo (3-mo post-intervention): BMI change: IG: -0.8 (calc) CG: -1.4 (calc) (could not calculate SD) BMI SDS change: IG: -0.14 (calc) CG: -0.13 (calc) (could not calculate SD) Compliance NR	Lipids: No Glucose tol: No BP: Yes Phys fitness: No	Fat mass, free fat mass	Any adverse effects. # events/# participants IG: 41/12 CG: 22/12 # participants with adverse effects IG: 12/12 (100%) CG: 9/12 (75.0%) NS Abdominal complaints IG: 7/12 (58.3%) CG: 0/12 (0.0%) p<0.01 No differences between groups in heart rate, blood pressure, ECG changes

Abbreviations: IG: Intervention; NR: Not reported; DM: Diabetes Mellitus; CG: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation

Appendix B Evidence Table 3. Pharmacological intervention trials

Study Reference Study Quality	Study Characteristics	Patient Characteristics	CONSORT Numbers Retention	Inclusion/Exclusion	Description of Intervention Groups	Dose/ Duration	Mean Entry Wt
Garcia-Morales et al, 2006[94] Fair	RCT 52 adolescents Primary care pediatric obesity clinic Mexico Outpatients attending endocrinology department of children's hospital. Weight loss August 2001-August 2003 Funding: Pharmaceutical	Age: 14-18 yrs (Mean 15.0 (c)) 56.5% Female(c) Race/Eth NR SES: NR Co-morb: NR	70 screened 52 randomized I: 26 C: 25 Drop-out before 1 mo of treatment I: 3 C: 2 Completed 6 mo I: 21 (81%) C: 19 (76%) Analyzed I: 23 C: 23	Inclusion: Living in the Mexico City metropolitan area; 14-18 yrs; BMI > 95 percentile for age and sex. Exclusion: Lactating or pregnant females; females sexually active without contraception; Systolic blood pressure ≥ 140 mmHg or Diastolic blood pressure ≥ 90 mmHg; history of anorexia nervosa or bulimia; no treatment within 30 days with corticosteroids, MAOIs, antidepressants, lithium, weight loss drugs, nasal or respiratory anticongestives, migraine treatment, gastrointestinal prokinetics, or antihistamines; using alcohol or recreational drugs; history of depression or weight loss treatment in last 6 mo; genetic disease associated with obesity; hypothyroidism; cancer; blood disease; gastrointestinal surgery; psychiatric disease; history of work or school problems; weight loss ≥ 3 kg in last 3 mo; unable to follow protocol.	I: Sibutramine + diet/exercise counseling C: Placebo + diet/exercise counseling	10 mg/day 6 month	BMI I: 35.1 ± 5.3 C: 36.6 ± 5.2 Weight I: 92.6 ± 14.6 C: 98.9 ± 22.7

Abbreviations: IG: Intervention; NR: Not reported; DM: Diabetes Mellitus; CG: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation

Appendix B Evidence Table 3. Pharmacological intervention trials

Study Reference Study Quality	Interv phase 6-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo	Post-Intervention	Physiological Outcomes Reported	Other anthropo-morphic Outcomes	Adverse Effects
Garcia-Morales et al, 2006[94] Fair	BMI IG: -3.4 (-2.5, -4.2) CG: -1.8 (-0.9, -2.6) p< 0.005 (ANOVA testing interaction between treatment and time) Weight IG: -7.7 (-5.2, -10.2) CG: -3.8 (-1.6, -5.9) p< 0.005 (ANOVA testing interaction between treatment and time)	NA	NA	NA	Lipids: Yes Glucose tol: Yes BP: Yes Phys fitness: No	Waist Circumference WC and % change in WC: NS between groups	Mild Adverse effects: IG: 3/23 patients (headache, dry mouth; Headache w/ nausea; Headache w/ weakness and paleness) CG: 3/23 patients (Headache, Headache w/ somlolence, headache w/ dry mouth) P > 0.05 between groups Withdrawl due to adverse effects: none in either group Sexual maturity: All patients were in Tanner stage IV at baseline and end of study Height: not different between groups

Appendix B Evidence Table 3. Pharmacological intervention trials

Study Reference Study Quality	Study Characteristics	Patient Characteristics	CONSORT Numbers Retention	Inclusion/Exclusion	Description of Intervention Groups	Dose/ Duration	Mean Entry Wt
Godoy-Matos, 2005[95] Fair	RCT 60 adolescents Research setting designed to reflect clinical practice Turkey Recruitment NR Weight loss January 2002-April 2003 Funding: Pharmaceutical	Age: 14-17 yrs 82% Female Race: NR SES: NR Co-morb: None	68 patients recruited 8 subjects were lost after run-in period 60 randomized I: 30 C: 30 Completed I: 28 C: 22	Inclusion: 14-17 yrs; BMI 30-45. Exclusion: Diabetes mellitus; endocrine diseases predisposing to obesity; severe hyperlipidemia; systemic or major psychiatric disorders; history of bulimia or anorexia; uncontrolled hypertension (Diastolic blood pressure > 110 mmHg) or other cardiac diseases; weight loss of 3 kg or more within 2 mo or use of weight loss/gain drugs within 3 mo; drug or alcohol abuse; recent tobacco cessation or intention to quit during study period; pregnancy or lactation.	I: Sibutramine + diet/exercise counseling C: Placebo + diet/exercise counseling	1 mo run-in: placebo 6 mo: 10 mg/day	BMI, at wk -4 I: Female 37.5 ± 3.8 Male 37.6 ± 4.3 C: Female 35.8 ± 4.2 Male 37.4 ± 1.9 NS Weight, kg at wk 0 I: Female 97.7 ± 14.9 Male 115.2 ± 14.7 C: Female 91.9 ± 13.1 Male 110.2 ± 8.8 NS

Abbreviations: IG: Intervention; NR: Not reported; DM: Diabetes Mellitus; CG: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation

Appendix B Evidence Table 3. Pharmacological intervention trials

Study Reference Study Quality	Interv phase 6-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo	Post-Intervention	Physiological Outcomes Reported	Other anthropo-morphic Outcomes	Adverse Effects
Godoy-Matos, 2005[95] Fair	BMI change I: -3.6 ± 2.5 C: -0.9 ± 0.9 p<0.001 Weight loss, kg I: -10.3 ± 6.6 C: -2.4 ± 2.5 p<0.001	NA	NA	NA	Lipids: Yes Glucose tol: Yes BP: Yes Phys fitness: No	Waist Circumference; waist to hip ratio	Constipation I: 40% C: 13.3% p=0.039 All others NS: dry mouth, heache, constipation, abdominal pain, cold dizzy. No one withdrew due to adverse effects

Abbreviations: IG: Intervention; NR: Not reported; DM: Diabetes Mellitus; CG: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation

Appendix B Evidence Table 3. Pharmacological intervention trials

Study Reference Study Quality	Study Characteristics	Patient Characteristics	CONSORT Numbers Retention	Inclusion/Exclusion	Description of Intervention Groups	Dose/ Duration	Mean Entry Wt
Orlistat							
Chanoine et al, 2005[93] Good	RCT 539 adolescents 32 institutions with established pediatric obesity treatment programs Canada and USA Advertisements in participant clinics and media, referrals from family physicians Weight loss August 2000-October 2002 Funding: Pharmaceutical	Age: 12-16 (Mean 13.6 (c)) 67% Female (c) 76.0% White (c) 16.9% Black (c) 7.1% Other (c) SES: NR 25.3% metabolic syndrome 1% DM	588 Evaluated 49 Excluded (did not meet incl crit (42), other (7)) 539 Randomized I: 357 C: 182 Retention: I: 232/257 (65.0%) C: 117/180 (64.3%)	Inclusion: Age 12-16; BMI ≥ 2 SD more than U.S. weighted mean of the 95th %ile based on age/sex per Rosner 1998 norms (ref 1); parent/guardian willing to attend study visits with them; willing to be actively involved in behavioral modification Exclusion: BMI ≥ 44; body weight ≥ 130 kg or <55 kg; weight loss of ≥ 3 kg in past 3 mos; diabetes requiring antidiabetic meds; obesity associated with genetic disorders; psychiatric disorder; use of dexamphetamine or methylphenidate; active gastro-intestinal tract disorder; bulimia or laxative abuse; use of anorexiants or weight-loss treatment in past 3 mos	I: Orlistat + Behavior Therapy C: Placebo + Behavior Therapy	Wks 1-2: placebo Wks 3-54: 360 mg/day Compliance I: 73% C:72%	BMI: I: 35.7 ± 4.2 C: 35.4 ± 4.1

Appendix B Evidence Table 3. Pharmacological intervention trials

Study Reference Study Quality	Interv phase 6-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo	Post-Intervention	Physiological Outcomes Reported	Other anthropo-morphic Outcomes	Adverse Effects
Orlistat							
Chanoine et al, 2005[93] Good	NA	12-mo: Adjusted Mean change in BMI: IG: -0.55 CG: +0.31 p<.001	NA	NA	Lipids: Yes Glucose tol: Yes BP: Yes Phys fitness: No	Waist & Hip Circumference, fat mass	Any adverse effects. IG: 97% CG: 94% Serious adverse effect I: 11/352 (3.1%) C: 5/181 (2.8%) Discontinued treatment due to adverse effects: IG: 12/352 (3.4%) CG: 3/181 (1.7%) Also assessed and found no group differences: levels of vitamin A, D, E, & beta carotene; levels of estradiol; change in height; sexual maturation, bone mineral density

Abbreviations: IG: Intervention; NR: Not reported; DM: Diabetes Mellitus; CG: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation

