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Behavioral and Pharmacotherapy Weight Loss Interventions to Prevent Obesity-Related Morbidity and Mortality in Adults

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

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IMPORTANCE Overweight and obesity have been associated with adverse health effects.

OBJECTIVE To systematically review evidence on benefits and harms of behavioral and pharmacotherapy weight loss and weight loss maintenance interventions in adults to inform the US Preventive Services Task Force.

DATA SOURCES MEDLINE, PubMed Publisher-Supplied Records, PsycINFO, and the Cochrane Central Register of Controlled Trials for studies published through June 6, 2017; ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform for ongoing trials through August 2017; and ongoing surveillance in targeted publications through March 23, 2018. Studies from previous reviews were reevaluated for inclusion.

STUDY SELECTION Randomized clinical trials (RCTs) focusing on weight loss or weight loss maintenance in adults.

DATA EXTRACTION AND SYNTHESIS Data were abstracted by one reviewer and confirmed by another. Random-effects meta-analyses were conducted for weight loss outcomes in behavior-based interventions.

MAIN OUTCOMES AND MEASURES Health outcomes, weight loss or weight loss maintenance, reduction in obesity-related conditions, and adverse events.

RESULTS A total of 122 RCTs (N = 62 533) and 2 observational studies (N = 209 993) were identified. Compared with controls, participants in behavior-based interventions had greater mean weight loss at 12 to 18 months (−2.39 kg [95% CI, −2.86 to −1.93]; 67 studies [n = 22065]) and less weight regain (−1.59 kg [95% CI, −2.38 to −0.79]; 8 studies [n = 1408]). Studies of medication-based weight loss and maintenance interventions also reported greater weight loss or less weight regain in intervention compared with placebo groups at 12 to 18 months (range, −0.6 to −5.8 kg; no meta-analysis). Participants with prediabetes in weight loss interventions had a lower risk of developing diabetes compared with controls (relative risk, 0.67 [95% CI, 0.51 to 0.89]). There was no evidence of other benefits, but most health outcomes such as mortality, cardiovascular disease, and cancer were infrequently reported. Small improvements in quality of life in some medication trials were noted but were of unclear clinical significance. There was no evidence of harm such as cardiovascular disease from behavior-based interventions; higher rates of adverse events were associated with higher dropout rates in medication groups than in placebo groups.

CONCLUSIONS AND RELEVANCE Behavior-based weight loss interventions with or without weight loss medications were associated with more weight loss and a lower risk of developing diabetes than control conditions. Weight loss medications, but not behavior-based interventions, were associated with higher rates of harms. Long-term weight and health outcomes data, as well as data on important subgroups, were limited.

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Between 2011 and 2014, 73.0% of US men and 66.2% of US women were overweight or had obesity,[1] which are associated with multiple negative health effects.[2-7] Although measuring weight at periodic health examinations is now part of standard clinical practice in most medical settings, rates of consistently and systematically documenting obesity and tracking weight over time are low,[8,9] as are rates of primary care–delivered, weight-related counseling.[8,10-14]

In 2012, the US Preventive Services Task Force (USPSTF) recommended that clinicians screen all adults for obesity and offer or refer patients with body mass index (BMI) of 30 or higher (calculated as weight in kilograms divided by height in meters squared) to intensive, multicomponent behavioral interventions (B recommendation).[15] This review was undertaken to provide current evidence to the USPTF for an updated recommendation on this topic.

Methods

Scope of Review

This review addressed 3 key questions (KQs) (**Figure 1**). Full methodological details (including study selection, excluded studies, and description of data analyses) are publicly available in the full evidence report at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/obesity-in-adults-interventions1.

Data Sources and Searches

In addition to considering all studies from the previous review on this topic,[17] a comprehensive search of MEDLINE, PubMed Publisher-Supplied Records, PsycINFO, and the Cochrane Central Register of Controlled Trials was performed. The search was between January 1, 2010, and June 6, 2017, building on the most recent full search for this topic. We worked with a research librarian to develop the search strategy, which was peer-reviewed by a second research librarian (eMethods in the Supplement). All searches were limited to articles published in English.

In addition to these database searches, ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (http://www.who.int/ictrp) were searched for ongoing trials through August 2017. The reference lists of previously published reviews, meta-analyses, and primary studies were also examined to identify any potential studies for inclusion. The US Food and Drug Administration (FDA) review documents for each included medication were examined to identify any additional studies not published in the primary literature. The searches were supplemented with suggestions from experts and articles identified through news and table-of-contents alerts such as those produced by the USPSTF Scientific Resource Center LitWatch activity.[16] Since June 2017, ongoing surveillance through article alerts and targeted searches of journals with a high impact factor and journals relevant to the topic was conducted to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and therefore the related USPSTF recommendation. The last surveillance was conducted on March 23, 2018, and identified no additional studies.

Study Selection

Two reviewers independently reviewed all identified titles and abstracts and relevant full-text articles against a priori inclusion and exclusion criteria for design, population, intervention, and outcomes (eMethods in the Supplement). Disagreements in the abstract and full-text review were resolved by discussion. Eligible studies included fair- and good-quality randomized clinical trials (RCTs) of primary care–relevant weight loss or weight loss maintenance interventions (behavioral counseling [either alone or part of a multicomponent intervention], training of clinicians, and pharmacologic interventions approved by the FDA as first-line long-term weight loss or weight loss maintenance medications [orlistat, lorcaserin, naltrexone-bupropion, phentermine-topiramate, and liraglutide]). Weight outcomes at least 12 months after intervention start were required. For harms, RCTs, systematic reviews, and large cohort, case-control, or event-monitoring studies were allowed; there was no minimum follow-up.

