Effectiveness of Primary Care–Relevant Treatments for Obesity in Adults: A Systematic Evidence Review for the U.S. Preventive Services Task Force

Erin S. LeBlanc, MD, MPH; Elizabeth O'Connor, PhD; Evelyn P. Whitlock, MD, MPH; Carrie D. Patnode, PhD, MPH; and Tanya Kapka, MD, MPH

Background: Overweight and obesity in adults are common and adversely affect health.

Purpose: To summarize effectiveness and harms of primary care–relevant weight-loss interventions for overweight and obese adults.

Data Sources: MEDLINE, Cochrane Central Register of Controlled Trials, and PsycINFO from January 2005 to September 2010; systematic reviews for identifying trials before 2005.

Study Selection: Two investigators appraised 6498 abstracts and 648 articles. Clinical trials were included if control groups received minimal interventions. Articles were rated as good, fair, or poor by using design-specific criteria.

Data Extraction: One investigator abstracted study characteristics and findings for good- and fair-quality studies; a second checked them.

Data Synthesis: Behaviorally based treatment resulted in 3-kg (6.6-lb) greater weight loss in intervention than control participants after 12 to 18 months, with more treatment sessions associated with greater loss. Limited data suggest weight-loss maintenance for 1 year or more. Orlistat plus behavioral intervention resulted in 3-kg (6.6-lb) more weight loss than did placebo after 12 months. Metformin resulted in less weight loss. Data on effects of weight-loss treatment on long-term health outcomes (for example, death and cardiovascular disease) were insufficient. Weight-loss treatment reduced diabetes incidence in participants with prediabetes. Effects on intermediate outcomes (for example, lipids and blood pressure) were mixed and small. Data on serious medication harms were insufficient. Medications commonly caused withdrawals due to gastrointestinal symptoms.

Limitations: Few studies reported health outcomes. Behaviorally based treatments were heterogeneous and specific elements were not well-described. Many studies could not be pooled because of insufficient reporting of variance data. Medication trials had high attrition, lacked postdiscontinuation data, and were inadequately powered for rare adverse effects.

Conclusion: Behaviorally based treatments are safe and effective for weight loss and maintenance.

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For author affiliations, see end of text.

The prevalence of adult obesity—defined as a body mass index (BMI) greater than 30 kg/m^2—is high in the United States, exceeding 30% in most age- and sex-specific groups. In 2007–2008, 32% of men and 36% of women were obese. In addition, 40% of men and 28% of women met overweight criteria (BMI >25 kg/m^2) (1). The prevalence of obesity and of overweight have increased by 134% and 48%, respectively, since 1976–1980 (2).

Obesity is associated with increased mortality (particularly in adults <65 years) (3–5), coronary heart disease (6), type 2 diabetes (7), some types of cancer (8), and many other deleterious effects (9). Whether being overweight is associated with an increased mortality risk is less clear, possibly because the association varies by sex, ethnicity, and age and depends on the obesity measure used (for example, BMI vs. waist circumference) (10–12). Maternal obesity is associated with pregnancy complications and adverse fetal and neonatal health outcomes (13).

In 2003, the U.S. Preventive Services Task Force (USPSTF) recommended that clinicians screen all adults for obesity and offer intensive counseling and behavioral interventions to promote sustained weight loss for obese adults (B recommendation: high certainty that net benefit was moderate or moderate certainty that net benefit was moderate to substantial). The USPSTF, however, concluded that evidence was insufficient to recommend for or against moderate- or low-intensity counseling together with behavioral interventions to promote sustained weight loss in obese adults (I recommendation: insufficient evidence to assess benefit and harm balance). The USPSTF concluded that evidence was insufficient to recommend for or against counseling of any intensity and/or behavioral interventions to promote sustained weight loss in overweight adults (I recommendation).

We undertook this systematic review to help update these recommendations. To conduct it, we developed an

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analytic framework with 4 key questions (**Appendix Figure 1**, available at www.annals.org). The first was whether primary care screening programs to identify obesity or overweight in adults improved health or physiologic outcomes or resulted in weight loss. The other questions asked whether primary care feasible or referable weight-loss interventions (behaviorally based, with or without pharmacologic adjuncts) improved health outcomes, improved physiologic outcomes, resulted in short-term (12 to 18 months) or long-term (>18 months) weight loss, or caused harm.

Context

Experts recommend that primary care clinicians offer obese adults interventions that promote weight loss.

Contribution

In this systematic review of 58 trials, overweight adults in behavioral treatment trials that provided 12 to 26 intervention sessions during the first year lost 9 to 15 lb, whereas control groups lost little or no weight. Adults who received orlistat plus intensive behavioral interventions lost 11 to 22 lb, and those receiving placebo lost 7 to 13 lb.

Caution

Behavioral treatment trials studied heterogeneous interventions, and orlistat trials had high rates of attrition.

Implication

Behavior-oriented interventions can help overweight adults achieve meaningful weight loss.

—The Editors

METHODS

The full report (9) describes our methods in detail.

Data Sources and Searches

We relied on existing reviews to cover part of the search window from the previous USPSTF review, following previously detailed guidance (14). We identified a 2006 National Institute for Clinical Excellence systematic review on behavioral weight-loss interventions and orlistat (15) and a 2008 review of metformin trials (16). Their inclusion and exclusion criteria were congruent with ours, and investigators for both searched multiple databases and examined reference lists of pertinent reports. The reviews' search and selection strategies were judged acceptable to substitute for ours through 2005. We bridge-searched MEDLINE, PsycINFO, and the Cochrane Central Register of Controlled Trials from 2005 through 9 September 2010. We supplemented our search with relevant existing systematic reviews identified through databases (Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and MEDLINE) and Web sites (Institute of Medicine, National Institutes of Health, and National Institute for Health and Clinical Excellence). We supplemented our searches with experts' suggestions and reference lists from relevant publications, including evaluating all studies from the previous USPSTF review (17).

Study Selection

Two investigators independently reviewed 6498 abstracts and 648 articles against prespecified inclusion and exclusion criteria (**Appendix Figure 2**, available at www.annals.org). For key questions 1 to 3, we included randomized or controlled clinical trials with interventions focused on weight loss in adults (age ≥18 years) conducted in settings relevant to primary care (studies conducted in primary care or those that could in theory be implemented in a health care system, to which primary care clinicians could refer patients). We defined criteria for acceptable control groups a priori so that they would represent usual care and not overlap with low-intensity intervention groups. Acceptable control groups could not receive a personalized intervention, at-home workbook materials, or advice more frequently than annually; they also could not participate in frequent weigh-ins (<3 months). Healthy lifestyle messages were considered equivalent to weight-loss messages. For harms (key question 4), we included additional study designs (large cohort studies or case–control studies; large event monitoring; systematic evidence reviews of randomized, controlled trials [RCTs] or controlled clinical trials) and did not require 12 months of follow-up.

Data Extraction and Quality Assessment

Two independent investigators appraised all included articles as good, fair, or poor quality according to design-specific criteria and USPSTF methods (18). A third investigator resolved discrepancies. We assessed validity of randomization and measurement procedures, attrition, baseline characteristics, intervention fidelity, and statistical methods. Good-quality trials blinded researchers to participant randomization if they performed tasks related to assessment, had follow-up data on 90% or more of participants with fewer than a 10–percentage point difference between groups, and described anthropomorphic measurements in detail. Trials were rated poor quality and excluded if attrition was greater than 40%, was missing, or differed by more than 20% between groups (except for harms data); key baseline characteristics differed substantially between groups and were not controlled for in analyses; or outcomes were measured unequally between groups. Additional issues caused trials to be downgraded but not excluded; these included inconsistently applied interventions, selective reporting, and unclear or suboptimal blinding or randomization procedures (9). A table of excluded studies is available in our full report (9).

For included studies, one investigator abstracted data on study design, setting, population characteristics, baseline health and weight, intervention characteristics, prespecified outcomes, funding source, and adverse events

into standardized evidence tables (9). A second investigator reviewed abstraction for accuracy.

Data Synthesis and Analysis

We conducted separate random-effects meta-analyses to estimate the effect size of behavioral and pharmacologic interventions on weight loss (expressed in kg) and intermediate health outcomes (adiposity, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and glucose). Within each intervention type, trials were grouped according to the study population's risk status—cardiovascular risk (diabetes, dyslipidemia, hypertension), subclinical risk (prediabetes [19], borderline high lipids [20], prehypertension [21], abdominal obesity as defined by study researchers [22, 23]), and unselected/low risk—and then ordered by the behavioral intervention's intensity (number of sessions for behavioral trials and brief or intensive behavioral component accompanying medication trials).