Appendix B Evidence Table 3. Pharmacological intervention trials

Study Reference Study Quality	Study Characteristics	Patient Characteristics	CONSORT Numbers Retention	Inclusion/Exclusion	Description of Intervention Groups	Dose/ Duration	Mean Entry Wt
Maahs et al 2006[96] Fair+A13	RCT 40 adolescents Research clinic USA Physician referal and newpaper advertisement Weight loss December 2002-February 2003 Funding: University supported	Age: 14-18 (Mean 15.8) 67.5% Female(c) 62.5% Hispanic (c) SES: NR Co-morb: NR	43 evaluated 3 excluded (parent refusal, not interested, psychological issues) 40 randomized I: 20 C: 20 Retention: I: 16/20 (80%) C: 18/20 (90%) p=0.68	Inclusion: Age 14-18; BMI >85th %ile of age and sex (norms NR) Exclusion: known secondary cause for obesity (e.g., hypothyroidism, daily corticosteroid exposure, genetic disorder); pregnancy	I: Orlistat + monthly diet/exercise counseling C: Placebo + monthly diet/exercise counseling	360 mg/day, 6 mos	BMI: I: 39.2 ± 1.2 C: 41.7 ± 2.6 Weight I: 111.1 ± 5.1 C: 114.3 ± 8.6

Abbreviations: IG: Intervention; NR: Not reported; DM: Diabetes Mellitus; CG: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation

Appendix B Evidence Table 3. Pharmacological intervention trials

Study Reference Study Quality	Interv phase 6-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo	Post-Intervention	Physiological Outcomes Reported	Other anthropo-morphic Outcomes	Adverse Effects
Maahs et al 2006[96] Fair+A13	<u>6-mo:</u> BMI: IG: 37.9 ± 1.6 CG: 40.9 ± 3.0 p=0.70, for time-by-group effect (including 3-mo values) Weight IG: 105.6 ± 6.2 CG: 112.7 ± 9.5 p=0.76	NA	NA	NA	Lipids: Yes Glucose tol: Yes BP: No Phys fitness: No	% body fat by bioelectrical impedance analysis	Discontinue due to A.E.: I: 2/20 (10%) C: 0/20 (0%) p-value NR I group reported higher levels of: soft stools (p=0.002); oily spotting (p<0.001); fatty or oily stools (p<0.001); oily evacuation (p<0.001); liquid stools (p=0.02); cramping (p=0.02); flatus w discharge (p<0.001); fecal incontinence (p<0.001)

Abbreviations: IG: Intervention; NR: Not reported; DM: Diabetes Mellitus; CG: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation

Appendix B Evidence Table 3. Pharmacological intervention trials

Study Reference Study Quality	Study Characteristics	Patient Characteristics	CONSORT Numbers Retention	Inclusion/Exclusion	Description of Intervention Groups	Dose/ Duration	Mean Entry Wt
Metformin-in special population							
Srinivasan et al, 2006[99] Fair	Cross-over RCT 28 children and adolescents Pediatric endocrine clinic Australia Physician referal to endocrine clinic of pediatric hospital Change in body composition	Age: 9-18 (Mean 12.5) 53.6% Female (c) 64% Pacific Islands or Indian subcontinent 25% Northern European 11% Mixed heritage SES: NR Co-morb: 0% DM	34 assessed for eligibility 28 randomized: Group A (metformin first): 13 Group B (placebo first): 15 Retention: A: 10/13 (76.9%) B: 12/15 (80.0%) follow-up	Inclusion: Age 9-18; referred to endocrine clinic with obesity per International Obesity Task Force definition; clinical suspicion of insulin resistance as defined by either a fasting insuline to glucose ratio >4.5 OR the presence of acanthosis nigricans. Exclusion: Known type 1 or 2 DM; contraindications to metformin; contraindications to MRI; weight >120 kg	A: Metformin, then placebo B: Placebo, then metformin	6 months metformin, gradually increased (over 3 wks) up to 2 g/day, 6 months placebo Compliance I: 78% (15-99%) C: 78% (35-98%) p=0.689	BMI, overall: 35.2 ± 5.1 BMI SDS, overall: 2.43 ± 0.28 Weight, kg, overall: 89.9 ± 17.6
Freemark et al., 2001[98] Fair	RCT 32 adolescents University research clinic USA Recruitment strategy: NR Funding: Pharmaceutical and General Clinical Research Center Grant	Age: 12 - 19 years (Mean for CG: 15.4 ± 0.5; IG: 14.4 ± 0.6) 62% Female (c*) 55%White(calc*) 45% Black (calc*) SES: NR % Co-morbid:NR 8 pts had acanthosis nigricans (all were black) *=data were reported only for 29/32 who completed trial	#assessed for eligibility: NR 32 randomized I: 15 C: 17 %retention: I: 93% C: 88% analyzed completers only	Inclusion: Age 12 - 19 who had reached Tanner stage III puberty; BMI > 30 kg/m2; fasting insulin concentration > 15 µU/mL; at least 1 first- or second-degree relative with type 2 diabetes; normal fasting glucose concentration (< 110 mg%) and HbA1c concentration (≤ 6.0%). Exclusion: NR	IG: Metformin CG: Placebo No attempt was made to control the caloric intake or food selection of the patients	Metformin 500 mg or Placebo, twice per day (1 at breakfast; 1 at dinner) x 6 months	BMI: IG: 41.5 ± 0.9 CG: 38.7 ± 1.3 (p < 0.05)

Abbreviations: IG: Intervention; NR: Not reported; DM: Diabetes Mellitus; CG: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation

Appendix B Evidence Table 3. Pharmacological intervention trials

Study Reference Study Quality	Interv phase 6-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo	Post-Intervention	Physiological Outcomes Reported	Other anthropo-morphic Outcomes	Adverse Effects
Metformin-in special population							
Srinivasan et al, 2006[99] Fair	Metformin treatment effect size: Weight, kg: -4.35 p=0.02 BMI -1.26 p=0.002 BMI SDS: -0.12 p=0.005				Lipids: Yes Glucose tol: Yes BP: Yes Phys fitness: No	Waist circumference, subcutaneous abdominal adipose tissue, visceral abdomnial adipose tissue, % total body fat.	Any adverse effects 2/28 (7%) nausea prevented full dose (both 9-year-olds, youngest age in study) They tolerated 750 mg x2/day Serious adverse effects 0/28 (0%) Discontinued treatment due to adverse effects: NR
Freemark et al., 2001[98] Fair	<u>6 mos:</u> BMI SDS IG: -0.12 CG: 0.23 p< 0.02 BMI IG: -0.5 kg/m2 CG: 0.9 kg/m2 p-value NR	N/A	N/A	N/A	Glucose tol=yes lipids=yes	No	No patients discontinued due to adverse events; no episodes of vomiting or lactic acidosis; serum lactate, liver and renal function parameters remained normal IG: 1 pt intermittent nausea in mos 3-4 until metforming dose was reduced by 50%; 3 abdominal discomfort during first 1-2 wks CG: 1 had abdominal discomfort

Abbreviations: IG: Intervention; NR: Not reported; DM: Diabetes Mellitus; CG: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation

Appendix B Evidence Table 3. Pharmacological intervention trials

Study Reference Study Quality	Study Characteristics	Patient Characteristics	CONSORT Numbers Retention	Inclusion/Exclusion	Description of Intervention Groups	Dose/ Duration	Mean Entry Wt
Love-Osborne et al, 2008[100] Fair	RCT 85 adolescents Setting: Research clinic; followup in schools or community USA Recruitment Strategy: posted advertisements or through primary care providers Funding: NIH, Barbara Davis Center for Childhood Diabetes, Children's Hospital Research Institute, Kettering Family Foundation	Age: 12 - 19 years (Mean for CG: 14.2 ± 4.6; IG: 15.5 ± 1.7) 71% Female (calc) %White NR 34% Black 56% Hispanic SES: NR %Co-morbid: 8% impaired glucose tolerance 0% DM	# Assessed for eligibility: NR # Randomized IG: 60 CG: 25 % Retention: IG: 80% CG: 64% Analyzed completers only	Inclusion: Age 12 - 19 with fasting insulin level > 25μU/mL or homeostasis model assessment > 3.5 and 2 of 3 risk factors (presence of acanthosis nigricans, obesity (BMI>95%ile), or family history of T2DM) Exclusion:preexisting diabetes, pregnancy, heart disease, serum gamma-glutamyl transferase over 1.5 times the upper limit of normal, or creatinine > 1.5 mg/dL	IG: Metformin + behavioral intervention (personal goal-setting) CG: Placebo + behavioral intervention (personal goal-setting)	Metformin 500 mg or Placebo, once per day x 1 month; then 500 mg twice per day x 1 month; then 850 mg twice per day x 4 months (lowered to previous dose if GI side effects for > 2 weeks)	BMI: IG:39.4 ± 6.5 CG:39.3 ± 7.2 BMI z-score: IG:4.6 ± 1.8 CG: 6.2 ± 8.9 Weight (kg): IG:108.8 ± 23.1 CG:110.6 ± 23.4

Abbreviations: IG: Intervention; NR: Not reported; DM: Diabetes Mellitus; CG: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation

Appendix B Evidence Table 3. Pharmacological intervention trials

Study Reference Study Quality	Interv phase 6-11 mo	Interv phase 12-23 mo	Interv phase 24+ mo	Post-Intervention	Physiological Outcomes Reported	Other anthropo-morphic Outcomes	Adverse Effects
Love-Osborne et al, 2008[100] Fair	6 mos: BMI IG: -0.16 ± 1.89 CG: 0.63 ± 1.29 p-value 0.11 >5% BMI decrease: IG: 11 (22.9%) CG: 0 (0%) p = 0.001 Increase in BMI IG: 20 (41.7%) CG: 11(68.8%) p=0.06	N/A	N/A	N/A	Lipids: NR Glucose tol: yes BP: NR Phys fitness: NR	NR	Gastro-intestinal side effects IG: 14/48 (29%) CG: 3/16 (19%) (among completers) Dropped out due to GI side effects IG: 2/12 (17%)calc CG: 1/9(11%) calc (Among 21 drop-outs)

Abbreviations: IG: Intervention; NR: Not reported; DM: Diabetes Mellitus; CG: Control Group;T2DM: Type 2 Diabetes Mellitus; SES: Socioeconomic status; A.E: Adverse effects; Mos: months; SD: standard deviation