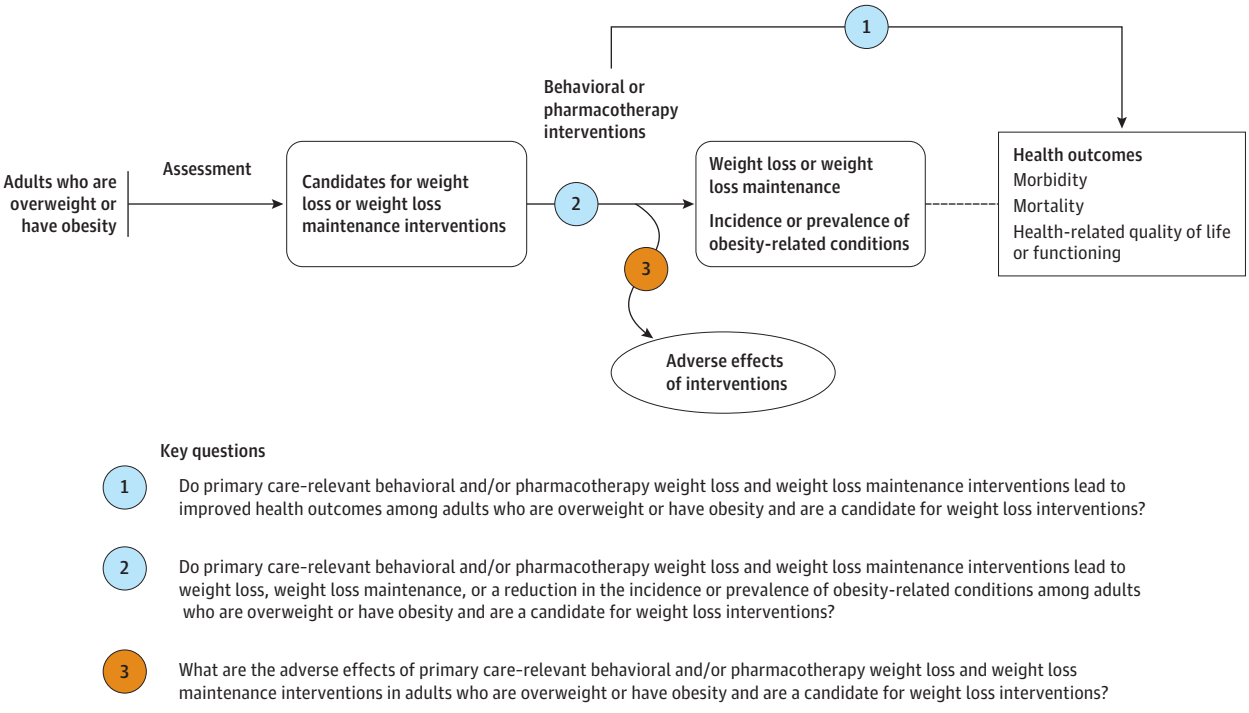
Studies were required to focus on weight loss in adults 18 years or older who were candidates for weight loss or weight loss maintenance interventions and selected based on an above-normal BMI (eg, ≥25) or other weight-related measure (eg, waist circumference). In cases in which lower BMI thresholds were used for eligibility (eg, ≥23) or in which participants were selected based on other cardiovascular risk factors without weight-related eligibility criteria and the focus of the intervention was clearly weight loss, the distribution of the mean BMI at baseline was examined to evaluate potential inclusion. Studies were included in which 100% of the sample had a BMI above 23, 95% of the sample had a BMI above 24, or 90% of the sample had a BMI above 25. Individuals may have had additional risk cardiovascular risk factors (eg, hypertension); however, studies of adults with a chronic disease for which weight loss or weight loss maintenance is part of disease management (eg, known cardiovascular disease, diabetes mellitus) were excluded. In addition, studies in adults with known chronic diseases not generalizable to the primary care population (eg, eating disorders, chronic kidney disease) were excluded. Studies in adults with secondary causes of obesity, in pregnant women, and in institutionalized adults were excluded.

For studies of behavior-based interventions, it was required that controls have no intervention (eg, wait list, usual care, assessment only), minimal intervention (eg, usual care limited to quarterly counseling sessions or generic brochures), or be attention controls (eg, similar format and intensity but different content). For studies of pharmacologic interventions, only placebo-controlled studies in which participants all received the same behavior-based interventions were included. Studies had to report a health outcome (mortality, morbidity, depression, health-related quality of life, and disability), intermediate outcomes (weight measurements, measures of total and central adiposity, incidence or prevalence of obesity-related conditions, and proportion of individuals taking medication for obesity-related conditions), or adverse events (treatment-related harms and discontinuation of medication because of adverse effects at any point during intervention).

Data Extraction and Quality Assessment

Two investigators independently assessed the methodological quality of each study using predefined study design–specific criteria developed by the USPSTF (eMethods in the Supplement).[16] Disagreements in quality were resolved by discussion. Each study was given a final quality rating of good, fair, or poor. Studies were excluded as poor quality if there were several important major risks of biases, including high attrition (generally >40%) or differential attrition

Figure 1. Analytic Framework: Behavioral and Pharmacotherapy Weight Loss Interventions to Prevent Obesity-Related Morbidity and Mortality in Adults



Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. A dashed line indicates a relationship between an intermediate outcome and a health outcome that is presumed to describe the natural progression of the disease. Refer to the USPSTF Procedure Manual for further details.[16]

between groups (generally >20%), lack of baseline comparability between groups without adjustment, methods for ascertainment of weight outcomes that were unclear or that differed between groups, or issues in trial conduct, analysis, or reporting of results that could invalidate results. Because this review was an update, critical appraisal of the original studies was not repeated, but the quality rating was confirmed during data abstraction. One reviewer extracted key elements and a second reviewer checked the data for accuracy. For each study, general characteristics of the study, clinical and demographic characteristics of the sample and setting, analytic methods, and results were extracted. This included both absolute weight change and percentage of participants who achieved 5% loss of their baseline weight, which is considered by the FDA to be clinically meaningful and a primary weight loss outcome.[18]