We assessed the presence of statistical heterogeneity among studies by using standard chi-square tests and estimated heterogeneity magnitude by using the I^2 statistic (24). Tests of publication bias included funnel plots and the Egger linear regression method (25) when there were 10 or more studies (26).

We explored heterogeneity of the effect size for weight loss with a series of meta-regressions (9). Factors we included were population risk status, recruitment strategy, retention, study focus (weight maintenance vs. loss), whether the trial was conducted in primary care, setting (United States or not), quality, and selected patient characteristics. For behavioral trials, we also examined the number of sessions during the first year and presence of several key intervention components (9). For medications, we also examined the percentage retained after run-in, medication type, and intensity of accompanying behavioral intervention.

All analyses were performed by using Stata 10.0 (StataCorp LP, College Station, Texas).

Role of the Funding Source

We worked with 4 USPSTF liaisons at key points throughout the process to develop and refine the analytic framework, address methodological issues, and define scope. This research was funded by the Agency for Healthcare Research and Quality under a contract to support the work of the USPSTF. Agency for Healthcare Research and Quality staff provided project oversight, reviewed the draft report, and assisted in external draft report review.

RESULTS

Key Question 1: Screening for Obesity/Overweight

We identified no trials comparing screening with not screening for adult obesity.

Key Questions 2 and 3: Benefits of Weight-Loss Interventions

We identified 58 trials of benefits of weight-loss interventions. Thirty-eight trials (13 495 participants) involved behaviorally based interventions (23, 27–64), 18 (11 256 participants) involved orlistat plus behavioral interventions (65–82), and 3 (2652 participants) involved metformin plus behavioral interventions (22, 27, 83). About one third of weight-loss trials could not be included in a weight-loss meta-analysis because of missing information, usually a measure of variability around the mean.

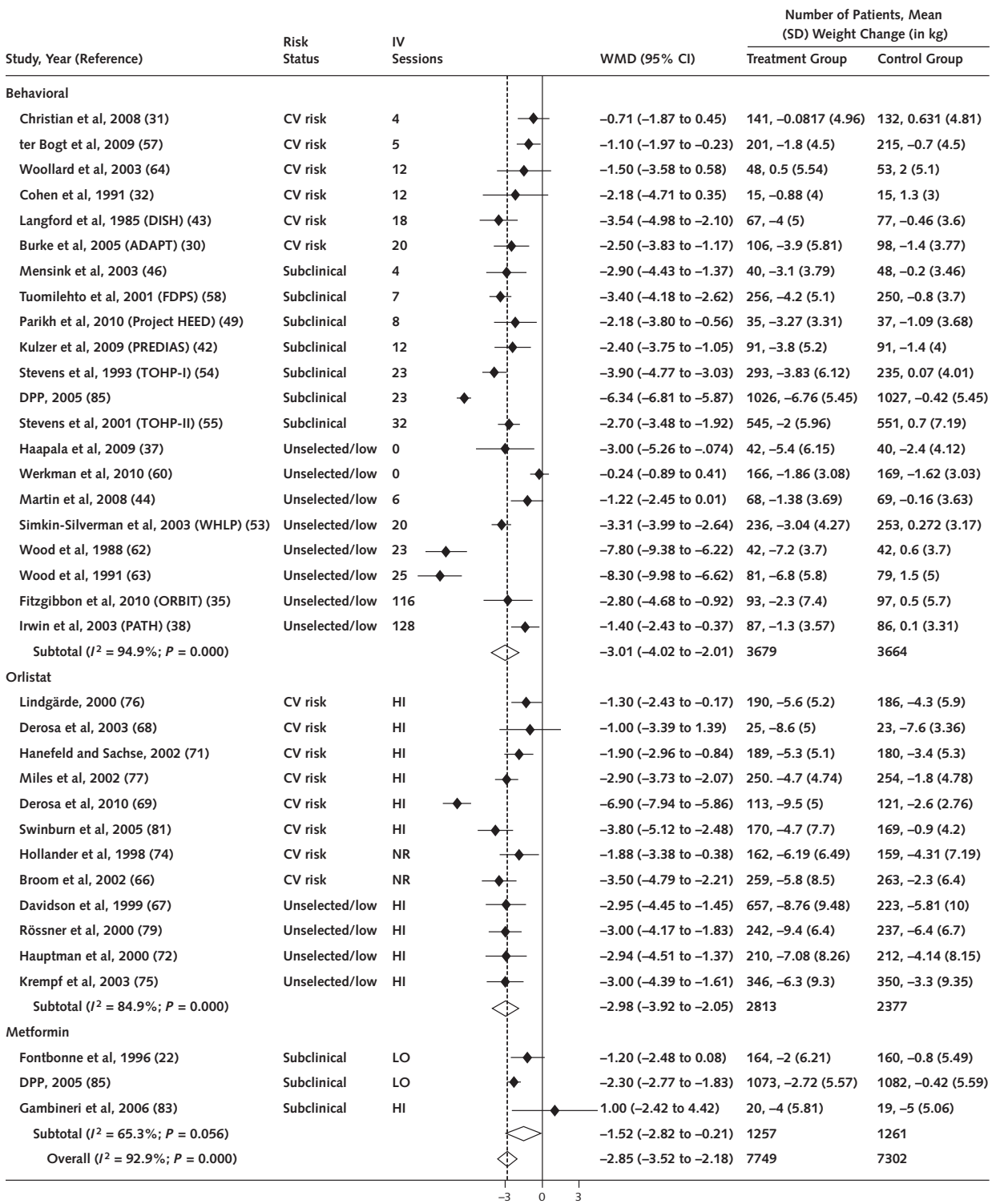
Behavioral trial participants had mean BMIs ranging from 25 to 39 kg/m^2, with an average baseline BMI across all trials (weighted for sample size) of 31.9 kg/m^2. Participants had mean ages of 34 to 70 years. Overall, 60% of participants were female; less than 40% of patients were nonwhite. Orlistat trial participants were 66% female, and less than 12% were nonwhite. Only 1 metformin trial reported ethnicity; 45.3% of patients were nonwhite (84). Fifty-five percent of behavioral trials and 57% of orlistat trials examined participants with clinical or subclinical cardiovascular risk factors. Metformin trials examined participants with diabetes risk factors (prediabetes or elevated waist-to-hip ratio).

Weight Loss

Behavioral treatment trials were fairly high quality, with 24% being rated "good" (**Appendix Table**, available at www.annals.org) (27, 28, 38, 53–56, 58, 61). Among those rated "fair," allocation concealment and blinding of outcomes assessment were frequently unclear or not reported (59% and 83% of trials, respectively). Approximately 30% of fair-quality trials had follow-up of 90% or more at 12 months (**Appendix Table**) (23, 29, 32, 40, 42, 48, 57, 60). Just over one half of all trials limited analyses to completers (23, 27–30, 34, 39, 40, 43, 46, 47, 49–51, 53–55, 57, 58, 60, 62, 63), although 3 trials had low (≤3%) attrition (32, 58, 61). When data substitution was used, studies used baseline-observation-carried-forward (33, 37, 38, 42, 52), multiple imputation (35, 56), last-observation-carried-forward (37, 41, 44, 59), imputation of missing data through random-effects regression (35, 45, 64), multiple imputation method (35, 56), or unspecified methods (31, 48, 61). We did not find an association between effect size and study quality, attrition, or presence of data imputation through meta-regression.

Most trials showed that behavioral interventions had a statistically significant effect on weight loss at 12 to 18 months (23, 27–64). Controls generally lost little or no weight, whereas intervention groups lost 1.5 to 5 kg (3.3 to 11 lb), an average of 4% of baseline weight. In 21 trials that could be combined by meta-analysis, patients receiving behavioral interventions lost 3.0 kg (6.6 lb) more (95% CI, −4.0 to −2.0 kg) than controls after 12 to 18 months (**Figure 1**). Statistical heterogeneity was high (I^2 = 95%)

Figure 1. **Difference between intervention and control groups in weight change at 12 to 18 months.**



Weights are from random-effects analysis. ADAPT = Activity, Diet and Blood Pressure Trial; CV = cardiovascular; DISH = Dietary Intervention to Study Hypertension; DPP = Diabetes Prevention Program; FDPS = Finnish Diabetes Prevention Study; HEED = Help Educate to Eliminate Diabetes; HI = intensive intervention; IV = intervention; LO = brief intervention; NR = not reported; ORBIT = Obesity Reduction Black Intervention Trial; PATH = Physical Activity for Total Health; PREDIAS = Prevention of Diabetes Self-Management Program; Subclinical = trials limited to those with elevated risk but without known disease (prehypertension; impaired glucose tolerance or elevated fasting glucose; borderline high total cholesterol, low-density lipoprotein, or triglyceride levels; low high-density lipoprotein levels; abdominal obesity); TOHP = Trials of Hypertension Prevention; WHLP = Women's Healthy Lifestyle Project; WMD = weighted mean difference.

because the amount of weight change varied greatly. Behavioral interventions lasting longer (24 to 54 months) continued to show greater weight loss (2 to 4 kg [4.4 to 8.8 lb]) compared with controls (28, 46, 53, 55, 58, 61). Weight loss could be maintained for an additional year or more after completion of an active weight-loss phase, particularly with additional support (27, 34, 39, 41, 52, 60).