Appendix B Table 4. List of excluded studies

Behavioral interventions

References	Reason for Exclusion
Alexy U, Reinehr T, Sichert-Hellert W, Wollenhaupt A, Kersting M, Andler W. Positive changes of dietary habits after an outpatient training program for overweight children. *Nutrition Research* 26 (5):202-208, 2006.	Did not meet quality criteria
Amador M, Ramos LT, Morono M, Hermelo MP. Growth rate reduction during energy restriction in obese adolescents. *Exp Clin Endocrinol.* 1990;96:73-82.	Setting
Ambler C, Eliakim A, Brasel JA, Lee WN, Burke G, Cooper DM. Fitness and the effect of exercise training on the dietary intake of healthy adolescents. *Int J Obes Relat Metab Disord.* 1998;22:354-362.	Relevance
Arnold, Linda L. The effects of a program of exercise and nutrition on body composition in adolescents and young adults with moderate cognitive disabilities: A descriptive study. Dissertation Abstracts International: Section B: The Sciences and Engineering 65[11-B], 6062. 2005.	Population
Ask AS, Hernes S, Aarek I, Johannessen G, Haugen M. Changes in dietary pattern in 15 year old adolescents following a 4 month dietary intervention with school breakfast--a pilot study. *Nutrition Journal 5:33.* 2006.	Did not report relevant outcomes
Atlantis E, Barnes EH, Singh MA. Efficacy of exercise for treating overweight in children and adolescents: a systematic review. *Int J Obes (Lond).* 2006;30:1027-1040.	Design
Balagopal P, George D, Patton N et al. Lifestyle-only intervention attenuates the inflammatory state associated with obesity: a randomized controlled study in adolescents. *Journal of Pediatrics 146(3):342 -8.* 2005.	Design
Balagopal P, George D, Yarandi H, Funanage V, Bayne E. Reversal of obesity-related hypoadiponectinemia by lifestyle intervention: a controlled, randomized study in obese adolescents. *Journal of Clinical Endocrinology & Metabolism 90(11):6192 -7.* 2005.	Design
Barbeau P, Johnson MH, Howe CA et al. Ten months of exercise improves general and visceral adiposity, bone, and fitness in black girls. *Obesity.* 2007;15:2077-2085.	Intervention not primary care feasible/referable
Bauer C, Fischer A, Keller U. Effect of sibutramine and of cognitive-behavioural weight loss therapy in obesity and subclinical binge eating disorder. *Diabetes, Obesity & Metabolism 8(3):289 -95 .* 2006.	Design
Baumer JH. Obesity and overweight: its prevention, identification, assessment and management. *Archives of Disease in Childhood Education & Practice 92(3):ep92 -6.* 2007.	Design
Becque MD, Katch VL, Rocchini AP, Marks CR, Moorehead C. Coronary risk incidence of obese adolescents: reduction by exercise plus diet intervention. *Am J Clin Nutr.* 1988;81:605-612.	Design
Beech BM, Klesges RC, Kumanyika SK et al. Child- and parent-targeted interventions: the Memphis GEMS pilot study. *Ethn Dis.* 2003;13:S40-S53.	Design
Berry D, Savoye M, Melkus G, Grey M. An intervention for multiethnic obese parents and overweight children. *Applied Nursing Research.* 2007;63-71, 2007.	Design
Berry D, Sheehan R, Heschel R, Knafl K, Melkus G, Grey M. Family-based interventions for childhood obesity: a review (Structured abstract). *SO: Journal of Family Nursing.* 2004;10:429-449.	Design

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References	Reason for Exclusion
Braet C, Van WM, Van LK. Follow-up results of different treatment programs for obese children. *Acta Paediatr.* 1997;86:397-402.	Design
Braet C, Tanghe A, Bode PD, Franckx H, Winckel MV. Inpatient treatment of obese children: A multicomponent programme without stringent calorie restriction. *Eur J Pediatr.* 2003;162:391-396.	Setting
Braet, C. and Winckel, M. V. Long-Term Follow-Up of a Cognitive Behavioral Treatment Program for Obese Children. Behavior Therapy 31, 55-74. 2000.	Design
Brown R, Sothern M, Suskind R, Udall J, Blecker U. Racial differences in the lipid profiles of obese children and adolescents before and after significant weight loss. *Clin Pediatr (Phila).* 2000;39:427-431.	Design
Brownell KD, Kaye FS. A school-based behavior modification, nutrition education, and physical activity program for obese children. *Am J Clin Nutr.* 1982;35:277-283.	Design
Butryn ML, Wadden TA. Treatment of overweight in children and adolescents: does dieting increase the risk of eating disorders? (Structured abstract). *SO: International Journal of Eating Disorders.* 2005;37:285-293.	Design
Campbell KJ, Hesketh KD. Strategies which aim to positively impact on weight, physical activity, diet and sedentary behaviours in children from zero to five years. A systematic review of the literature. *Obesity Reviews 8(4):327-38.* 2007.	Did not report relevant outcomes
Carrel AL, Clark RR, Peterson SE, Nemeth BA, Sullivan J, Allen DB. Improvement of fitness, body composition, and insulin sensitivity in overweight children in a school-based exercise program: Arandomized, controlled study. *Archives of pediatrics & adolescent medicine.* 2005;159:963-968.	Setting
Carrel AL, Clark RR, Peterson S, Eickhoff J, Allen DB. School-based fitness changes are lost during the summer vacation. *Archives of pediatrics & adolescent medicine.* 2007;161:561-564.	Setting
Chang FT, Hu SH, Wang RS. The effectiveness of dietary instruction in obese school children of southern Taiwan. *Kaohsiung J Med Sci.* 1998;14:528-535.	Setting
Chen W, Chen SC, Hsu HS, Lee C. Counseling clinic for pediatric weight reduction: program formulation and follow-up. *J Formos Med Assoc.* 1997;96:59-62.	Setting
Clemmens D, Hayman LL. Increasing activity to reduce obesity in adolescent girls: a research review (Provisional record). *SO: Journal of Obstetric, Gynecologic and Neonatal Nursing.* 2004;33:801-808.	Design
Cliff DP, Wilson A, Okely AD, Mickle KJ, Steele JR. Feasibility of SHARK: A physical activity skill-development program for overweight and obese children. *Journal of Science & Medicine in Sport 10(4):263-7.* 2007.	Design
Cole K, Waldrop J, D'Auria J, Garner H. An integrative research review: effective school-based childhood overweight interventions. *J Spec Pediatr Nurs.* 2006;11:166-177.	Design
Coleman KJ, Tiller CL, Sanchez J et al. Prevention of the epidemic increase in child risk of overweight in low-income schools: the El Paso coordinated approach to child health. *Archives of Pediatrics & Adolescent Medicine 159(3):217 -24.* 2005.	Relevance

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References	Reason for Exclusion
Collins CE, Warren J, Neve M, McCoy P, Stokes BJ. Measuring effectiveness of dietetic interventions in child obesity: a systematic review of randomized trials. *Arch Pediatr Adolesc Med.* 2006;160:906-922.	Design
Collins CE, Warren JM, Neve M, McCoy P, Stokes B. Systematic review of interventions in the management of overweight and obese children which include a dietary component (Provisional record). *SO: International Journal of Evidence Based Healthcare.* 2007;5:2-53.	Design
Daley AJ, Copeland RJ, Wright NP, Roalfe A, Wales JK. Exercise therapy as a treatment for psychopathologic conditions in obese and morbidly obese adolescents: a randomized, controlled trial. *Pediatrics 118 (5):2126 -34.* 2006.	Relevance
Daley AJ, Copeland RJ, Wright NP, Wales JK. Protocol for: Sheffield Obesity Trial (SHOT): a randomised controlled trial of exercise therapy and mental health outcomes in obese adolescents. *BMC Public Health 5:113.* 2005.	Relevance
Danielzik, S., Pust, S., Landsberg, B., and Muller, M. J. First lessons from the Kiel Obesity Prevention Study (KOPS). International Journal of Obesity 29[Suppl2], S78-S83. 2005.	Relevance
Davee AM, Blum JE, Devore RL et al. The vending and a la carte policy intervention in Maine public high schools. *Preventing Chronic Disease 2 Spec no:A14 .* 2005.	Design
Davis CE, Hunsberger S, Murray DM et al. Design and statistical analysis for the Pathways study. *Am J Clin Nutr.* 1999;69:760S-763S.	Relevance
Deforche B, De Bourdeaudhuij I, Tanghe A, Debode P, Hills AP, Bouckaert J. Post-treatment phone contact: A weight maintenance strategy in obese youngsters. *Int J Obes.* 2005;29:543-546.	Study design
DeJongh ED, Binkley TL, Specker BL. Fat mass gain is lower in calcium-supplemented than in unsupplemented preschool children with low dietary calcium intakes. *American Journal of Clinical Nutrition 84(5):1123 -7.* 2006.	Relevance
DeMattia L, Lemont L, Meurer L. Do interventions to limit sedentary behaviours change behaviour and reduce childhood obesity? A critical review of the literature. *Obesity Reviews 8(1):69 -81 .* 2007.	Design
Dennison BA, Russo TJ, Burdick PA, Jenkins PL. An intervention to reduce television viewing by preschool children. *Arch Pediatr Adolesc Med.* 2004;158:170-176.	Relevance
Dicken KR, Bell MM. Pedometers as a means to increase walking and achieve weight loss. *SO: Journal of the American Board of Family Medicine : JABFM.* 2006;19:524-525.	Population
Donnelly JE, Jacobsen DJ, Whatley JE, Hill JO, Swift LL, Cherrington A, Polk B, Tran ZV, Reed G. Nutrition and physical activity program to attenuate obesity and promote physical and metabolic fitness in elementary school children. *Obes Res* 4 (3):229-243, 1996.	Prevention trial
Dreimane D, Safani D, MacKenzie M et al. Feasibility of a hospital-based, family-centered intervention to reduce weight gain in overweight children and adolescents. *Diabetes Research & Clinical Practice 75(2):159-68 .* 2007.	Design
Duffy G, Spence SH. The effectiveness of cognitive self-management as an adjunct to a behavioural intervention for childhood obesity: a research note. *J Child Psychol Psychiatry.* 1993;34:1043-1050.	Quality