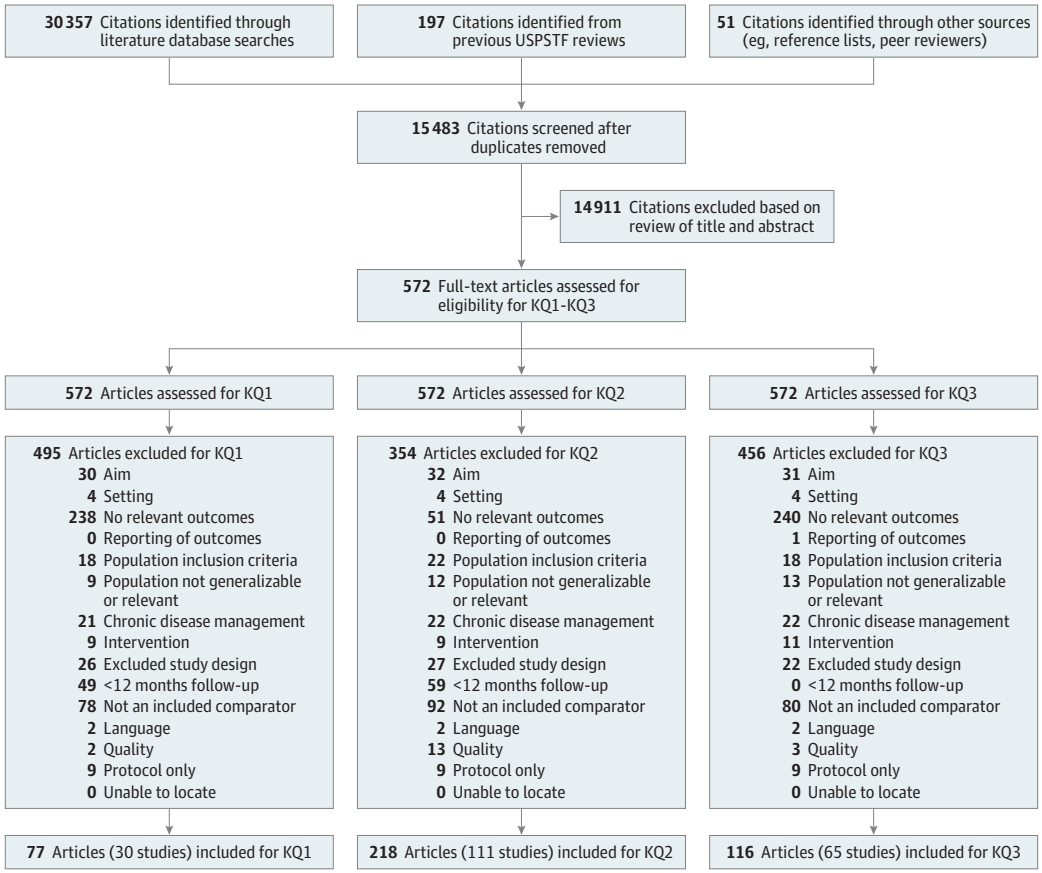
Data Synthesis and Analysis

Summary tables of study, population, and intervention characteristics, as well as outcomes for each KQ, were created according to the focus of the intervention (ie, behavior-based weight loss interventions, behavior-based weight loss maintenance interventions, medication-based weight loss interventions, and medication-based weight loss maintenance interventions). The data on health outcomes (KQ1) and adverse events (KQ3) did not allow for quantitative pooling because of the limited number of contributing studies and the variability in outcomes measured.

Details of the data analysis methods are included in the full report. For weight outcomes in behavior-based interventions, random-effects meta-analyses were conducted using the method of DerSimonian and Laird to calculate the pooled differences in mean changes (for continuous data) and a pooled risk ratio (for binary data) for weight outcomes (KQ2).[19] Statistical heterogeneity among the pooled studies was examined using standard χ^2 tests, and the proportion of total variability in point estimates was estimated using the I^2 statistic.[20] Funnel plots were generated to evaluate small-study effects (a possible indication of publication bias) and the Egger[21] or Peters[22] tests were used to assess the statistical significance of imbalance in study size as well as findings that suggested a pattern. Data from medication trials could not be pooled because of the small number of studies for each medication or variability in reporting between trials.

A series of meta-regression analyses were conducted to investigate whether variability among the results was associated with any prespecified study, population, or intervention characteristics. Specifically, we examined study quality (good vs fair), percentage of participants retained at 12 to 18 months, link to primary care (conducted in or recruited from primary care), whether the trial was set in the United States, risk status of the sample (increased cardiovascular risk [eg, hypertension], subclinical cardiovascular risk [eg, impaired fasting glucose], or cancer risk vs low risk or unselected), participant selection approach (self-selected vs directly recruited), and

Figure 2. Literature Search Flow Diagram: Behavioral and Pharmacotherapy Weight Loss Interventions to Prevent Obesity-Related Morbidity and Mortality in Adults



Reasons for exclusion: Aim: Study aim was not relevant. Setting: Study was not conducted in a country relevant to United States practice or not conducted in, recruited from, or feasible for primary care or a health system. No relevant outcomes: Study did not have relevant outcomes or had incomplete outcomes. Reporting of outcomes: Outcomes not presented in a way that could be abstracted for the review. Population inclusion criteria: Study was not conducted in an included population. Population not generalizable or relevant: Included population was not generalizable to a primary care population. Chronic disease management: Aim of the intervention was the management of an existing chronic disease. Intervention: Intervention was out of scope. Excluded study design: Study did not use an included design. <12 months of follow-up: Follow-up for health or weight loss outcomes was less than 12 months. Not an included comparator: Comparator did not meet review criteria. Language: Publication not in English. Quality: Study was poor quality. Protocol only: Publication represented a study protocol without an identified publication of full study results. Unable to locate: Full text not available. USPSTF indicates US Preventive Services Task Force.

several intervention characteristics (number of sessions and contacts in the first year; intervention duration; main mode of intervention delivery; presence of any group, individual, or technology-based components; and use of self-monitoring).