Interventions with more sessions showed more weight loss—patients receiving 12 to 26 intervention sessions generally lost 4 to 7 kg (8.8 to 15.4 lb) (6% of baseline weight) compared with 1.5 to 4 kg (3.3 to 8.8 lb) (2.8% of baseline weight) in intervention groups with fewer than 12 sessions in the first year. After adjustment for number of sessions in the first year, none of the following demonstrated a relationship with effect size: physical activity sessions, group sessions, individual sessions, technology-based intervention, specific weight-loss goals, spouse or family involvement, addressing barriers to weight loss, motivational assessment (for example, pros and cons of weight loss), self-monitoring, incentives, or support after active intervention phase. However, our confidence in these null results is limited because some behavioral trials did not detail their interventions. These studies may have provided one or more components but not reported them. In addition, more intensive interventions tended to involve more components; disentangling the effect of intensity from specific components was not possible.

The orlistat data were limited in that there was only 1 good-quality trial (69) (**Appendix Table**). Randomization procedures (including allocation concealment) and medication adherence rates were rarely reported. Only 1 study specifically stated that funding was not from a pharmaceutical company (69). Only 5 studies had greater than 80% follow-up at 12 to 18 months (range, 61% to 96%) (69, 72, 74, 79, 82). Follow-up in control groups was often greater than 10% lower than in orlistat groups (72, 74, 79, 82). Over 70% of orlistat trials (65–67, 70–73, 77–82) and 33% of metformin trials (22) used last-observation-carried-forward for data substitution. The remaining analyzed only those with complete data (27, 68, 75, 83) or did not describe data substitution methods (69, 74, 76). We did not note an association between effect size and attrition or presence of data imputation through meta-regression, although power and range of attrition would be somewhat limited.

Orlistat treatment with accompanying behavioral component resulted in weight loss of 5 to 10 kg (11 to 22 lb; 8% of baseline weight) compared with 3 to 6 kg (7 to 13 lb; 5% of baseline weight) with placebo and the same behavioral component (65–82). Almost all orlistat trials used intensive behavioral components. In the 12 trials that could be combined by meta-analysis, participants randomly assigned to orlistat lost 3.0 kg (6.6 lb) more (95% CI, −3.9 to −2.0 kg) than those receiving placebo after 12 months (**Figure 1**). With 1 exception (69), the studies were not highly variable. Limited data showed no dose response (72, 79). Weight loss was maintained with up to 24 to 36 months of orlistat therapy (78, 79). No trials reported weight outcomes after orlistat therapy was stopped. Metformin plus a behavioral intervention was associated with a smaller degree of weight loss (2 to 4 kg [4.4 to 8.8 lb]) (22, 83, 85), although the best evidence was limited to patients with prediabetes (85).

The effect of weight-loss programs among participant subgroups was sparsely reported and often mixed. Behaviorally based interventions seemed on average to lead to less weight loss in black patients and women than nonblack patients and men; effects of baseline BMI and age were mixed (30, 38, 43, 54, 56, 57, 61, 63, 86–88). Medication trials did not examine subgroups, or their findings applied only to patients with prediabetes (27, 87).

Health Outcomes

Included trials did not demonstrate an effect on mortality, cardiovascular disease, hospitalizations, or depression, although data were sparse for all outcomes (**Table 1**) (22, 27, 42, 49, 56, 58, 63, 66, 72, 79, 81, 82, 84, 89–91). The 2 good-quality trials reporting 1 or more of these health outcomes were not powered to detect group differences in any health outcomes other than depressive symptoms (27, 58, 89).

Diabetes Incidence

All intervention types reduced diabetes incidence, particularly in patients with elevated risk (**Table 1**). Behaviorally based interventions (7 to 23 sessions in first year), which led to weight loss of 4 to 7 kg (8.8 to 15.4 lb), cut diabetes incidence by about 50% or more over 2 to 3 years (58, 84). Metformin and orlistat reduced diabetes incidence (22, 78, 82, 84). However, orlistat data may not be reliable and generalizable (78, 82); by year 4, 1 trial had 48% and 68% attrition in the orlistat and placebo groups, respectively (82), and the other administered orlistat after participants experienced at least 5% weight loss during an 8-week very-low-calorie diet (78).

Glucose Tolerance

Behaviorally based interventions, orlistat, and metformin all led to declines in fasting glucose levels in prediabetic and diabetic patients at 12 to 18 months compared with controls (31, 42, 45, 46, 49, 58, 69, 71, 74, 77, 85). Mean decreases in glucose levels were 0.30 and 0.31 mmol/L (5.4 and 5.5 mg/dL) with behavioral interventions and metformin, respectively. Glucose reductions were greater with orlistat (0.672 mmol/L [12.1 mg/dL] greater than placebo), possibly because those studies were conducted in diabetic patients.

Table 1. **Summary of Evidence for Effect of Weight-Loss Interventions on Clinical Outcomes**

Outcome	Trials, *n*	Overall Quality	Summary of Findings
Distal health outcomes			
Behaviorally based interventions			
Death	2	Good	No differences in death rate, but small number of deaths limits conclusions
CVD	4	Fair to good	No differences in CVD events or CVD-related deaths in 3 large good-quality trials; additional fair-quality trial showed no difference in percentage taking cardiovascular medication at 1 y
Hospitalization	1	Fair to good	No differences in hospitalization, but low hospitalization rate limits conclusions
HRQL/depression	3	Fair	None of 3 trials found group differences in depression outcomes; small change in HRQL correlated with weight change in the 1 good-quality trial (DPP)
Pharmacotherapy			
Orlistat			
Death	4	Fair	Each study only had 1 death; in all studies, deaths were in the orlistat group but there was no clear relationship with treatment
HRQL/depression	2	Fair	No difference in depression scores; orlistat group had greater satisfaction with treatment, less overweight distress, and improvement on 1 of 8 subscales (vitality) of SF-36
Metformin			
Death	2	Fair to good	No difference between groups, but small number of deaths limits conclusions
Hospitalization	1	Good	No difference in hospitalization, but low hospitalization rate limits conclusions
CVD	2	Fair to good	No difference in CVD events
HRQL/depression	1	Good	No difference in depression
Intermediate health outcome			
Behaviorally based interventions			
DM	3	Good	In 2 large good-quality trials, approximately twice as many participants in the control group than in the lifestyle intervention group developed DM, but no DM reduction was seen in the small trial, which had very high baseline rates of elevated fasting glucose levels
Pharmacotherapy			
Orlistat			
DM	2	Fair	Both trials reported lower incidence of diabetes (by 9–10 percentage points) in orlistat group, but we had concerns about the generalizability and reliability of these findings
Metformin			
DM	2	Fair to good	Incidence of diabetes was reduced with metformin in the good-quality trial in participants with prediabetes after 3 y (21.7% vs. 28.9%); the smaller trial with unclear adjudication also found decreased risk for diabetes in participants randomly assigned to metformin

CVD = cardiovascular disease; DM = type 2 diabetes mellitus; DPP = Diabetes Prevention Program; HRQL = health-related quality of life; SF-36 = Short Form-36.

Lipids

Pooled estimates for lipid changes with behavioral interventions were at high risk for reporting bias because lipid outcomes were rarely reported (**Figure 2**). Trials included in meta-analyses were more likely to show effects than those not included. Although some trials did find statistically significant results, effect sizes were consistently small (most had reductions in low-density lipoprotein cholesterol level ≤0.26 mmol/L [10 mg/dL]). We concluded that behavioral weight-loss interventions had low or very small effects on low-density and high-density lipoprotein cholesterol and triglyceride levels (23, 29–31, 38, 41, 42, 46, 48, 49, 53, 57, 58, 62–64). Orlistat reduced low-density lipoprotein cholesterol levels by a slightly greater amount (0.29 mmol/L [11 mg/dL] more than placebo), but high-density lipoprotein cholesterol levels were reduced and triglyceride levels did not change (65–82). Metformin did not improve lipid profiles (22, 83, 90).