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References	Reason for Exclusion
Ebbeling CB, Feldman HA, Osganian SK, Chomitz VR, Ellenbogen SJ, Ludwig DS. Effects of decreasing sugar-sweetened beverage consumption on body weight in adolescents: a randomized, controlled pilot study. *Pediatrics 117 (3):673 -80 .* 2006.	Relevance
Ebbeling CB, Garcia-Lago E, Leidig MM, Seger-Shippee LG, Feldman HA, Ludwig DS. Altering portion sizes and eating rate to attenuate gorging during a fast food meal: effects on energy intake. *Pediatrics 119 (5):869 -75.* 2007.	Relevance
Ebbeling CB, Leidig MM, Feldman HA, Lovesky MM, Ludwig DS. Effects of a low-glycemic load vs low-fat diet in obese young adults: a randomized trial. *JAMA 297 (19):2092 -102 .* 2007.	Population
Ebbeling CB, Leidig MM, Sinclair KB, Hangen JP, Ludwig DS. A reduced-glycemic load diet in the treatment of adolescent obesity. *Archives of Pediatrics & Adolescent Medicine.* 2003;157:773-779.	Design
Economos CD, Hyatt RR, Goldberg JP et al. A community intervention reduces BMI z-score in children: Shape Up Somerville first year results. *Obesity 15(5):1325 -36.* 2007.	Relevance
Edwards B. Childhood obesity: a school-based approach to increase nutritional knowledge and activity levels. *Nurs Clin North Am.* 2005;40:661-6ix.	Not primary care feasible or referable
Eliakim A, Kaven G, Berger I, Friedland O, Wolach B, Nemet D. The effect of a combined intervention on body mass index and fitness in obese children and adolescents - a clinical experience. *Eur J Pediatr.* 2002;161:449-454.	Did not report relevant outcomes
Epstein LH, Kuller LH, Wing RR, Valoski A, McCurley J. The effect of weight control on lipid changes in obese children. *Am J Dis Child.* 1989;143:454-457.	Precedes search period
Epstein LH, McCurley J, Wing RR, Valoski A. Five-year follow-up of family-based behavioral treatments for childhood obesity. *J Consult Clin Psychol.* 1990;58:661-664.	Design
Epstein LH, McKenzie SJ, Valoski A, Klein KR, Wing RR. Effects of mastery criteria and contingent reinforcement for family-based child weight control 3838. *Addictive Behaviors.* 1994;19:135-145.	Design
Epstein LH, Paluch RA, Raynor HA. Sex differences in obese children and siblings in family-based obesity treatment. *Obesity Research.* 2001;9:746-753.	Design
Epstein LH, Saelens BE, O'Brien JG. Effects of reinforcing increases in active behavior versus decreases in sedentary behavior for obese children. *Int J Behav Med.* 1995;2:41-50.	Did not report relevant outcomes
Epstein LH, Valoski A, McCurley J. Effect of weight loss by obese children on long-term growth. *Am J Dis Child.* 1993;147:1076-1080.	Design
Epstein LH, Valoski A, Wing RR, McCurley J. Ten-year outcomes of behavioral family-based treatment for childhood obesity. *Health Psychol.* 1994;13:373-383.	Design
Epstein LH, Valosk Ai, Wing RR, McCurley J. Ten-year follow-up of behavioral, family-based treatment for obese children. *JAMA* 264 (19):2519-2523, 1990.	Precedes search period
Epstein LH, Valoski AM, Kalarchian MA, McCurley J. Do children lose and maintain weight easier than adults: a comparison of child and parent weight changes from six months to ten years. *Obes Res.* 1995;3:411-417.	Did not report relevant outcomes

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References	Reason for Exclusion
Epstein LH, Wing RR, Koeske R, Andrasik F, Ossip DJ. Child and parent weight loss in family-based behavior modification programs. *J Consult Clin Psychol.* 1981;49:674-685.	Design
Epstein LH, Wing RR, Koeske R, Valoski A. Effect of parent weight on weight loss in obese children. *J Consult Clin Psychol.* 1986;54:400-401.	Did not report relevant outcomes
Epstein LH, Wing RR, Koeske R, Valoski A. Long-term effects of family-based treatment of childhood obesity. *J Consult Clin Psychol.* 1987;55:91-95.	Precedes search period
Epstein LH, Valoski A, Koeske R, Wing RR. Family-based behavioral weight control in obese young children. *J Am Diet Assoc* 86 (4):481-484, 1986.	Design
Epstein LH, Valoski AM, Vara LS, McCurley J, Wisniewski L, Kalarchian MA, Klein KR, Shrager LR. Effects of decreasing sedentary behavior and increasing activity on weight change in obese children 3814. *Health Psychology.* 14 (2):109-115, 1995	Design
Epstein LH, R. Paluch RA, Gordy CC, Dorn J. Decreasing sedentary behaviors in treating pediatric obesity. *Arch Pediatr Adolesc Med* 154 (3):220-226, 2000.	Design
Epstein LH, Paluch RA, Saelens BE, Ernst MM, Wilfley DE. Changes in eating disorder symptoms with pediatric obesity treatment. *J Pediatr* 139 (1):58-65, 2001	Design
Epstein LH, Paluch RA, Kilanowski CK, Raynor HA. The effect of reinforcement or stimulus control to reduce sedentary behavior in the treatment of pediatric obesity. *Health Psychol* 23 (4):371-380, 2004.	Design
Epstein LH, Paluch RA, Roemmich JN, Beecher MD. Family-based obesity treatment, then and now: Twenty-five years of pediatric obesity treatment. *Health Psychol.* 26(4):381-391, 2007.	Design
Epstein LH, Wing RR, Valoski A, Penner BC. Stability of food preferences during weight control. A study with 8- to 12-year-old children and their parents. *Behav Modif.* 1987;11:87-101.	Did not report relevant outcomes
Epstein LH, Wing RR, Penner BC, Kress MJ. Effect of diet and controlled exercise on weight loss in obese children. *J Pediatr.* 1985;107:358-361.	Comparative effectiveness study
Epstein LH, Wing RR, Koeske R, Valoski A. Effects of diet plus exercise on weight change in parents and children. *J Consult Clin Psychol.* 1984;52:429-437.	Precedes search date
Epstein LH. Effects of family-based behavioral treatment on obese 5-to-8-year-old children. *Behavior Therapy.* 1985;16:205-212.	Comparative effectiveness study
Epstein LH, Paluch RA, Beecher MD, Roemmich JN. Increasing healthy eating vs. reducing high energy-dense foods to treat pediatric obesity. *Obesity.* 2008;16:318-326.	Comparative effectiveness study
Figueroa-Colon R, von Almen TK, Franklin FA, Schuftan C, Suskind RM. Comparison of two hypocaloric diets in obese children. *Am J Dis Child.* 1993;147:160-166.	Design
Figueroa-Colon R, Franklin FA, Lee JR, von Almen TK, Suskind RM. Feasibility of a clinic-based hypocaloric dietary intervention implemented in a school setting for obese children. *Obes Res* 4 (5):419-429, 1996.	Design

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References	Reason for Exclusion
Fitzgibbon ML, Stolley MR, Schiffer L, Van HL, KauferChristoffel K, Dyer A. Two-year follow-up results for Hip-Hop to Health Jr.: a randomized controlled trial for overweight prevention in preschool minority children. *Journal of Pediatrics 146(5):618 -25.* 2005.	Prevention only
Flodmark, C.-E., Marcus, C., and Britton, M. Interventions to prevent obesity in children and adolescents: A systematic literature review. International Journal of Obesity 30[4], 579-589. 2006.	Relevance
Flores R. Dance for health: improving fitness in African American and Hispanic adolescents. *Public Health Rep* 110 (2):189-193, 1995.	Outcomes < 6 months
Foster GD, Wadden TA, Brownell KD. Peer-led program for the treatment and prevention of obesity in the schools. *J Consult Clin Psychol.* 1985;53:538-540.	Design
Gately PJ, Cooke CB, Barth JH, Bewick BM, Radley D, Hill AJ. Children's residential weight-loss programs can work: a prospective cohort study of short-term outcomes for overweight and obese children. *Pediatrics 116(1):73-7.* 2005.	Design
Gately PJ, King NA, Greatwood HC et al. Does a High-protein Diet Improve Weight Loss in Overweight and Obese Children? *Obesity 15(6):1527 -34.* 2007.	Design
Gibson LJ, Peto J, Warren JM, dos SS, I. Lack of evidence on diets for obesity for children: a systematic review. *International Journal of Epidemiology 35(6):1544 -52.* 2006.	Design
Golan M, Crow S. Targeting parents exclusively in the treatment of childhood obesity: long-term results. *Obes Res.* 2004;12:357-361.	Information provided in another publication
Golan M, Weizman A, Apter A, Fainaru M. Parents as the exclusive agents of change in the treatment of childhood obesity. *Am J Clin Nutr.* 1998;67:1130-1135.	Comparative effectiveness study
Golan M, Kaufman V, Shahar DR. Childhood obesity treatment: Targeting parents exclusively v. parents and children. *Br J Nutr.* 2006;95:1008-1015.	Comparative effectiveness study
Goldfield GS, Mallory R, Parker T et al. Effects of modifying physical activity and sedentary behavior on psychosocial adjustment in overweight/obese children. *Journal of Pediatric Psychology 32(7):783-93.* 2007.	Design
Goldfield GS, Epstein LH, Kilanowski CK, Paluch RA, Kogut-Bossler B. Cost-effectiveness of group and mixed family-based treatment for childhood obesity. *Int J Obes Relat Metab Disord* 25 (12):1843-1849, 2001.	Design
Goldfield GS, Mallory R, Parker T et al. Effects of open-loop feedback on physical activity and television viewing in overweight and obese children: a randomized, controlled trial. *Pediatrics 118 (1):e157 -66.* 2006.	< 6 months followup
Gortmaker SL, Peterson K, Wiecha J et al. Reducing obesity via a school-based interdisciplinary intervention among youth: Planet Health. *Arch Pediatr Adolesc Med.* 1999;153:409-418.	Relevance
Graf C, Koch B, Bjarnason-Wehrens B et al. Who benefits from intervention in, as opposed to screening of, overweight and obese children? *Cardiology in the Young 16(5):474 -80 .* 2006.	Did not report relevant outcomes