Quantitative analyses were conducted using Stata version 13.1 (Stata Corp LP). All significance testing was 2-sided, and results were considered statistically significant if the *P* value was .05 or less.

Results

A total of 15 483 titles and abstracts and 572 articles were reviewed to determine if they met inclusion criteria, and 124 trials reported in 238 publications, including 122 RCTs (N = 62 533) and 2 observational studies (N = 209 993), were included (**Figure 2**; eTables 1 and 2 in the Supplement).[23-147] Forty-one studies were carried over from the prior review and were synthesized with 83 newly identified studies. Eighty-nine trials examined the effectiveness of behavior-based weight loss and weight loss maintenance interventions,[24,25,27,29,32,34-36,39-44,46,47,49,53,55,56,58,62-71,73,75,76,78-81,83-86,88-98,100,102-105,107-110,115-118,121,122,124-127,130-147] and 35 examined the effectiveness or harms of medication for weight loss and weight loss maintenance.[23,26,28,30,31,33,37,38,45,48,50-52,54,57,59-61,72,74,77,82,87,99,101,106,111-114,119,120,123,128,129]

Within the 89 behavior-based weight loss and weight loss maintenance trials, 120 unique weight loss interventions were evaluated. Although interventions were highly variable, specific weight loss messages and behavior change techniques were consistent across the trials (eTable 3 in the Supplement). To better summarize the interventions, each intervention group was categorized according to the main mode of intervention delivery into the following groups: (1) group (41 groups in 28 trials) , (2) individual (37 groups in 33 trials), (3) mixed (18 groups in 16 trials), (4) technology-based (22 groups in 20 trials), and (5) print-based (2 groups in 1 trial). The comparison groups in these trials included (1) minimal intervention

(44 trials), (2) usual care (25 trials), (3) no intervention (9 trials), (4) wait list (7 trials), and (5) attention control (4 trials). Medication-based weight loss and weight loss maintenance studies examined FDA-approved dosages of medications: liraglutide (1.8 mg or 3.0 mg daily), lorcaserin (20 mg [10 mg twice daily]), naltrexone and bupropion (32/360 mg [16/180 mg 3 times daily]), orlistat (prescription-strength dosage of 360 mg daily [120 mg 3 times daily] and over-the-counter dosage of 180 mg [60 mg 3 times daily]), and phentermine-topiramate (15/92 mg and 7.5/46 mg). Medication and placebo groups both received identical behavioral interventions.

Benefits for Health Outcomes

Key Question 1. Do primary care–relevant behavioral and/or pharmacotherapy weight loss and weight loss maintenance interventions lead to improved health outcomes among adults who are overweight or have obesity and are a candidate for weight loss interventions?

Health outcomes were infrequently reported in the behavior-based weight loss and maintenance trials (20 trials [n = 9910]). In 4 weight loss trials (n = 4442) reporting mortality, there were no significant differences between groups over 2 to 16 years.[73,116,122,143,148-150] Two weight loss trials (n = 2666) reported on cardiovascular events, with neither trial finding significant differences between groups over 3 and 10 years.[73,122,149,151] Health-related quality of life (QOL) was evaluated in 17 weight loss and maintenance trials (n = 7120), with 14 showing no differences between groups on any measure; in the 3 trials that noted statistically significant findings, the differences were only for some QOL components and were of unclear clinical significance (**Table 1**).[29,46,47,56,62,65,73,76,89,92,96,102,110,126,127,132,140]

Trials of medications for weight loss examined few health outcomes beyond QOL (10 trials [n = 13 145]).[28,31,51,54,57,99,106,113,119,128] Although there was evidence of greater improvement on an obesity-specific QOL scale in participants randomized to receive medications for weight loss compared with placebo within most of the trials, the differences were small and of unclear clinical significance, especially given high dropout rates in medication trials (eTable 4 in the Supplement). None of the medication-based maintenance trials reported the effects of the interventions on health outcomes.

Benefits for Weight Control

Key Question 2. Do primary care–relevant behavioral and/or pharmacotherapy weight loss and weight loss maintenance interventions lead to weight loss, weight loss maintenance, or a reduction in the incidence or prevalence of obesity-related conditions among adults who are overweight or have obesity and are a candidate for weight loss interventions?