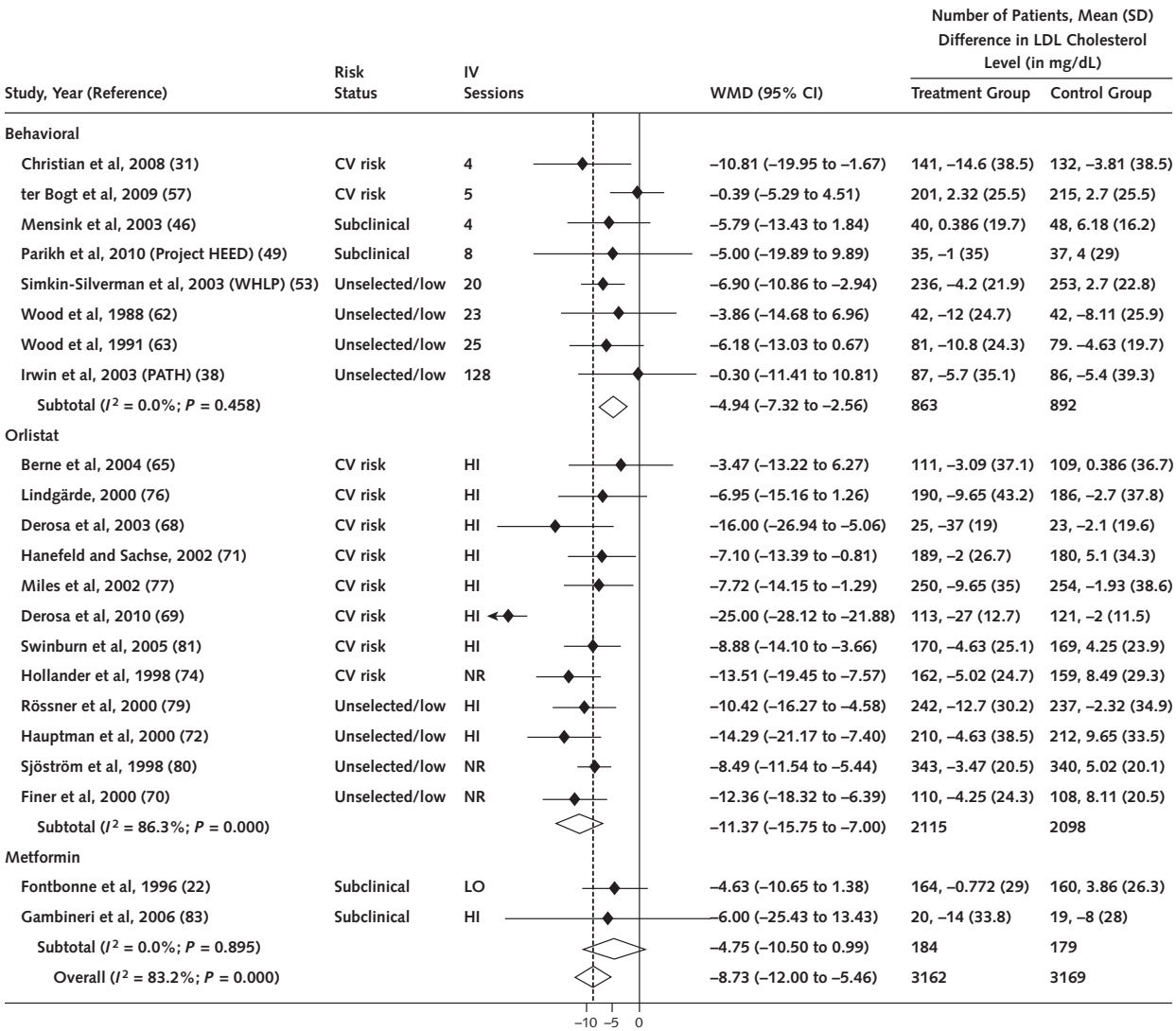
Blood Pressure

Absolute reductions of 2 to 5 mm Hg in systolic and diastolic blood pressure were reported in behaviorally based and orlistat (plus behavioral intervention) trials over 12 to 36 months. When examined with meta-analyses, this translated into approximately 2–mm Hg greater decreases than control conditions after 12 to 18 months with either treatment (**Figure 3**) (23, 29–31, 42, 49, 53–55, 57, 58, 60, 63, 67, 68, 72, 77, 79–81, 90, 91). Behavioral treatment reduced the risk for a hypertension diagnosis in participants with prehypertension (34% and 22% reduced risk at 12 and 18 months, respectively) (54, 55). Metformin did not have favorable effects on blood pressure (22, 90).

Waist Circumference

Waist circumference decreased by 2.7 cm more (CI, −4.1 to −1.4 cm) in behavioral intervention groups

Figure 2. **Difference between intervention and control groups in changes in LDL cholesterol levels.**



Weights are from random-effects analysis. Pooled estimates for lipid changes with behavioral interventions were at high risk for reporting bias because lipid outcomes were rarely reported. To convert LDL cholesterol values to mmol/L, multiply by 0.0259. CV = cardiovascular; HEED = Help Educate to Eliminate Diabetes; HI = intensive intervention; IV = intervention; LDL = low-density lipoprotein; LO = brief intervention; NR = not reported; PATH = Physical Activity for Total Health; Subclinical = trials limited to those with elevated risk but without known disease (prehypertension; impaired glucose tolerance or elevated fasting glucose; borderline high total cholesterol, low-density lipoprotein, or triglyceride levels; low high-density lipoprotein levels; abdominal obesity); WHLP = Women's Healthy Lifestyle Project; WMD = weighted mean difference.

than in control groups. Statistical heterogeneity was high (I^2 = 93.8%), but most trials showed statistically significant group differences (23, 30, 31, 37, 38, 41, 42, 46, 48, 49, 57, 58, 60, 85). Orlistat and metformin reduced waist circumference by 2.3 cm (CI, −3.6 to −0.9 cm) and 1.5 cm (CI, −2.0 to −1.0 cm), respectively, compared with placebo (65, 66, 68, 69, 71, 74–76, 78, 79, 81–83, 85).

Key Question 4: Harms of Weight-Loss Interventions

Behavioral Studies

Ten studies reported on possible harms of behavioral weight-loss interventions. Weight loss reduced total (61) or hip (53, 59) bone mineral density in 3 fair- to good-quality trials (53, 59, 61). Increased physical activity did not result in serious adverse effects or injuries over 1- to 2-year interventions (38, 46, 92, 93). One study reported no increased risk for eating disorder pathology in those participating in weight-loss interventions (94).

Orlistat

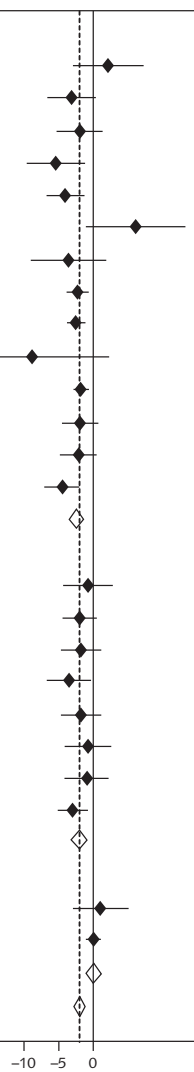
We included 18 RCTs from key questions 2 and 3 (65–82), 5 additional published RCTs not included in key questions 2 and 3 (95–99) (12 174 participants in all trials combined), and 1 United Kingdom event-

monitoring study (100) (16 021 persons) on the harms of orlistat (120 mg 3 times per day). Sixty-two percent of trials recruited participants with at least 1 clinical or subclinical cardiovascular risk factor (65, 66, 68, 69, 71, 74, 76–78, 81, 82, 95–98). Participants were 41 to 59 years of age; 66% of patients were female, and less than 15% were nonwhite. Although median trial duration was 52 weeks, 5 trials provided data beyond 52 weeks.

Participants randomly assigned to receive orlistat were more likely to experience adverse effects and withdraw from trials because of adverse effects than those assigned to placebo (**Table 2**) (65–82, 95–99, 101). Withdrawals were primarily due to gastrointestinal symptoms. In included studies, serious adverse effects were not increased with orlistat compared with placebo (66, 68, 69, 75, 76, 78–82, 95, 96, 99). Orlistat was associated with a decrease in some fat-soluble vitamin levels compared with placebo (73, 74, 79, 82, 99). Data did not suggest that higher dosages were associated with elevated adverse effect rates, although results were mixed (72, 73, 79, 99).