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References	Reason for Exclusion
Graf C, Rost SV, Koch B et al. Data from the StEP TWO programme showing the effect on blood pressure and different parameters for obesity in overweight and obese primary school children. *Cardiol Young.* 2005;15:291-298.	Setting
Graves T, Meyers AW, Clark L. An evaluation of parental problem-solving training in the behavioral treatment of childhood obesity. *J Consult Clin Psychol.* 1988;56:246-250.	Design
Grey M, Berry D, Davidson M, Galasso P, Gustafson E, Melkus G. Preliminary testing of a program to prevent type 2 diabetes among high-risk youth. *J Sch Health* 74 (1):10-15, 2004.	Design
Gutin B, Barbeau P, Owens S et al. Effects of exercise intensity on cardiovascular fitness, total body composition, and visceral adiposity of obese adolescents. *American Journal of Clinical Nutrition.* 2002;75:818-826.	Comparative effectiveness study
Gutin B, Yin Z, Johnson M, Barbeau P. Preliminary findings of the effect of a 3-year after-school physical activity intervention on fitness and body fat: the Medical College of Georgia Fitkid Project. *International Journal of Pediatric Obesity.* 2008;3:Suppl-9.	Intervention not primary care feasible/referable
Harrell JS, Gansky SA, McMurray RG, Bangdiwala SI, Frauman AC, Bradley CB. School-based interventions improve heart health in children with multiple cardiovascular disease risk factors. *Am J Clin Nutr.* 1998;102:371-380.	Relevance
Harvey-Berino J, Rourke J. Obesity prevention in preschool native-american children: a pilot study using home visiting. *Obes Res.* 2003;11:606-611.	Relevance
Heymsfield SB, van-Mierlo CA, van-der-Knaap HC, Heo M, Frier H, I. Weight management using a meal replacement strategy: meta and pooling analysis from six studies (Structured abstract). *SO: International Journal of Obesity.* 2003;27:537-549.	Population
Hills AP, Parker AW. Obesity management via diet and exercise intervention. *Child Care Health Dev.* 1988;14:409-416.	Design
Huang JS, Norman GJ, Zabinski MF, Calfas K, Patrick K. Body image and self-esteem among adolescents undergoing an intervention targeting dietary and physical activity behaviors. *Journal of Adolescent Health 40(3):245 -51.* 2007.	Relevance
Hughes AR, Stewart L, Chapple J et al. Randomized, controlled trial of a best-practice individualized behavioral program for treatment of childhood overweight: Scottish Childhood Overweight Treatment Trial (SCOTT). *Pediatrics.* 2008;121:e539-e546.	Comparative effectiveness study
Ildiko V, Zsofia M, Janos M et al. Activity-related changes of body fat and motor performance in obese seven-year-old boys. *Journal of Physiological Anthropology 26(3):333-7.* 2007.	Setting
Intense diet, behavior, and physical activity intervention effective for obese children. *J Fam Pract.* 2005;54:579.	Design
Israel A, Solotar LC, Zimand E. An Investigation of Two Parental Involvement Roles in the Treatment of Obese Children. *Int.J.Eat.Disord.* 9(5):557-564, 1990.	Design
Israel, A., Stolmaker, Laurie, Sharp, Jeanette P, Silverman, W. K., and Simon, Linda G. An Evaluation of Two Methods of Parental Involvement in Treating Obese Children. Behavior Therapy 15, 266-272. 1984.	Comparative effectiveness study

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Behavioral interventions

References	Reason for Exclusion
Israel AC, Stolmaker L, Andrian CA. The effects of training parents in general child management skills on a behavioral weight loss program for children. *Behavior Therapy.* 1985;16:169-180.	Comparative effectiveness study
Jago R, Jonker ML, Missaghian M, Baranowski T. Effect of 4 weeks of Pilates on the body composition of young girls. *Preventive Medicine 42(3):177-80 .* 2006.	Relevance
Jago R, Baranowski T, Baranowski JC, Thompson D, Cullen KW, Watson K, Liu Y. Fit for Life Boy Scout badge: outcome evaluation of a troop and Internet intervention. *SO: Preventive medicine* 42 (3):181-187, 2006.	Prevention Trial
Jelalian E, Mehlenbeck R, Lloyd-Richardson EE, Birmaher V, Wing RR. 'Adventure therapy' combined with cognitive-behavioral treatment for overweight adolescents. *International Journal of Obesity 30(1):31-9.* 2006.	Design
Jelalian E, Wember YM, Bungeroth H, Birmaher V. Practitioner review: bridging the gap between research and clinical practice in pediatric obesity. *Journal of Child Psychology & Psychiatry & Allied Disciplines 48 (2):115-27.* 2007.	Design
Jiang JX, Xia XL, Greiner T, Lian GL, Rosenqvist U. A two year family based behaviour treatment for obese children. *Archives of Disease in Childhood 90(12):1235 -8.* 2005.	Setting
Johnson WG, Hinkle LK, Carr RE et al. Dietary and exercise interventions for juvenile obesity: long-term effect of behavioral and public health models. *Obes Res.* 1997;5:257-261.	<6 months followup
Johnston, Craig A. and Steele, Ric G. Treatment of Pediatric Overweight: An Examination of Feasibility and Effectiveness in an Applied Clinical Setting. Journal of Pediatric Psychology 32[1], 106-110. 2007.	Design
Johnston CA, Tyler C, Fullerton G et al. Results of an intensive school-based weight loss program with overweight Mexican American children. *Int J Pediatr Obes.* 2007;2:144-152.	Setting
Johnston CA, Tyler C, McFarlin B et al. Weight Loss in Overweight Mexican American Children: A Randomized Controlled Trial. *Pediatrics.* 2007;120:e1450-e1457.	Setting
Jones RA, Okely AD, Collins CE et al. The HIKCUPS trial: a multi-site randomized controlled trial of a combined physical activity skill-development and dietary modification program in overweight and obese children. *BMC Public Health 7:15.* 2007.	Did not report relevant outcomes
Jones M, Luce KH, Osborne MI et al. Randomized, controlled trial of an internet-facilitated intervention for reducing binge eating and overweight in adolescents. *Pediatrics.* 2008;121:453-462.	Population
Kalavainen MP, Korppi MO, Nuutinen OM. Clinical efficacy of group-based treatment for childhood obesity compared with routinely given individual counseling. *Int J Obes (Lond).* 2007;31:1500-1508.	Setting
Kang HS, Gutin B, Barbeau P et al. Physical training improves insulin resistance syndrome markers in obese adolescents. *Medicine & Science in Sports & Exercise.* 2002;34:1920-1927.	Comparative effectiveness study
Kelly AS, Steinberger J, Olson TP, Dengel DR. In the absence of weight loss, exercise training does not improve adipokines or oxidative stress in overweight children. *Metabolism: Clinical & Experimental 56(7):1005 -9.* 2007.	Design

Appendix B Table 4. List of excluded studies

Behavioral interventions

References	Reason for Exclusion
Kitzmann, Katherine M. and Beech, Bettina M. Family-Based Interventions for Pediatric Obesity: Methodological and Conceptual Challenges From Family Psychology. Journal of Family Psychology 20[2], 175-189. 2006.	Design
Klijn PH, van der Baan-Slootweg OH, van Stel HF. Aerobic exercise in adolescents with obesity: preliminary evaluation of a modular training program and the modified shuttle test. *BMC Pediatrics 7:19.* 2007.	Design
Korsten-Reck U, Kromeyer-Hauschild K, Wolfarth B, Dickhuth HH, Berg A. Freiburg Intervention Trial for Obese Children (FITOC): results of a clinical observation study. *International Journal of Obesity 29(4):356 -61.* 2005.	Did not report relevant outcomes
Lansky D, Vance MA. School-based intervention for adolescent obesity: analysis of treatment, randomly selected control, and self-selected control subjects. *J Consult Clin Psychol.* 1983;51:147-148.	Design
Lauer RM, Obarzanek E, Hunsberger SA, et al. Efficacy and safety of lowering dietary intake of total fat, saturated fat, and cholesterol in children with elevated LDL cholesterol: the Dietary Intervention Study in Children. *Am J Clin Nutr* 72 (5 Suppl):1332S-1342S, 2000.	Not a weight loss trial
Levine MD, Ringham RM, Kalarchian MA, Wisniewski L, Marcus MD. Is family-based behavioral weight control appropriate for severe pediatric obesity? *Int J Eat Disord.* 2001;30:318-328.	Design
Lytle LA, Stone EJ, Nichaman MZ et al. Changes in nutrient intakes of elementary school children following a school-based intervention: results from the CATCH Study. *Prev Med.* 1996;25:465-477.	Relevance
Maffeis C, Castellani M. Physical activity: an effective way to control weight in children? *Nutrition Metabolism & Cardiovascular Diseases 17(5):394 -408 .* 2007.	Design
Martinez V, V, Salcedo AF, Franquelo GR et al. Assessment of an after-school physical activity program to prevent obesity among 9- to 10-year-old children: a cluster randomized trial. *Int J Obes.* 2008;32:12-22.	Intervention not primary care feasible/referable
Manios Y, Moschandreas J, Hatzis C, Kafatos A. Evaluation of a health and nutrition education program in primary school children of Crete over a three-year period. *Prev Med.* 1999;28:149-159.	Relevance
McLean N, Griffin S, Toney K, Hardeman W. Family involvement in weight control, weight maintenance and weight-loss interventions: a systematic review of randomised trials (Provisional record). *SO: International Journal of Obesity.* 2003;27:987-1005.	Design
Meyer AA, Kundt G, Lenschow U, Schuff-Werner P, Kienast W. Improvement of early vascular changes and cardiovascular risk factors in obese children after a six-month exercise program. *Journal of the American College of Cardiology 48 (9):1865 -70.* 2006.	Did not meet quality criteria
Miraglia del GE, Santoro N, Marotta A, Nobili B, Di TR, Perrone L. Inadequate leptin level negatively affects body fat loss during a weight reduction programme for childhood obesity. *Acta Paediatr.* 2002;91:132-135.	Study design
Moore, Brie A. and O'Donohue, William T. Physchilogical Approaches to Disease Management. 225-270. 2005.	Design
Moreno LA. Interventions to improve cardiovascular risk factors in obese children. *Journal of Pediatric Gastroenterology & Nutrition 43(4):433 -5.* 2006.	Design