Participants who received behavior-based weight loss interventions generally lost more weight and had greater reductions in waist circumference than those in control conditions at up to 24 months of follow-up. Intervention participants had a pooled −2.4 kg (−5.3 lb) (95% CI, −2.8 to −1.9 kg; 67 trials [n = 22 065]; I^2 = 90.0%) greater weight loss at 12 to 18 months (**Figure 3**). Mean absolute changes in weight ranged from −0.5 kg (−1.1 lb) to −9.3 kg (−20.5 lb) among intervention participants and from 1.4 kg (3.0 lb) to −5.6 (−12.3 lb) among control participants. In addition, intervention participants were more likely to achieve 5% weight loss from baseline compared with control participants (pooled risk ratio, 1.94 [95% CI, 1.70 to 2.22]; 38 trials [n = 12 231]; I^2 = 67.2%), which translated into a number needed to treat of 8 (eFigure 1 in the Supplement). Heterogeneity in the interventions, confounded with differences in the populations, settings, and trial quality, made it difficult to identify which variables (ie, number of sessions, in-person vs remote sessions, group- vs individual-based) may be driving larger effects. Although weight outcomes were less well reported beyond 12 months (eFigure 2 in the Supplement), weight loss remained significantly greater in intervention compared with control conditions in interventions lasting up to 36 months. Participants who received behavior-based weight loss maintenance interventions generally maintained more of their weight loss compared with those in control conditions (pooled mean difference, −1.6 kg [−3.5 lb] [95% CI, −2.4 to −0.8 kg]; 8 trials [n = 1408]; I^2 = 26.8%) in the intervention vs control groups (eFigure 3 in the Supplement).

In the 2 largest and longest good-quality trials (n = 1818), participants randomized to behavior-based weight loss interventions had a decreased probability of developing type 2 diabetes compared with control conditions, with an absolute risk reduction of approximately 14.5% in both trials over 3 to 9 years.[73,122,159] Although 11 smaller and generally shorter-duration weight loss trials did not find significant differences between groups, when pooled with the larger trials, there was a significant reduction in risk of developing diabetes over 1 to 9 years (pooled risk ratio, 0.67 [95% CI, 0.51 to 0.89]; 9 trials [n = 3140]; I^2 = 49.2%) (**Figure 4**). Across all 13 of these trials, almost all were limited to adults with impaired fasting glucose. Three large trials (n = 3916) noted benefits of behavior-based weight loss on hypertension and hyperlipidemia diagnosis, medication use, or both[116,148,151]; however, effects were not found in 5 smaller trials.[43,66,102,105,144] Effects on the metabolic syndrome[56,73,79,100,105] and cardiovascular disease risk score were mixed.[24,56]

Participants randomized to receive weight loss medications had more weight loss, were more likely to lose 5% of their weight, and experienced a greater decrease in waist circumference than those receiving placebo (**Table 2**; eFigure 4 in the Supplement). Participants who received medications to assist with weight loss maintenance generally maintained more of their weight loss and waist circumference decrease compared with those in control conditions. However, the results were limited by high dropout rates and relatively short follow-up duration in some trials. The most common intermediate outcome reported (4 studies [n = 9763]) was incident diabetes, and there was a decreased risk of developing diabetes over 1 to 4 years in participants given medications; however, these trials were similarly limited by high dropout rates. Other intermediate outcomes were sparsely reported and showed mixed results.

Harms of Interventions

Key Question 3. What are the adverse effects of primary care–relevant behavioral and/or pharmacotherapy weight loss and weight loss maintenance interventions in adults who are overweight or have obesity and are a candidate for weight loss interventions?

Rates of adverse events were infrequently reported in the behavior-based weight loss and weight loss maintenance trials (30 trials [n = 12 824]).[25,27,29,35,36,47,49,55,62,64,66,71,73,78,80,92,96,103-105,110,121,125,127,137,138,140,142,145,147] In general, there were no serious harms related to the interventions and most trials noted no differences between groups in the rates of adverse events, including cardiovascular events.

Table 1. Health-Related Quality of Life Results in Behavior-Based Weight Loss and Behavior-Based Weight-Loss Maintenance Randomized Clinical Trials (Key Question 1) (17 Trials [n = 7120])