Figure 3. **Difference between intervention and control groups in changes in systolic blood pressure.**

Study, Year (Reference)	Risk Status	IV Sessions	WMD (95% CI)	Number of Patients, Mean (SD) Change in Blood Pressure (in mm Hg)	
				Treatment Group	Control Group
Behavioral					
Christian et al, 2008 (31)	CV risk	4	2.11 (–2.78 to 7.00)	141, –2.55 (20.4)	132, –4.66 (20.8)
ter Bogt et al, 2009 (57)	CV risk	5	–3.20 (–6.45 to 0.05)	201, –6.9 (18.6)	215, –3.7 (14.9)
Burke et al, 2005 (ADAPT) (30)	CV risk	20	–2.00 (–5.10 to 1.10)	106, 2 (11.4)	98, 4 (11.1)
Anderssen et al, 1995 (ODES) (29)	CV risk	159	–5.40 (–9.41 to –1.39)	65, –5.9 (9.1)	43, –0.5 (11.2)
Tuomilehto et al, 2001 (FDPS) (58)	Subclinical	7	–4.00 (–6.53 to –1.47)	256, –5 (14)	250, –1 (15)
Parikh et al, 2010 (Project HEED) (49)	Subclinical	8	6.00 (–0.97 to 12.97)	35, –1 (13)	37, –7 (17)
Kulzer et al, 2009 (PREDIAS) (42)	Subclinical	12	–3.60 (–8.81 to 1.61)	91, –4.6 (19.1)	91, –1 (16.7)
Stevens et al, 1993 (TOHP-I) (54)	Subclinical	23	–2.30 (–3.69 to –0.91)	293, –5.4 (8.56)	235, –3.1 (7.66)
DPP et al, 2005 (90)	Subclinical	23	–2.50 (–3.61 to –1.39)	1026, –3.4 (12.8)	1027, –0.9 (12.8)
Mitsui et al, 2008 (23)	Subclinical	24	–8.80 (–19.60 to 2.00)	22, –10 (21.6)	21, –1.2 (13.9)
Stevens et al, 2001 (TOHP-II) (55)	Subclinical	32	–1.80 (–2.70 to –0.90)	533, –3.6 (7.9)	525, –1.8 (7)
Werkman et al, 2010 (60)	Unselected/low	0	–1.91 (–4.32 to 0.50)	166, –6.5 (9.93)	169, –4.59 (12.4)
Simkin-Silverman et al, 2003 (WHLP) (53)	Unselected/low	20	–2.20 (–4.62 to 0.22)	236, –2.7 (13.7)	253, –0.5 (13.5)
Wood et al, 1991 (63)	Unselected/low	25	–4.50 (–6.84 to –2.16)	81, –4.5 (8)	79, 0 (7.1)
Subtotal (I^2 = 32.8%; P = 0.112)			–2.48 (–3.25 to –1.71)	3252	3175
Orlistat					
Lindgärde, 2000 (76)	CV risk	HI	–0.80 (–4.18 to 2.58)	190, –4.9 (17.7)	186, –4.1 (15.7)
Derosa et al, 2003 (68)	CV risk	HI	–2.00 (–4.26 to 0.26)	25, –6 (3.2)	23, –4 (4.59)
Miles et al, 2002 (77)	CV risk	HI	–1.80 (–4.48 to 0.88)	250, –2.1 (15.3)	254, –0.3 (15.4)
Swinburn et al, 2005 (81)	CV risk	HI	–3.54 (–6.49 to –0.59)	170, –4.05 (13)	169, –0.51 (14.7)
Davidson et al, 1999 (67)	Unselected/low	HI	–1.80 (–4.46 to 0.86)	657, –0.8 (15.3)	223, 1 (18.3)
Rössner et al, 2000 (79)	Unselected/low	HI	–0.80 (–3.96 to 2.36)	242, –2.7 (16.5)	237, –1.9 (18.6)
Hauptman et al, 2000 (72)	Unselected/low	HI	–1.00 (–3.96 to 1.96)	210, 2 (15.5)	212, 3 (15.5)
Sjöström et al, 1998 (80)	Unselected/low	NR	–3.00 (–4.95 to –1.05)	343, –2 (12.9)	340, 1 (13)
Subtotal (I^2 = 0.0%; P = 0.828)			–2.04 (–2.97 to –1.11)	2087	1644
Metformin					
Fontbonne et al, 1996 (22)	Subclinical	LO	1.00 (–2.84 to 4.84)	164, –0.88 (18)	160, –1.88 (17.3)
DPP, 2005 (90)	Subclinical	LO	–0.01 (–0.89 to 0.87)	1017, –0.91 (12.8)	1027, –0.9 (6.41)
Subtotal (I^2 = 0.0%; P = 0.615)			0.04 (–0.81 to 0.89)	1181	1187
Overall (I^2 = 49.0%; P = 0.004)			–2.01 (–2.68 to –1.34)	6520	6006



Weights are from random-effects analysis. ADAPT = Activity, Diet and Blood Pressure Trial; CV = cardiovascular; DPP = Diabetes Prevention Program; FDPS = Finnish Diabetes Prevention Study; HEED = Help Educate to Eliminate Diabetes; HI = intensive intervention; IV = intervention; LO = brief intervention; NR = not reported; ODES = Oslo Diet and Exercise Study; PATH = Physical Activity for Total Health; PREDIAS = Prevention of Diabetes Self-Management Program; Subclinical = trials limited to those with elevated risk but without known disease (prehypertension; impaired glucose tolerance or elevated fasting glucose; borderline high total cholesterol, low-density lipoprotein, or triglyceride levels; low high-density lipoprotein levels; abdominal obesity); TOHP = Trials of Hypertension Prevention; WHLP = Women's Healthy Lifestyle Project; WMD = weighted mean difference.

Table 2. **Summary of Medication Harms**

Adverse Events	Trials in Meta-analysis, Additional Trials, *n*, *n*	Meta-analysis Results: Relative Risk (95% CI)	Weighted Means, %	Results From Studies Not in Meta-analysis	Comments
Orlistat					
Withdrawals due to adverse effects	23, 0	1.67 (1.32–2.13)	IG: 8 CG: 4	–	GI symptoms were main reason for withdrawal
Any	8, 0	1.10 (1.03–1.17)	IG: 78 CG: 70	–	GI symptoms were main reason for AEs
Serious	11, 2	1.21 (0.88–1.68)	IG: 10 CG: 9	0 serious AEs in either treatment group in 2 trials	Examples of serious events included fecal incontinence, diverticulitis, abdominal pain
GI	18, 0	1.42 (1.33–1.52)	IG: 83 CG: 59	–	GI symptoms were of mild to moderate intensity and often resolved spontaneously
Hypoglycemia	0, 3	–	–	2 of 3 found increased incidence of hypoglycemia with orlistat	–
Bone mineral density	0, 1	–	–	In small subsample (n = 30) of larger study, bone density did not differ between group	–
Vitamin deficiencies	0, 5	–	–	5 of 5 studies found lower vitamin E with orlistat; 4 of 4 studies found lower β-carotene levels with orlistat; 1 of 2 trials found lower vitamin A levels; 1 of 1 study found lower vitamin K levels; 5 of 5 studies found that orlistat recipients required more vitamin supplementation during the study	–
Liver injury	0, 1 (event monitoring cohort)	–	–	UK monitoring study reported elevated liver test results in 2 cases of 16 021 dispenses analyzed; no cases of serious hepatic adverse reactions	FDA recently added warning to label to orlistat about possible risk for severe liver disease
Metformin					
Withdrawals	2, 0	3.92 (1.23–12.57)	IG: 5 CG: 1	–	–
Any	2, 0	4.83 (0.84–27.63)	IG: 46 CG: 16	–	–
Serious	0	–	–	–	–
GI	1, 3	–	–	Increased risk of GI AEs in metformin group	Main GI symptoms included diarrhea, flatulence, nausea, vomiting
Hypoglycemia	0	–	–	–	–
Bone density	0	–	–	–	–

AE = adverse event; CG = control group; FDA = U.S. Food and Drug Administration; GI = gastrointestinal; IG = intervention group; UK = United Kingdom.

Metformin

We included 4 trials on harms of metformin (850 mg twice daily): 3 trials from key questions 2 and 3 (22, 83, 86) and 1 additionally published RCT (102) (2712 participants). Participants randomly assigned to receive metformin were more likely than placebo recipients to have and withdraw because of adverse events (**Table 2**) (22, 83, 102). Gastrointestinal symptoms were the main reason for excess adverse effects (22, 83, 86, 102). No studies reported serious adverse effects.

DISCUSSION

Because we found no trials directly examining the benefits and harms of obesity screening followed by expected appropriate treatment in adults, we focused on effectiveness and harms of primary care–relevant weight-loss interventions. Behavioral treatment trials were fairly recent and of high quality. However, orlistat trials were generally lower quality. Participants in behavioral treatment trials providing 12 to 26 intervention sessions during the first year lost 4 to 7 kg (8.8 to 15.4 lb) (average, 6% of baseline weight) at 12 to 18 months, compared with little to no weight loss in control groups. Participants receiving orlistat plus intensive behaviorally based intervention lost 5 to 10 kg (11 to 22 lb) (average, 8% of baseline weight), compared with 3 to 6 kg in the placebo groups. Metformin was associated with less weight loss (2 to 4 kg [4.4 to 8.8 lb]). Long-term weight loss (>18 months) was sparsely reported, but weight loss generally persisted with continued treatment. Five percent weight loss is considered clinically meaningful and is a primary weight-loss outcome according to the U.S. Food and Drug Administration (103).