Appendix B Table 4. List of excluded studies

Behavioral interventions

References	Reason for Exclusion
Mo-suwan L, Pongprapai S, Junjana C, Puetpaiboon A. Effects of a controlled trial of a school-based exercise program on the obesity indexes of preschool children. *Am J Clin Nutr.* 1998;68:1006-1011.	Setting
Muller MJ, Asbeck I, Mast M, Langnase K, Grund A. Prevention of obesity--more than an intention. Concept and first results of the Kiel Obesity Prevention Study (KOPS). *Int J Obes Relat Metab Disord* 25 Suppl 1:S66-S74, 2001.	Prevention trial
Nemet D, Berger-Shemesh E, Wolach B, Eliakim A. A combined dietary-physical activity intervention affects bone strength in obese children and adolescents. *International Journal of Sports Medicine 27(8):666 -71.* 2006.	Design
Nova E, Varela P, Lopez-Vidriero I, Toro O, Cena MJ, Casas J, Marcos A. A one-year follow-up study in anorexia nervosa. Dietary pattern and anthropometrical evolution. *Eur J Clin Nutr* 55 (7):547-554, 2001.	Population
Nowicka P, Pietrobelli A, Flodmark CE. Low-intensity family therapy intervention is useful in a clinical setting to treat obese and extremely obese children. *International Journal of Pediatric Obesity.* 2007;2:211-217.	Study design
Nuutinen O, Knip M. Long-term weight control in obese children: persistence of treatment outcome and metabolic changes. *Int J Obes Relat Metab Disord.* 1992;16:279-287.	Relevance
O'Dea JA, Abraham S. Improving the body image, eating attitudes, and behaviors of young male and female adolescents: a new educational approach that focuses on self-esteem. *Int J Eat Disord.* 2000;28:43-57.	Relevance
Obarzanek E, Kimm SYS, Barton BA et al. Long-Term Safety and Efficacy of a Cholesterol-Lowering Diet in Children With Elevated Low-Density Lipoprotein Cholesterol: Seven-Year Results of the Dietary Intervention Study in Children (DISC). *Pediatrics.* 2001;107:256-264.	Quality
Owens S, Gutin B, Allison J et al. Effect of physical training on total and visceral fat in obese children. *Med Sci Sports Exerc.* 1999;31:143-148.	Design
Paineau DL, Beaufils F, Boulier A et al. Family dietary coaching to improve nutritional intakes and body weight control: a randomized controlled trial. *Archives of pediatrics & adolescent medicine.* 2008;162:34-43.	Prevention only
Patrick K, Calfas KJ, Norman GJ et al. Randomized controlled trial of a primary care and home-based intervention for physical activity and nutrition behaviors: PACE+ for adolescents. *SO: Archives of pediatrics & adolescent medicine.* 2006;160:128-136.	Relevance
Peterson KE, Fox MK. Addressing the epidemic of childhood obesity through school-based interventions: what has been done and where do we go from here? *Journal of Law, Medicine & Ethics 35(1):113-30.* 2007.	Design
Poland BD. Learning to 'walk our talk': the implications of sociological theory for research methodologies in health promotion. *Can J Public Health.* 1992;83 Suppl 1:S31-S46.	Relevance
Ray R, Lim LH , Ling SL. Obesity in preschool children: an intervention programme in primary health care in Singapore. *Ann Acad Med Singapore* 23 (3):335-341, 1994.	Design
Reinehr T, Kersting M, Alexy U, Andler W. Long-term follow-up of overweight children: after training, after a single consultation session, and without treatment. *J Pediatr Gastroenterol Nutr* 37 (1):72-74, 2003.	Did not meet quality criteria

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Behavioral interventions

References	Reason for Exclusion
Reinehr T, de SG, Wabitsch M. Changes of cardiovascular risk factors in obese children effects of inpatient and outpatient intervention. *Journal of Pediatric Gastroenterology & Nutrition 43(4):506-11.* 2006.	Information provided in another publication
Reinehr T, de SG, Andler W. Hyperthyrotropinemia in obese children is reversible after weight loss and is not related to lipids. *Journal of Clinical Endocrinology & Metabolism 91(8):3088 -91.* 2006.	Study design
Resnicow K, Davis R, Rollnick S. Motivational interviewing for pediatric obesity: Conceptual issues and evidence review. *Journal of the American Dietetic Association 106(12):2024-33.* 2006.	Design
Resnicow K, Yaroch AL, Davis A et al. GO GIRLS!: results from a nutrition and physical activity program for low-income, overweight African American adolescent females. *Health Educ Behav.* 2000;27:616-631.	Design
Reybrouck T, Vinckx J, Van den BG, Vanderschueren-Lodeweyckx M. Exercise therapy and hypocaloric diet in the treatment of obese children and adolescents. *Acta Paediatr Scand.* 1990;79:84-89.	Did not meet quality criteria
Reybrouck T, Weymans M, Vinckx J, Stijns H, Vanderschueren-Lodeweyckx M. Cardiorespiratory function during exercise in obese children. *Acta Paediatr Scand.* 1987;76:342-348. kq1e7	Did not meet quality criteria
Robbins LB, Gretebeck KA, Kazanis AS, Pender NJ. Girls on the move program to increase physical activity participation. *Nursing Research 55(3):206 -16.* 2006;-Jun.	Design
Robinson TN. Reducing children's television viewing to prevent obesity: a randomized controlled trial. *JAMA.* 1999;282:1561-1567.	Relevance
Rocchini AP, Katch V, Anderson J et al. Blood pressure in obese adolescents: effect of weight loss. *Am J Clin Nutr.* 1988;82:16-23.	Design
Rocchini AP, Katch V, Schork A, Kelch RP. Insulin and blood pressure during weight loss in obese adolescents. *Hypertension.* 1987;10:267-273.	Design
Rodearmel SJ, Wyatt HR, Barry MJ et al. A family-based approach to preventing excessive weight gain. *Obesity 14(8):1392 -401 .* 2006.	Design
Rolland-Cachera MF, Thibault H, Souberbielle JC, et al. Massive obesity in adolescents: dietary interventions and behaviours associated with weight regain at 2 y follow-up. *Int J Obes Relat Metab Disord* 28 (4):514-519, 2004.	Design
Rosenbaum M, Nonas C, Weil R et al. School-based intervention acutely improves insulin sensitivity and decreases inflammatory markers and body fatness in junior high school students. *Journal of Clinical Endocrinology & Metabolism 92(2):504 -8.* 2007.	Design
Salmon J, Booth ML, Phongsavan P, Murphy N, Timperio A. Promoting Physical Activity Participation among Children and Adolescents. *Epidemiologic Reviews 29:144 -59.* 2007.	Design
Salmon J, Ball K, Hume C, Booth M, Crawford D. Outcomes of a group-randomized trial to prevent excess weight gain, reduce screen behaviours and promote physical activity in 10-year-old children: switch-play. *Int J Obes.* 2008;32:601-612.	Intervention not primary care feasible/referable
Sasaki J, Shindo M, Tanaka H, Ando M, Arakawa K. A long-term aerobic exercise program decreases the obesity index and increases the high density lipoprotein cholesterol concentration in obese children. *Int J Obes.* 1987;11:339-345.	Design

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Behavioral interventions

References	Reason for Exclusion
Schwartz RP, Hamre R, Dietz WH et al. Office-based motivational interviewing to prevent childhood obesity: a feasibility study. *Archives of Pediatrics & Adolescent Medicine 161(5):495 -501 .* 2007.	Did not meet quality criteria
Schwingshandl J, Sudi K, Eibl B, Wallner S, Borkenstein M. Effect of an individualised training programme during weight reduction on body composition: a randomised trial. *Arch Dis Child.* 1999;81:426-428.	Design
Shaibi GQ, Cruz ML, Ball GD et al. Effects of resistance training on insulin sensitivity in overweight Latino adolescent males. *Medicine & Science in Sports & Exercise 38(7):1208 -15.* 2006.	Design
Sharma M. School-based interventions for childhood and adolescent obesity. *Obesity Reviews 7(3):261 -9.* 2006.	Design
Shelton, D., LeGros, K., Norton, L., Stanton-Cook, S., Morgan, J., and asterman, P. Randomised controlled trial: A parent-based group education programme for overweight children. Journal of Paediatrics and Child Health 43[12], 799-805. 2007.	<6 months followup
Sherry B. Food behaviors and other strategies to prevent and treat pediatric overweight. *International Journal of Obesity 29 Suppl 2:S116 -26.* 2005.	Design
Simon C, Wagner A, Platat C et al. ICAPS: a multilevel program to improve physical activity in adolescents. *Diabetes & Metabolism 32(1):41-9.* 2006.	Prevention only
Singh AS, Paw MJ, Brug J, van MW. Short-term effects of school-based weight gain prevention among adolescents. *Archives of Pediatrics & Adolescent Medicine 161(6):565 -71.* 2007.	Relevance
Snethen JA, Broome ME, Cashin SE. Effective weight loss for overweight children: a meta-analysis of intervention studies. *Journal of Pediatric Nursing 21(1):45-56.* 2006.	Design
Sondike SB, Copperman N, Jacobson MS. Effects of a low-carbohydrate diet on weight loss and cardiovascular risk factor in overweight adolescents. *J Pediatr.* 2003;142:253-258.	Design
Sothern MS, Despinasse B, Brown R, Suskind RM, Udall JN, Jr., Blecker U. Lipid profiles of obese children and adolescents before and after significant weight loss: differences according to sex. *South Med J.* 2000;93:278-282.	Design
Sothern MS, Hunter S, Suskind RM, Brown R, Udall JN, Jr., Blecker U. Motivating the obese child to move: the role of structured exercise in pediatric weight management. *South Med J.* 1999;92:577-584.	Design
Sothern MS, Loftin JM, Udall JN et al. Safety, feasibility, and efficacy of a resistance training program in preadolescent obese children. *Am J Med Sci.* 2000;319:370-375.	Design
Sothern MS, Schumacher H, von Almen TK, Carlisle LK, Udall JN. Committed to kids: an integrated, 4-level team approach to weight management in adolescents. *J Am Diet Assoc.* 2002;102:S81-S85.	Design
Sothern, Udall JN, Jr., Suskind RM, Vargas A, Blecker U. Weight loss and growth velocity in obese children after very low calorie diet, exercise, and behavior modification. *Acta Paediatr.* 2000;89:1036-1043.	Design
Southard DR, Southard BH. Promoting physical activity in children with MetaKenkoh. *Clinical & Investigative Medicine - Medecine Clinique et Experimentale 29(5):293 -7.* 2006.	Design