Source	Planned Follow-up, mo	Intervention					Control			Study-Reported Between-Group Mean Difference (95% CI or SD)	Study Quality
		Group	No.	Instrument	Mean (SD) Score at Baseline	Mean Change (95% CI or SD)	No.	Mean (SD) Score at Baseline	Mean Change (95% CI or SD)		
WRAP Ahern et al,[140] 2017	12	1	504	EQ5D-3L	0.793 (0.249)	−0.012 (0.011)[a]	197	0.786 (0.266)	−0.014 (0.018)[a]	0.014 (−0.025 to 0.054) P = 0.476	Fair
		2	508		0.783 (0.249)	0.009 (0.011)[a]	197	0.786 (0.266)	−0.014 (0.018)[a]	0.029 (−0.011 to 0.069); P = 0.150	
	24	1	504		0.793 (0.249)	−0.018 (0.011)[a]	197	0.786 (0.266)	−0.005 (0.018)[a]	−0.014 (−0.052 to 0.025) P = 0.486	
		2	508		0.783 (0.249)	−0.015 (0.012)[a]	197	0.786 (0.266)	−0.005 (0.018)[a]	−0.011 (−0.050 to 0.028) P = 0.486	
POWER Hopkins Appel et al,[29] 2011 Rubin et al,[152] 2013[b]	24	1	100	SF-12 mental	52.16 (9.60)	−0.50 (0.76)[a]	88	51.06 (8.71)	0.62 (0.95)[a]	−1.12 (−3.52 to 1.27)	Good
				SF-12 physical	47.06 (8.92)	2.23 (0.75)		46.83 (7.95)	−0.29 (0.97)	2.52 (0.11 to 4.93) P < .05	
				EQ-5D VAS	75.12 (18.95)	6.14 (1.78)		73.34 (17.63)	4.31 (1.77)	1.83 (−3.07 to 6.74)	
				EQ-5D single index	0.88 (0.12)	−0.01 (0.01)		0.87 (0.11)	−0.01 (0.01)	−0.0003 (−0.04 to 0.03)	
		2	115	SF-12 physical	47.53 (8.42)	1.16 (0.77)		46.83 (7.95)	−0.29 (0.97)	1.45 (−0.99 to 3.90)	
				SF-12 mental	52.53 (7.40)	−1.07 (0.68)		51.06 (8.71)	0.62 (0.95)	−1.70 (−3.99 to 0.60)	
				EQ-5D VAS	76.64 (15.72)	3.45 (1.53)		73.34 (17.63)	4.31 (1.77)	−0.86 (−5.47 to 3.75)	
				EQ-5D single index	0.88 (0.12)	−0.01 (0.01)		0.87 (0.11)	−0.01 (0.01)	−0.004 (−0.04 to 0.03)	
PROOF de Vos et al,[46] 2014	30	1	186	EQ-5D	NR	NR	180	NR	NR	NR[c]	Fair
DAMES Demark-Wahnefried et al,[47] 2014	12	1	23	SF-36 mental	56.6 (8.2)	−1.9 (−6.0 to 2.2)	18	53.7 (8.5)	2.4 (−1.0 to 5.8)	P = .35	Good
		2			52.1 (11.7)	0.6 (−3.8 to 5.0)	18	53.7 (8.5)	2.4 (−1.0 to 5.8)	P = .46	
		1	23	SF-36 physical	44.3 (8.3)	2.2 (−2.1 to 6.5)	18	45.3 (8.5)	0.9 (−1.4 to 3.2)	P = .73	
		2			44.3 (11.9)	−2.3 (−5.0 to 0.4)	18	45.3 (8.5)	0.9 (−1.4 to 3.2)	P = .16	
Waste the Waist Greaves et al,[56] 2015	12	1	55	EQ-5D VAS	77.0 (14.9)	NR	53	76.4 (17.0)	NR	1.36 (−3.37 to 6.04)	Fair
Jansson et al,[65] 2013	12	1	45	SF-36 and EQ-5D	NR	NR	49	NR	NR	NR[c]	Fair
FFIT Hunt et al,[62] 2014	12	1	316	SF-36 mental	48.9 (10.1)	1.9 (0.9 to 2.8)	351	48.3 (9.2)	1.6 (0.8 to 2.4)	0.50 (−0.62 to 1.62) P = .3822	Good
				SF-36 physical	47.0 (7.9)	2.3 (1.5 to 3.2)	351	47.7 (7.5)	0.2 (−0.6 to 0.9)	1.89 (0.89 to 2.90) P = .0002	
DPP Knowler et al,[73] 2002[d] Florez et al,[153] 2012[e] Ackermann et al,[154] 2009[f]	12	1	1017	SF-36 mental	53.7 (7.6)	−0.70 (8.67)	1018	54.0 (7.4)	−1.16 (8.33)	NR	Good
				SF-36 physical	50.6 (6.9)	1.33 (7.0)	1018	50.4 (7.2)	−0.04 (7.12)	NR	
	38	1	1048	SF-36 mental	53.7 (7.6)	NR	850	50.4 (7.2)	NR	0.29 (0.32)	
				SF-36 physical	50.6 (6.9)	NR	850	50.4 (7.2)	NR	1.57 (0.30) P < .01	
	12	1	268	QWB-SA	0.7 (0.1)	0.02 (0.1)	252	0.7 (0.1)	0.01 (0.1)	NR	
	12	1	1015	SF-6D health utility index	0.8 (0.1)	0.0 (0.1)	1018	0.8 (0.1)	−0.01 (0.1)	NR	
	38	1	1048	SF-6D health utility index	0.8 (0.1)	NR	850	0.8 (0.1)	NR	0.01 (0.004) P < .05	
PREDIAS Kulzer et al,[76] 2009[d]	12	1	91	WHO-5	15.3 (5.1)	1.4 (3.9)	91	14.3 (4.9)	0.0 (4.2)	1.40 (0.22 to 2.58) P = .101	Fair

(continued)

Table 1. Health-Related Quality of Life Results in Behavior-Based Weight Loss and Behavior-Based Weight-Loss Maintenance Randomized Clinical Trials (Key Question 1) (17 Trials [n = 7120]) (continued)

Source	Planned Follow-up, mo	Intervention					Control			Study-Reported Between-Group Mean Difference (95% CI or SD)	Study Quality
		Group	No.	Instrument	Mean (SD) Score at Baseline	Mean Change (95% CI or SD)	No.	Mean (SD) Score at Baseline	Mean Change (95% CI or SD)		
CAMWEL Nanchahal et al,[89] 2012	12	1	103	EQ-VAS	47.42 (30.68)	NR	114	NR	NR	NR[c]	Fair
				Obesity-related QOL	48.22 (30.18)	NR	114	NR	NR	NR[c]	
Ockene et al,[92] 2012	12	1	147	SF-12	NR	NR	142	NR	NR	NR[c]	Fair
Pekkarinen et al,[96] 2015[g]	24	1	50	SF-36	NR	NR	38	NR	NR	NR[c]	Fair
ENERGY Rock et al,[102] 2015 Demark-Wahnefried et al,[155] 2015	12	1	269	SF-36 vitality subscale	58.7 (21.35)	NR	244	58.7	NR	P = .51	Good
			270	SF-36 physical function subscale	80.2 (18.67)	NR	244	79.0 (18.38)	NR	P = .05	
	24	1	257	SF-36 vitality subscale	58.7 (21.35)	NR	248	58.7	NR	P = .19	
				SF-36 physical function subscale	80.2 (18.67)	NR	248	79.0 (18.38)	NR	P = .62	
WILMA Simpson et al,[110] 2015[g]	12	1	45	EQ-5D index score	NA	NA	51	NA	NA	OR, 0.85 (0.29 to 2.46)[h]	Fair
		2	43	EQ-5D index score	NA	NA	51	NA	NA	OR, 1.39 (0.49 to 3.94)[h]	
SUCCEED von Gruenigen et al,[126] 2012 McCarroll et al,[156] 2014	12	1	41	FACT-G	NR	NR	34	NR	NR	NR[c]	Fair
POWER-UP Wadden et al,[127] 2011[d] Sarwer et al,[157] 2013	12	1	131	IWQOL-Lite (total)	69.4 (17.5)	NR	130	68.8 (17.5)	NR	NR[c]	Good
				SF-12 mental	48.9 (9.8)	NR		48.7 (10.5)	NR	NR[c]	
				SF-12 physical	43.9 (9.0)	NR		43.4 (9.5)	NR	NR[c]	
				EQ-5D index score	70.4 (18.8)	NR		67.0 (20.0)	NR	NR[c]	
Wylie-Rosett et al,[132] 2001 Swencionis et al,[158] 2013	12	1	194	Psychological Well-Being Index	NR	NR	97	NR	NR	NR[c,i]	Fair
		2	183		NR	NR		NR	NR	NR[c,i]	