Most (104–107), but not all (108), epidemiologic data suggest that intentional weight loss less than 9 kg is not associated with reduced mortality. Epidemiologic data, however, are mixed and confounded by several factors, particularly health status. Prospective cohort studies of patients undergoing bariatric surgery show substantial improvements in health. Weight loss with surgery, however, is generally 25 to 50 kg (55 to 110 lb) (109, 110).

Because health outcome data were insufficient, we examined the metabolic consequences of weight-loss interventions. Two fair- to good-quality trials showed that diabetes incidence was reduced by 30% to 50% with behavioral weight-loss interventions among overweight and obese patients with elevated plasma glucose levels. Behavioral weight-loss interventions had little to no effect on lipids. Improved cholesterol levels may require large amounts of weight loss (111). Lowering low-density lipoprotein cholesterol levels with orlistat may reflect reduced fat absorption (112). Although summary measures showed small blood pressure reductions, absolute reductions of 2 to 5 mm Hg were reported in some orlistat and behaviorally based trials over 12 to 36 months, consistent with findings of a previous meta-analysis (113). Reductions in diastolic blood pressure of 5 to 6 mm Hg over 5 to 10 years have been associated with small reductions in stroke and coronary heart disease events (114).

Higher treatment intensity was associated with greater weight loss, despite limitations in our measure of treatment intensity. Most higher-intensity interventions included self-monitoring, setting goals, addressing barriers to change, and strategizing about maintaining long-term changes. However, we found that no component was associated with degree of weight loss in meta-regression. Specific articulation of essential elements of effective interventions was not possible.

Methods used to measure obesity in clinical practice (for example, BMI and waist circumference) are low cost and cause no direct physical harms. Secondary harms could include labeling stigma, higher insurance premiums, or reinforcement of poor self-esteem. Misclassifying a person's risk status is possible if current BMI cut-offs are used during screening because BMI may predict future health risk differently among various ethnic and age groups (115, 116).

Weight loss may be associated with decreased bone density, but data are lacking on post–weight-loss bone density and subsequent fracture risk. The validity of measuring bone changes during weight loss is also unclear. Fat distribution changes may alter bone measurement despite stable bone (117–119). Limited data suggested no increased risk for serious injuries or eating disorders.

Orlistat and metformin caused mild to moderate gastrointestinal side effects resulting in discontinuation of therapy. Our inclusion and exclusion criteria were not designed to identify rare harms. We did not find studies associating orlistat with liver, kidney, or pancreas damage, other than case reports. However, in May 2010, the U.S. Food and Drug Administration revised its label for orlistat, 120 mg (prescription) and 60 mg (over-the-counter), to include "new safety information about cases of severe liver injury that have been reported rarely with the use of this medication" (120). Orlistat has been recently associated with possible kidney and pancreas damage (121). Indeed, antiobesity medications have a long history of removal from the market or failing U.S. Food and Drug Administration approval (122–124).

Several factors limited this evidence review. Because of missing information, we could not include about one third of trials in meta-analyses. Intermediate physiologic outcomes were even less likely to be studied and available for meta-analyses. We excluded 143 studies because control groups had more than minimal interventions (considered comparative effectiveness), including Look AHEAD, a weight-loss intervention trial in diabetic patients (125). Its findings were similar to and slightly more positive than the findings of included trials. Comparative-effectiveness trials would shed more light on effective intervention components and are being reviewed elsewhere (126).

Few studies were conducted in primary care. Interventions were often intensive and possibly difficult to implement in primary care settings (although providers could refer to them). No trial had a mean BMI in the class III obese range (>40 kg/m^2), so generalizability to extreme obesity is unknown. Because most medication trials had run-in periods, participants were probably more motivated, adherent, and responsive than primary care populations. Our results, especially medication findings, are possibly biased by high attrition.

We did not systematically examine the best screening approach for obesity. A growing body of evidence suggests that waist-to-hip ratio or waist circumference may be better predictors of future health effects than is BMI (127–135), especially for some subgroups (116, 136). Systematically rereviewing the best screening tool for adult obesity should be of high priority. We did not systematically review cost-effectiveness data. The economic impact of weight-loss interventions is an important clinical consideration.

Metformin is the only off-label medication we included. Other medications used off-label for weight loss include zonisamide, an antiepileptic agent (137). We did not examine antiobesity drugs in development, including lorcaserin; a combination of phentermine plus topiramate; or a combination naltrexone plus bupropion. We did not include phentermine because it is approved only for short-term use.

In summary, we found no direct evidence on benefits and harms of primary care–based obesity screening but did find that behavioral weight-loss interventions with or without orlistat or metformin yielded clinically meaningful weight loss; however, health outcomes data were sparse.

Harms of behavioral weight-loss interventions were minimal; data were insufficient on serious harms from medications. Long-term weight and health outcomes data were lacking and should be a high priority for future study. Research should clarify which benefits are derived specifically from weight loss itself or from behavioral mediators, such as physical activity or dietary changes.

From Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon.

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Current author addresses and author contributions are available at www.annals.org.

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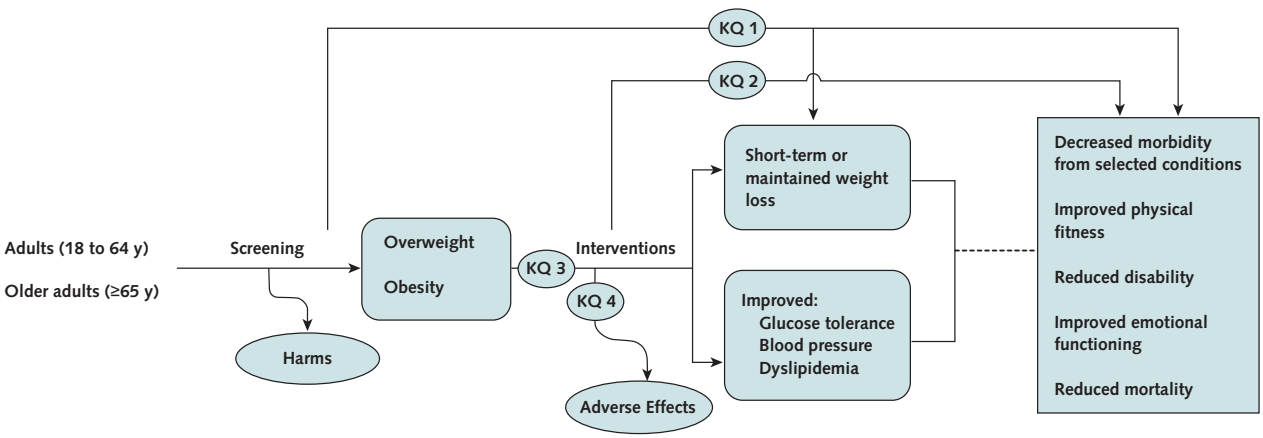
Current Author Addresses: Drs. LeBlanc, O'Connor, Whitlock, Patnode, and Kapka: Center for Health Research, Kaiser Permanente Northwest, 3800 North Interstate Avenue, Portland, OR 97227.