Appendix B Table 4. List of excluded studies

Behavioral interventions

References	Reason for Exclusion
Speroni KG, Earley C, Atherton M. Evaluating the effectiveness of the Kids Living Fit program: a comparative study. *J Sch Nurs.* 2007;23:329-336.	<6 months followup
Spieth LE, Harnish JD, Lenders CM et al. A low-glycemic index diet in the treatment of pediatric obesity. *Arch Pediatr Adolesc Med.* 2000;154:947-951.	Design
Tanas R, Marcolongo R, Pedretti S, Gilli G. A family-based education program for obesity: a three-year study. *BMC Pediatr* 7 (1):33, 2007.	Design
Temple JL, Wrotniak BH, Paluch RA, Roemmich JN, Epstein LH. Relationship between sex of parent and child on weight loss and maintenance in a family-based obesity treatment program. *International Journal of Obesity 30(8):1260 -4.* 2006.	Design
Tsiros MD, Sinn N, Brennan L et al. Cognitive behavioral therapy improves diet and body composition in overweight and obese adolescents. *Am J Clin Nutr.* 2008;87:1134-1140.	<6 months followup
van den Akker, Erica L. T., Puman, Patrycja J., Groen, Mieke, Timman, Reinier, Jongejan, Mieke T. M., and Trijsburg, Wim. A cognitive behavioral therapy program for overweight children. The Journal of Pediatrics 151[3], 280-283. 2007.	Study design
Viner R, Nicholls D. Managing obesity in secondary care: a personal practice. *Arch Dis Child.* 2005;90:385-390.	Design
Vido L, Facchin P, Antonello I, Gobber D, Rigon F. Childhood obesity treatment: double blinded trial on dietary fibres (glucomannan) versus placebo. *Padiatr Padol.* 1993;28:133-136.	None of our outcomes
Viski-Stalec N, Stalec J, Kati R, Podvorac D, Katovi D. The impact of dance-aerobics training on the morpho-motor status in female high-schoolers. *Collegium Antropologicum 31(1):259-66.* 2007.	Setting
Wadden TA, Stunkard AJ, Rich L, Rubin CJ, Sweidel G, McKinney S. Obesity in black adolescent girls: A controlled clinical trial of treatment by diet, behavior modification, and parental support 3928. *Pediatrics.* 1990;85:345-352.	Comparative effectiveness study
Warschburger P, Fromme C, Petermann F, Wojtalla N, Oepen J. Conceptualisation and evaluation of a cognitive-behavioural training programme for children and adolescents with obesity. *Int J Obes Relat Metab Disord.* 2001;25 Suppl 1:S93-S95.	Design
White MA. Mediators of weight loss in an internet-based intervention for African-American adolescent girls. *Obes Res.* 2004;12:1050-1059. kq1e2c; kq3e5a; kq2e2c; kq4e2c; kq5e2c	Comparative effectiveness study
Wilfley DE, Stein RI, Saelens BE et al. Efficacy of maintenance treatment approaches for childhood overweight: A randomized controlled trial. *JAMA.* 2007;298:1661-1673.	Study design
Williams CL, Strobino BA, Bollella M, Brotanek J. Cardiovascular risk reduction in preschool children: the "Healthy Start" project. *J Am Coll Nutr.* 2004;23:117-123.	Relevance
Williams CL, Strobino BA, Brotanek J. Weight control among obese adolescents: A pilot study. *International Journal of Food Sciences & Nutrition 58 (3):217 -30.* 2007.	Design
Williamson DA, Martin PD, White MA et al. Efficacy of an internet-based behavioral weight loss program for overweight adolescent African-American girls. *Eating & Weight Disorders: EWD 10(3):193-203 .* 2005	Comparative effectiveness study

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Behavioral interventions

References	Reason for Exclusion
Williamson DA, Walden HM, White MA et al. Two-year internet-based randomized controlled trial for weight loss in African-American girls. *Obesity 14(7):1231 -43.* 2006.	Comparative effectiveness study
Wong PC, Chia MY, Tsou IY et al. Effects of a 12-week Exercise Training Programme on Aerobic Fitness, Body Composition, Blood Lipids and C-Reactive Protein in Adolescents with Obesity. *Ann Acad Med Singapore.* 2008;37:286-288.	Study<6 months followup
Woo J, Sea MM, Tong P et al. Effectiveness of a lifestyle modification programme in weight maintenance in obese subjects after cessation of treatment with Orlistat. *J Eval Clin Pract.* 2007;13:853-859.	Age
Woo KS, Chook P, Yu CW et al. Effects of diet and exercise on obesity-related vascular dysfunction in children. *Circulation.* 2004;109:1981-1986.	Comparative effectiveness study
Young KM, Northern JJ, Lister KM, Drummond JA, O'Brien WH. A meta-analysis of family-behavioral weight-loss treatments for children. *Clinical Psychology Review 27(2):240 -9.* 2007.	Design
Young-Hyman D, Schlundt DG, Herman L, De LF, Counts D. Evaluation of the insulin resistance syndrome in 5- to 10-year-old overweight/obese African-American children. *Diabetes Care.* 2001;24:1359-1364.	Relevance
Zemel MB, Richards J, Mathis S, Milstead A, Gebhardt L, Silva E. Dairy augmentation of total and central fat loss in obese subjects. *International Journal of Obesity 29(4):391 -7.* 2005.	Relevance

Appendix B Table 4. List of excluded studies

Pharmacological interventions

Reference	Reason for Exclusion
Appolinario JC, Bacaltchuk J, Sichieri R et al. A randomized, double-blind, placebo-controlled study of sibutramine in the treatment of binge-eating disorder. *Archives of General Psychiatry 60(11):1109 -16.* 2003.	Population
Bauer C, Fischer A, Keller U. Effect of sibutramine and of cognitive-behavioural weight loss therapy in obesity and subclinical binge eating disorder. *Diabetes, Obesity & Metabolism 8(3):289 -95 .* 2006.	Design
Birkenfeld AL, Schroeder C, Pischon T et al. Paradoxical effect of sibutramine on autonomic cardiovascular regulation in obese hypertensive patients--sibutramine and blood pressure. *Clinical Autonomic Research 15(3):200 -6.* 2005.	Population
Cuellar GE, Ruiz AM, Monsalve MC, Berber A. Six-month treatment of obesity with sibutramine 15 mg; a double-blind, placebo-controlled monocenter clinical trial in a Hispanic population. *Obes Res.* 2000;8:71-82.	Population
Curran MP, Scott LJ. Orlistat: a review of its use in the management of patients with obesity. *Drugs 64(24):2845 -64.* 2004.	Design
Danielsson P, Janson A, Norgren S, Marcus C. Impact sibutramine therapy in children with hypothalamic obesity or obesity with aggravating syndromes. *J Clin Endocrinol Metab.* 2007.	Population
Dastjerdi, M. Siavash, Kazemi, F., Najafian, A., Mohammady, M., Aminorroaya, A., and Amini, M. An open-label pilot study of the combination therapy of metformin and fluoxetine for weight reduction. International Journal of Obesity 31[4], 713-717. 2007.	Population
Erdmann J, Lippl F, Klose G, Schusdziarra V. Cholesterol lowering effect of dietary weight loss and orlistat treatment--efficacy and limitations. *Alimentary Pharmacology & Therapeutics.* 2004;1173-1179.	Population
Fanghanel G, Cortinas L, Sanchez-Reyes L, Berber A. A clinical trial of the use of sibutramine for the treatment of patients suffering essential obesity. *Int J Obes Relat Metab Disord.* 2000;24:144-150.	Population
Freemark M. Pharmacotherapy of childhood obesity: an evidence-based, conceptual approach. *Diabetes Care.* 2007;30:395-402.	Design
Gilliam FG, Veloso F, Bomhof MA et al. A dose-comparison trial of topiramate as monotherapy in recently diagnosed partial epilepsy. *Neurology 60(2):196-202 .* 2003.	Relevance
Gottschalk M, Danne T, Vlajnic A, Cara JF. Glimepiride versus metformin as monotherapy in pediatric patients with type 2 diabetes: a randomized, single-blind comparative study. *Diabetes Care 30(4):790 -4.* 2007.	Comparative effectiveness study
Greenway FL, De JL, Blanchard D, Frisard M, Smith SR. Effect of a dietary herbal supplement containing caffeine and ephedra on weight, metabolic rate, and body composition. *Obesity Research 12(7):1152 -7.* 2004.	Population

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Pharmacological interventions