Abbreviations: CAMWEL, Camden Weight Loss; DAMES, Daughters and Mothers Against Breast Cancer; DPP, Diabetes Prevention Program; ENERGY, Exercise and Nutrition to Enhance Recovery and Good Health for You; EQ-5D, EuroQol Five Dimensions; EQ-5D-3L, 3-level version of EQ-5D; EQ-VAS, EuroQol Visual Analogue Scale; FACT-G, Functional Assessment of Cancer Therapy—General; FFIT, Football Fans in Training; IWQOL, Impact of Weight on Quality of Life; NA, not applicable; NR, not reported; NS, not statistically significant; OR, odds ratio; PA, physical activity; POWER, Practice-based Opportunities for Weight Reduction; POWER-UP, Practice-based Opportunities for Weight Reduction at the University of Pennsylvania; PREDIAS, Prevention of Diabetes Self-Management Program; PROOF, Prevention of Knee Osteoarthritis in Overweight Females; QOL, quality of life; QWB-SA, Quality of Well-Being Index—Self-Administered; SF-6D, Medical Outcomes Study 6-Dimension Short Form; SF-12, Medical Outcomes Study 12-Item Short Form Health Survey; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey; SUCCEED, Survivors of Uterine Cancer Empowered by Exercise and Healthy Diet; VAS, visual analogue scale; WHO-5, WHO (5) Well-Being Index; WILMA, Weight Loss Maintenance in Adults; WRAP, Weight-Loss Program Referrals for Adults in Primary Care.

[a] Standard error reported in parentheses.

[b] Study used both the SF-12 and the EQ-5D.

[c] Study did not report actual values that could be used for a between-group mean difference in score.

[d] Included in previous review.

[e] Study used the SF-36 (38 months of follow-up) and SF-6D (38 months of follow-up).

[f] Study used the SF-6D (12 months of follow-up), QWB-SA, and SF-36 (12 months of follow-up).

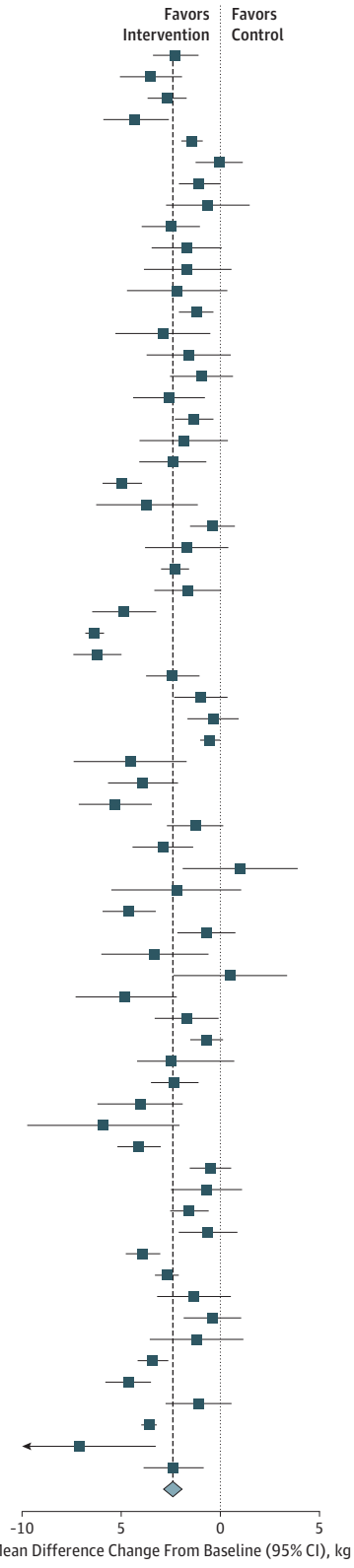
[g] Weight loss maintenance study.

[h] Reported as dichotomized analysis of participants with scores <100 vs those with scores of 100 because of skewed and bimodal distribution of follow-up scores. The odds of scoring 100 was 15% lower in intervention group 1 than in the control group (OR, 0.85 [95% CI, 0.29 to 2.46]), whereas in intervention group 2 it was 39% greater than in the control group (OR, 1.39 [95% CI, 0.49 to 3.94]).

[i] Results not reported by group, but no significant differences in well-being were found between groups at 12 months (P = .53 for anxiety, P = .32 for depression, P = .39 for positive well-being, P = .11 for self-control, P = .38 for general health, P = .35 for vitality, P = .29 for total well-being).