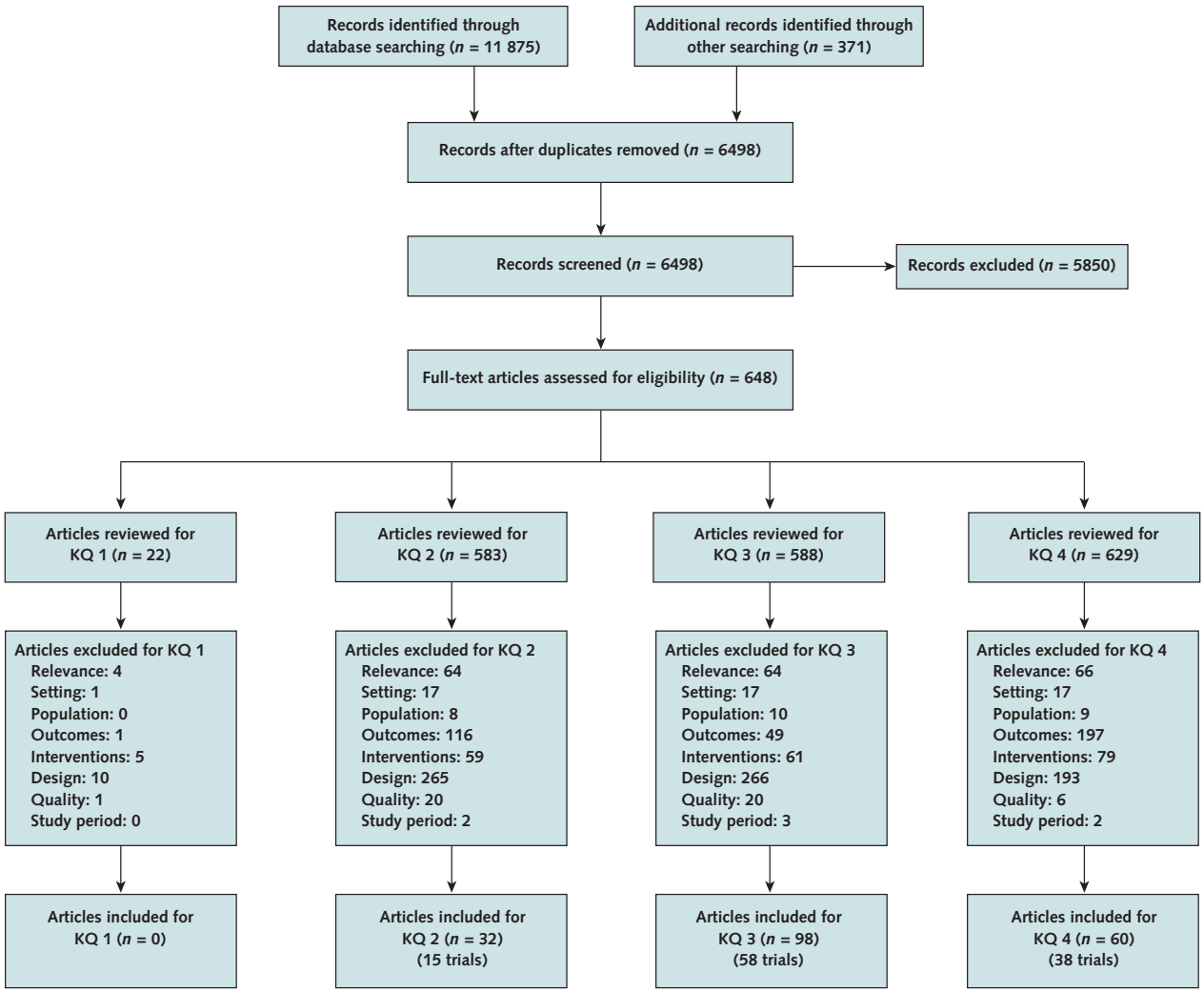
Author Contributions: Conception and design: E.S. LeBlanc, E. O'Connor, E. Whitlock, C.D. Patnode.
Analysis and interpretation of the data: E.S. LeBlanc, E. O'Connor, E. Whitlock, T. Kapka.
Drafting of the article: E.S. LeBlanc, E. Whitlock, C.D. Patnode, T. Kapka.
Critical revision of the article for important intellectual content: E.S. LeBlanc, E. O'Connor, E. Whitlock, C.D. Patnode, T. Kapka.
Final approval of the article: E.S. LeBlanc, E. O'Connor, E. Whitlock, C.D. Patnode, T. Kapka.
Statistical expertise: E. O'Connor.
Obtaining of funding: E. Whitlock.
Collection and assembly of data: E.S. LeBlanc, E. O'Connor, T. Kapka.

Appendix Figure 1. **Analytic framework: primary care screening and interventions for obesity and overweight.**



KQ 1: Is there direct evidence that primary care screening programs for adult obesity or overweight improve health outcomes or result in short-term (12 to 18 mo) or sustained (>18 mo) weight loss or improved physiologic measures (i.e., glucose tolerance, blood pressure, and dyslipidemia)? a) How well is weight loss maintained after an intervention is completed? KQ 2: Do primary care–relevant interventions (behaviorally based interventions and/or pharmacotherapy) in obese or overweight adults lead to improved health outcomes (morbidity from diabetes mellitus, cardiovascular disease, cancer, arthritis, asthma, sleep apnea, depression, emotional functioning, physical fitness capacity or performance, physical functioning, disability, mortality)? a) What are common elements of efficacious interventions? b) Are there differences in efficacy between patient subgroups (i.e., age 65 y or older, sex, race/ethnicity, degree of obesity, baseline cardiovascular risk)? KQ 3: Do primary care–relevant interventions in obese or overweight adults lead to short-term or sustained weight loss, with or without improved physiologic measures? a) How well is weight loss maintained after an intervention is completed? b) What are common elements of efficacious interventions? c) Are there differences in efficacy between patient subgroups (i.e., age 65 y or older, sex, race/ethnicity, degree of obesity, baseline cardiovascular risk)? KQ 4: What are the adverse effects of primary care–relevant interventions in obese or overweight adults (e.g., nutritional deficits, cardiovascular disease, bone mass loss, injuries, death)? a) Are there differences in adverse effects between patient subgroups (i.e., age 65 y or older, sex, race/ethnicity, degree of obesity, baseline cardiovascular risk status)? KQ = key question.

Appendix Figure 2. **Literature search and selection.**



KQ = key question.

Appendix Table. Outcomes Reported and Quality Issues for Included Trials

Study, Year (Reference)	Outcomes								Allocation Concealment	Quality Issues			
	Weight Loss	Distal Health Outcome	DM	Glucose Tolerance	Lipids	Blood Pressure	Waist Circumference	Adverse Events		BOA	Retention*	ITT Analysis	Overall Quality and Other Quality Concerns or Clarifications
Behavioral trials													
With CV risk factor													
Diabetes													
Christian et al, 2008 (31)	XX			X	XX	XX	XX		Yes	NR	88%	Unclear	Fair Use of the term "ITT" not clear
Mayer-Davis et al, 2004 (45)	X			X	X	X			NR	NR	81%	RER	Fair
Hypertension													
Burke et al, 2005 (ADAPT) (30)	XX					XX	XX		Yes	NR	80%	No	Fair
Cohen et al, 1991 (32)	XX					X			NR	NR	100%	NA	Fair Small number of participants
Davis et al, 1992 (TAIM) (34)	X	X				X			Yes	Yes (blood pressure) NR (weight loss)	Unclear	No	Fair Retention NR at 12 mo, 89% at 6 mo, 59% at 24 mo
Jones et al, 1999 (HOT) (40)	X					X			Unclear	NR	91%	No	Fair Unclear information on outcome blinding (described as "single blind"), assessment and statistical methods not well described
Kastarinen et al, 2002 (LIHEF) (41)	X			X	X	X	X		Yes	NR	83%	LOCF	Fair Retention lower in control than intervention group at 12 mo (77% vs. 88%)
Langford et al, 1985 (DISH) (43)	XX								NR	NR	82%	No	Fair Attrition lower in control than intervention group (77% vs. 87%) Minimal description of control group contact
Whelton et al, 1998 (TONE) (61)	X	X				X		X	NR	Yes	98%	NR	Good
Multiple risk factors													
Anderssen et al, 1995 (ODES) (29)	X	X			X	XX			Yes	NR	95%	No	Fair Lack of information about assessment blinding, but well-defined procedures probably minimized bias
Svetkey et al, 2008 (WLM) (56)	X	X							Yes	Yes	95%	MImp	Good
ter Bogt et al, 2009 (57)	XX			XX	XX	XX	XX		NR	NR	91%	No	Fair Lack of information about assessment blinding, but well-defined procedures probably minimized bias
Woollard et al, 2003 (64)	XX				X				NR	No (weight loss), yes (lipid)	71%	RER	Fair Outcome measurement by nurse giving intervention Details of outcome measures NR
Subclinical													
Parikh et al, 2010 (Project HEED) (49)	XX		X	XX	XX	XX	XX		NR	NR	73%	No	Fair Small number of participants
HPT, 1990 (28)	X					X			Yes	Likely	91%	No	Good