Reference	Reason for Exclusion
Guimaraes C, Pereira LR, Iucif JN et al. Tolerability and effectiveness of fluoxetine, metformin and sibutramine in reducing anthropometric and metabolic parameters in obese patients. *Arq Bras Endocrinol Metabol.* 2006;50:1020-1025.	Age
Hamilton J, Cummings E, Zdravkovic V, Finegood D, Daneman D. Metformin as an adjunct therapy in adolescents with type 1 diabetes and insulin resistance: a randomized controlled trial. *Diabetes Care 26(1):138-43.* 2003.	Population
Henness S, Perry CM. Orlistat: a review of its use in the management of obesity. *Drugs 66(12):1625 -56.* 2006.	Design
Ioannides-Demos LL, Proietto J, Tonkin AM, McNeil JJ. Safety of drug therapies used for weight loss and treatment of obesity. *Drug Safety 29(4):277 -302 .* 2006.	Design
James WP, Astrup A, Finer N et al. Effect of sibutramine on weight maintenance after weight loss: a randomised trial. STORM Study Group. Sibutramine Trial of Obesity Reduction and Maintenance. *Lancet.* 2000;356:2119-2125.	Population
Jordan J, Scholze J, Matiba B, Wirth A, Hauner H, Sharma AM. Influence of Sibutramine on blood pressure: evidence from placebo-controlled trials. *International Journal of Obesity 29(5):509 -16.* 2005.	Population
Junior AC, Savassi-Rocha PR, Coelho LG et al. Botulinum A toxin injected into the gastric wall for the treatment of class III obesity: a pilot study. *Obesity Surgery 16(3):335 -43.* 2006.	Population
Kay JP, Alemzadeh R, Langley G, D'Angelo L, Smith P, Holshouser S. Beneficial effects of metformin in normoglycemic morbidly obese adolescents. *Metabolism.* 2001;50:1457-1461.	Did not meet quality criteria
Larsen TM, Toubro S, Gudmundsen O, Astrup A. Conjugated linoleic acid supplementation for 1 y does not prevent weight or body fat regain. *American Journal of Clinical Nutrition 83 (3):606 -12.* 2006.	Population
Li Z, Maglione M, Tu W et al. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med.* 2005;142:532-546.	Population
McDuffie JR, Calis KA, Booth SL, Uwaifo GI, Yanovski JA. Effects of orlistat on fat-soluble vitamins in obese adolescents. *Pharmacotherapy.* 2002;22:814-822.	Design
McDuffie JR, Calis KA, Uwaifo GI et al. Efficacy of orlistat as an adjunct to behavioral treatment in overweight African American and Caucasian adolescents with obesity-related co-morbid conditions. *Journal of Pediatric Endocrinology 17(3):307-19.* 2004.	Design
McDuffie JR, Calis KA, Uwaifo GI et al. Three-month tolerability of orlistat in adolescents with obesity-related comorbid conditions. *Obes Res.* 2002;10:642-650.	Design
McElroy SL, Shapira NA, Arnold LM et al. Topiramate in the long-term treatment of binge-eating disorder associated with obesity. *Journal of Clinical Psychiatry 65(11):1463 -9.* 2004.	Population
Norgren S, Danielsson P, Jurold R, Lotborn M, Marcus C. Orlistat treatment in obese prepubertal children: a pilot study. *Acta Paediatrica 92(6):666 -70.* 2003.	Design

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Pharmacological interventions

Reference	Reason for Exclusion
Ozkan B, Bereket A, Turan S, Keskin S. Addition of orlistat to conventional treatment in adolescents with severe obesity. *Eur.J.Pediatr.* 163 (12):738-741, 2004	Design
Reith D, Burke C, Appleton DB, Wallace G, Pelekanos J. Tolerability of topiramate in children and adolescents. *Journal of Paediatrics & Child Health 39(6):416 -9.* 2003.	Relevance
Reisler G, Tauber T, Afriat R, Bortnik O, Goldman M. Sibutramine as an adjuvant therapy in adolescents suffering from morbid obesity. *Isr.Med Assoc J* 8 (1):30-32, 2006.	Design
Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF, and RIO-Diabetes Study Group. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. *Lancet.368.(9548.):1660-72,* 2006.	Population
Summaries for patients. Effects of drug treatment for obesity in adolescence.[original report in Ann Intern Med. 2006 Jul 18;145(2):81-90; PMID: 16847290]. *Annals of Internal Medicine 145 (2):I16.* 2006.	Design
Zhi J, Moore R, Kanitra L. The effect of short-term (21-day) orlistat treatment on the physiologic balance of six selected macrominerals and microminerals in obese adolescents. *Journal of the American College of Nutrition 22(5):357 -62.* 2003.	Not relevant outcomes
Zilberstein B, Pajecki D, Garcia de Brito AC, Gallafrio ST, Eshkenazy R, Andrade CG. Topiramate after adjustable gastric banding in patients with binge eating and difficulty losing weight. *Obesity Surgery 14(6):802 -5.* 2004;-Jul.	Population

Appendix C Table 1. Behavioral intervention trials, sorted by the presence of organized physical activity

Study Reference	Age Range (Mean) N	Treatment Hours	PA+	Fam	Age Grp	Beh Mod
Savoye et al 2007[77]	8-16 (12.1) n=174	97.5	1	2	B	1
Reinehr et al 2006[79]	6-14 (10.4) n=240	76	1	2	B	1
Nemet et al 2005[85]	Avg age 11.1 n=54	35.75	1	2	C	1
Mellin et al1987[104]	12-18 (15.6) n=66	24	1	1	A	1
Golley 2007[80]	6-9 (8.2) n=111	22	1*	2	C	1
Flodmark et al, 1993[103]	10-11 (Avg NR) n=93	24	0	2	C	0
Rooney 2005[82]	5-12 (9.7) n=98	21	0	2	C	0
Celio/Doyle et al 2007[88]	12-18 (14.5) n=43	16	0	0	A	1
Senediak et al 1985[84]	6-12 (10.3) n=45	12	0	2	C	1
Gillis 2007[78]	7-16 (10.6) n=27	8	0	1	B	1
McCallum et al, 2007[81,90]	5-9 (7.4) n=163	4	0	2	C	1
Saelens et al 2002[83]	12-16 (14.2) n=44	3.8	0	0	A	1
Epstein et al 2008[87]	4-7 (5.9) N=70	(very low)	0	2	C	0

*Organized physical activity in only one of two treatment arms
Note: Grayed interventions show statistically significant weight benefits compared with controls.
PA=Physical Activity (1=included organized PA sessions, 0=no organized PA session)
Fam=Family Involvement (2=parent a primary participant, 1=parent invited to 1-3 treatment sessions, 0=minimal parental involvement)
Age Grp=Age Group (A=adolescent, exclusively aged 10 and older; B=age spans younger children and adolescents; C=exclusively aged 12 and younger)
Beh Mod=Behavior Modification (1=Behavior modification employed, 0=not employed)

Appendix C Table 2. Behavioral intervention trials, sorted by family involvement, within age group

Study Reference	Age Range (Mean) N	Treatment Hours	PA	Fam	Age Grp	Beh Mod
Mellin et al1987[104]	12-18 (15.6) n=66	24	1	1	A	1
Celio/Doyle et al 2007[88]	12-18 (14.5) n=43	16	0	0	A	1
Saelens et al 2002[83]	12-16 (14.2) n=44	3.8	0	0	A	1
Savoye et al 2007[77]	8-16 (12.1) n=174	97.5	1	2	B	1
Reinehr et al 2006[79]	6-14 (10.4) n=240	76	1	2	B	1
Gillis 2007[78]	7-16 (10.6) n=27	8	0	1	B	1
Nemet et al 2005[85]	Avg age 11.1 n=54	35.75	1	2	C	1
Golley 2007[80]	6-9 (8.2) n=111	22	1*	2	C	1
Flodmark et al, 1993[103]	10-11 (Avg NR) n=93	24	0	2	C	0
Rooney 2005[82]	5-12 (9.7) n=98	21	0	2	C	0
Senediak et al 1985[84]	6-12 (10.3) n=45	12	0	2	C	1
McCallum et al, 2007[81,90]	5-9 (7.4) n=163	4	0	2	C	1
Epstein et al 2008[87]	4-7 (5.9) N=70	(very low)	0	2	C	0

*Organized physical activity in only one of two treatment arms
Note: Grayed interventions show statistically significant weight benefits compared with controls.
PA=Physical Activity (1=included organized PA sessions, 0=no organized PA session)
Fam=Family Involvement (2=parent a primary participant, 1=parent invited to 1-3 treatment sessions, 0=minimal parental involvement)
Age Grp=Age Group (A=adolescent, exclusively aged 10 and older; B=age spans younger children and adolescents; C=exclusively aged 12 and younger)
Beh Mod=Behavior Modification (1=Behavior modification employed, 0=not employed)

Appendix C Table 3. Behavioral intervention trials, sorted by the presence of behavioral management techniques

Study Reference	Age Range (Mean) N	Treatment Hours	PA	Fam	Age Grp	Beh Mod
Savoye et al 2007[77]	8-16 (12.1) n=174	97.5	1	2	B	1
Reinehr et al 2006[79]	6-14 (10.4) n=240	76	1	2	B	1
Nemet et al 2005[85]	Avg age 11.1 n=54	35.75	1	2	C	1
Mellin et al1987[104]	12-18 (15.6) n=66	24	1	1	A	1
Golley 2007[80]	6-9 (8.2) n=111	22	1*	2	C	1
Celio/Doyle et al 2007[88]	12-18 (14.5) n=43	16	0	0	A	1
Senediak et al 1985[84]	6-12 (10.3) n=45	12	0	2	C	1
Gillis 2007[133]	7-16 (10.6) n=27	8	0	1	B	1
McCallum et al, 2007[81,90]	5-9 (7.4) n=163	4	0	2	C	1
Saelens et al 2002[83]	12-16 (14.2) n=44	3.8	0	0	A	1
Flodmark et al, 1993[103]	10-11 (Avg NR) n=93	24	0	2	C	0
Rooney 2005[82]	5-12 (9.7) n=98	21	0	2	C	0
Epstein et al 2008[87]	4-7 (5.9) N=70	(very low)	0	2	C	0

*Organized physical activity in only one of two treatment arms
Note: Grayed interventions did not show statistically significant weight benefits compared with controls.
PA=Physical Activity (1=included organized PA sessions, 0=no organized PA session)
Fam=Family Involvement (2=parent a primary participant, 1=parent invited to 1-3 treatment sessions, 0=minimal parental involvement)
Age Grp=Age Group (A=adolescent, exclusively aged 10 and older; B=age spans younger children and adolescents; C=exclusively aged 12 and younger)
Beh Mod=Behavior Modification (1=Behavior modification employed, 0=not employed)