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Appendix Table—Continued

Study, Year (Reference)	Outcomes								Allocation Concealment	Quality Issues			
	Weight Loss	Distal Health Outcome	DM	Glucose Tolerance	Lipids	Blood Pressure	Waist Circumference	Adverse Events		BOA	Retention*	ITT Analysis	Overall Quality and Other Quality Concerns or Clarifications
DPP, 2005 (85)	XX	X	X	XX		XX	XX	X	Yes	Partial	95%	No	Good Outcomes assessment seems unblinded but required initial certification and annual recertification of assessment staff, which should minimize if not eliminate bias introduced by lack of blinding
Stevens et al, 1993 (TOHP I) (54)	XX					XX			Yes	Yes	94%	No	Good
Stevens et al, 2001 (TOHP II) (55)	XX					XX			Yes	Yes	92%	No	Good
Villareal et al, 2008 (59)	X	X		X	X	X		X	Yes	Yes	89%	LOCF	Fair
Mensink et al, 2003 (46)	XX			XX	XX		XX	X	Unclear	NR	81%	No	Fair
Tuomilehto et al, 2001 (58)	XX	X	X	XX	XX	XX	XX		Unclear	NR	97%	No	Good Uncertain if allocation concealed; person scheduling baseline appointments was blinded to randomization list, but there is uncertainty whether this was the person who conducted the assessment
Kulzer et al, 2009 (42)	XX	X		XX	XX	XX	XX		NR	NR	91%	BOCF	Fair Group-specific follow-up NR
Mitsui et al, 2008 (23)	X			XX	XX	XX	XX		NR	NR	94%	No	Fair Small number of participants higher proportion of control group had the metabolic syndrome than intervention group (32% vs. 21%)
Low risk or unselected													
Cussler et al, 2008 (33)	X								NR	NR	82%	BOCF	Fair Did not adjust analysis for cluster randomization
Fitzgibbon et al, 2010 (ORBIT) (35)	XX								Yes	No	89%	MImp	Fair Assessment not blinded, but well-defined procedures probably minimized bias
Haapala et al, 2009 (37)	XX						XX		Yes	NR	68%	BOCF or LOCF (value that was highest)	Fair
Irwin et al, 2003 (PATH) (38)	XX			X	XX		XX	X	Yes	Yes	98%	BOCF	Good
Jeffery et al, 1993 (39)	X								NR	NR	87%	No	Fair Measurement procedures not well described, attrition by group NR
Martin et al, 2008 (44)	XX								NR	NR	65%	LOCF	Fair Group-specific attrition not provided at 12 mo, retention was lower in intervention group than control group at 6-mo (71% vs. 88%) and 18-mo (54% vs. 77%) follow-up
Moore et al, 2003 (47)	X								Yes	Yes	67%	No	Fair
Narayan et al, 1998 (48)	X		X	X	X	X	X		NR	NR	93%	NR	Fair BMI, weight, waist circumference, and fasting glucose levels higher in intervention group at baseline; measurement procedures not clearly described.

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Appendix Table—Continued

Study, Year (Reference)	Outcomes								Allocation Concealment	Quality Issues			
	Weight Loss	Distal Health Outcome	DM	Glucose Tolerance	Lipids	Blood Pressure	Waist Circumference	Adverse Events		BOA	Retention*	ITT Analysis	Overall Quality and Other Quality Concerns or Clarifications
Perri et al, 1988 (50)	X								NR	NR	74%	No	Fair Little information about baseline comparability
Pritchard et al, 1999 (51)	X							Likely	NR	66%	No	Fair	Lower retention in dietitian group than other 2 groups (54.5% vs. 71% and 71%); outcomes reported only for overweight/obesity, hypertension, and DM subgroups, although randomization was not stratified by disease status; statistical procedures not well-described
Silva et al, 2010 (52)	X								NR	NR	81%	BOCF	Fair Lower retention in control group than intervention group (80% vs. 93%); lack of information about blinding of assessment and blinding, but well-defined procedures probably minimized bias
Simkin-Silverman et al, 2003 (WHLP) (53)	XX			XX	XX	XX			Yes	Yes	94%	No	Good
Werkman et al, 2010 (60)	XX					XX	XX		No	NR	95%	No	Fair Did not have blinded outcomes assessment, but well-defined procedures probably minimized bias; analyzed only male participants (so not truly randomized comparison)
Wood et al, 1991 (63)	XX	X			XX	XX			NR	NR	88%	No	Fair
Wood et al, 1988 (62)	XX				XX				Yes	NR	85%	No	Fair Retention higher in exercise than other groups (90% vs. 81% and 82%)
Medication trials													
Orlistat													
Berne et al, 2005 (65)	X			X	XX	X	XX	XX	NR	Yes	86%	LOCF	Fair Possible selective reporting of weight outcomes
Broom et al, 2002 (66)	XX			X	X	X	X	XX	NR	Yes	65%	LOCF	Fair Statistical procedures not well described
Davidson et al, 1999 (67)	XX			X	X	XX		XX	NR	Yes	66%	LOCF	Fair High dropout during run-in
Derosa et al, 2003 (68)	XX				XX	XX	XX	XX	Yes	Yes	96%	No	Fair Small sample measurement methods not clearly described

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Appendix Table—Continued

Study, Year (Reference)	Outcomes								Allocation Concealment	Quality Issues			
	Weight Loss	Distal Health Outcome	DM	Glucose Tolerance	Lipids	Blood Pressure	Waist Circumference	Adverse Events		BOA	Retention*	ITT Analysis	Overall Quality and Other Quality Concerns or Clarifications
Derosa et al, 2010 (69)	XX			XX	XX		XX	XX	Yes	Yes	92%	NR	Good
Finer et al, 2000 (70)	X				XX			XX	Yes	Yes	61%	LOCF	Fair
Hanefeld and Sachse, 2002 (71)	XX			XX	XX	X	XX	XX	NR	Yes	69%	LOCF	Fair Measurement procedures not well described
Hauptman et al, 2000 (72)	XX	X		XX	XX	XX		XX	NR	Yes	67%	LOCF	Fair
Hill et al, 1999 (73)	X			X	X	X		XX	NR	Yes	74%	LOCF	Fair Measurement procedures not well described Did not report whether placebo matched active medicine
Hollander et al, 1998 (74)	XX			XX	XX		XX	XX	NR	Yes	79%	Unclear	Fair
Krempf et al, 2003 (75)	XX				X		XX	XX	NR	Yes	61%	No	Fair
Lindgärde, 2000 (76)	XX			XX	XX	XX	X	XX	NR	Yes	86%	NR	Fair
Miles et al, 2002 (77)	XX			XX	XX	XX		XX	NR	Yes	60%	LOCF	Fair Did not report whether placebo matched active medicine
Richelsen et al, 2007 (78)	X		X	X	X	X	X	XX	Yes	Yes	65%	LOCF	Fair
Rössner et al, 2000 (79)	XX	X		XX	XX	XX	X	XX	NR	Yes	72%	LOCF	Fair
Sjöström et al, 1998 (80)	X			XX	XX	XX		XX	Likely	Yes	79%	LOCF	Fair
Swinburn et al, 2005 (81)	XX	X		XX	XX	XX	XX	XX	NR	Yes	79%	LOCF	Fair Did not report whether placebo matched active medicine
Torgerson et al, 2004 (XENDOS) (82)	X		X	X	X	X	X	XX	Yes	Yes	83%	LOCF	Fair Higher retention in control than intervention group (90 vs. 78)
Metformin													
Fontbonne et al, 1996 (BIGPRO) (22)	XX	X	X	XX	XX	XX		XX	NR	Yes	71%	LOCF	Fair
Gambineri et al, 2006 (83)	XX			XX	XX		XX	XX	NR	NR	98%	No	Fair Not double blind—only participants blinded
DPP, 2005 (85)	XX	X	X	XX	X	XX	XX	X	Yes	Partial	95%	No	Good Nonlaboratory outcomes assessment seems unblinded but required initial certification and annual recertification of assessment staff, which should minimize if not eliminate bias introduced by lack of blinding

ADAPT = Activity, Diet and Blood Pressure Trial; BIGPRO = BIGuanides and Prevention of the Risks in Obesity; BMI = body mass index; BOA = blinding of outcomes assessment; BOCF = baseline-observation-carried-forward method; CV = cardiovascular; DM = diabetes mellitus; DISH = Dietary Intervention to Study Hypertension; DPP = Diabetes Prevention Program; HEED = Help Educate to Eliminate Diabetes; HOT = Hypertension Optimal Treatment; HPT = Hypertension Prevention Trial; ITT = intention-to-treat; LIHEF = Lifestyle Intervention against Hypertension in Eastern Finland; LOCF = last-observation-carried-forward method; MImp = multiple imputation method; NA = not applicable; NR = not reported; ODES = Oslo Diet and Exercise Study; ORBIT = Obesity Reduction Black Intervention Trial; PATH = Physical Activity for Total Health; RER = imputation of missing data through use of random-effects regression; TAIM = Trial of Antihypertensive Interventions and Management; TOHP = Trials of Hypertension Prevention; TONE = Trial of Nonpharmacologic Interventions in the Elderly; WHLP = Women's Healthy Lifestyle Project; WLM = Weight Loss Maintenance; X = outcome was reported; XENDOS = XENical in the Prevention of Diabetes in Obese Subjects; XX = outcome was included in the meta-analysis.

* Proportion with follow-up data.