Figure 3. Pooled Analysis of Weight Change at 12-18 Months in Behavior-Based Weight Loss Interventions Compared With Controls (Key Question 2)

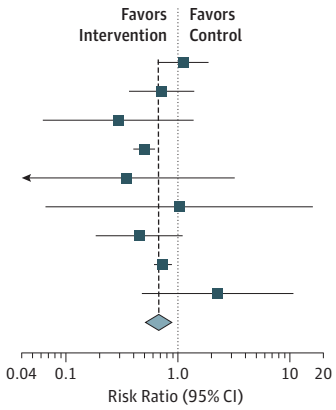
Source	Intervention Main Mode (Total mo)	Intervention No.	Intervention Change From Baseline, Mean (SD), kg	Control No.	Control Change From Baseline, Mean (SD), kg	Mean Difference Change From Baseline (95% CI), kg
Ackermann et al,[25] 2015	Group (12)	257	-2.5 (NR)	252	-0.2 (NR)	-2.30 (-3.40 to -1.10)
Ahern et al,[140] 2017	Group (12)	528	-6.8 (9.7)	211	-3.3 (9.9)	-3.50 (-5.07 to -1.93)
Anderson et al,[27] 2014	Individual (12)	148	-3.5 (4.9)	157	-0.8 (3.8)	-2.69 (-3.67 to -1.70)
Appel et al,[29] 2011	Mixed (24)	123	-5.4 (7.8)	108	-1.1 (5.2)	-4.30 (-5.90 to -2.60)
Aveyard et al,[32] 2016	Group (3)	940	-2.4 (6.5)	942	-1.0 (5.5)	-1.43 (-1.97 to -0.89)
Beeken et al,[135] 2017	Individual (3)	143	-2.4 (5.5)	152	-2.3 (5.0)	-0.06 (-1.25 to 1.13)
Bennett et al,[35] 2012	Individual (24)	180	-1.4 (5.1)	185	-0.3 (4.9)	-1.05 (-2.09 to -0.01)
Bhopal et al,[36] 2014	Individual (36)	84	-0.9 (7.2)	83	-0.3 (6.7)	-0.63 (-2.74 to 1.48)
Burke et al,[39] 2005	Mixed (16)	106	-3.9 (5.5)	98	-1.4 (5.2)	-2.50 (-3.9 to -1.03)
Cadmus-Bertram et al,[40] 2016	Individual (12)	59	-2.9 (4.3)	29	-1.2 (3.8)	-1.70 (-3.47 to 0.07)
Christian et al,[42] 2011	Technology (6)	133	-1.5 (5.3)	130	0.1 (4.0)	-1.65 (-3.85 to 0.56)
Cohen et al,[43] 1991	Individual (12)	15	-0.9 (4.0)	15	1.3 (3.0)	-2.18 (-4.71 to 0.35)
de Vos et al,[46] 2014	Individual (30)	187	-0.6 (5.5)	181	0.6 (5.4)	-1.22 (-2.09 to -0.35)
Demark-Wahnefried et al,[47] 2014	Technology (12)	23	-3.8 (4.8)	18	-0.9 (3.0)	-2.90 (-5.29 to -0.51)
Eaton et al,[49] 2016	Individual (24)	106	-5.4 (7.9)	105	-3.8 (7.8)	-1.60 (-3.72 to 0.52)
Fischer et al,[136] 2016	Technology (12)	78	-1.2 (5.8)	79	-0.3 (4.4)	-0.95 (-2.54 to 0.63)
Fitzgibbon et al,[53] 2010	Mixed (18)	93	-2.3 (7.4)	97	0.5 (5.7)	-2.59 (-4.40 to -0.78)
Godino et al,[55] 2016	Technology (24)	202	NR	202	NR	-1.33 (-2.30 to -0.35)
Greaves et al,[56] 2015	Group (9)	55	-3.7 (5.2)	53	-1.9 (6.7)	-1.85 (-4.08 to 0.38)
Haapala et al,[58] 2009	Technology (12)	62	-3.1 (4.9)	62	-0.7 (4.7)	-2.40 (-4.09 to -0.71)
Hunt et al,[62] 2014	Group (12)	333	-5.6 (8.1)	355	-0.6 (5.2)	-4.94 (-5.94 to -3.95)
Huseinovic et al,[63] 2016	Individual (12)	44	-9.3 (4.8)	45	-5.6 (7.3)	-3.70 (-6.26 to -1.14)
Jakicic et al,[64] 2011	Mixed (18)	88	-1.3 (3.8)	84	-0.9 (3.8)	-0.40 (-1.53 to 0.73)
Jansson et al,[65] 2013	Individual (24)	45	-2.5 (5.0)	49	-0.8 (5.4)	-1.70 (-3.80 to 0.40)
Jebb et al,[66] 2011	Group (12)	377	-4.1 (6.0)	395	-1.8 (3.8)	-2.29 (-2.99 to -1.58)
Jolly et al,[68] 2011	Group (3)	100	-2.5 (5.9)	100	-1.1 (5.1)	-1.65 (-3.33 to 0.04)
Katula et al,[71] 2011	Mixed (24)	151	-6.9 (6.9)	150	-2.1 (7.4)	-4.85 (-6.46 to -3.24)
Knowler et al,[73] 2002	Individual (38)	1026	-6.8 (5.4)	1027	-0.4 (5.4)	-6.34 (-6.81 to -5.87)
Kuller et al,[75] 2012	Group (36)	208	-7.8 (7.1)	213	-1.6 (5.5)	-6.20 (-7.42 to -4.98)
Kulzer et al,[76] 2009	Group (10)	91	-3.8 (5.2)	91	-1.4 (4.0)	-2.40 (-3.75 to -1.05)
Kumanyika et al,[145] 2012	Individual (12)	89	-1.6 (5.1)	98	-0.6 (4.1)	-0.98 (-2.33 to 0.36)
Little et al,[78] 2016	Technology (6)	221	-3.8 (7.4)	227	-2.6 (9.2)	-0.37 (-1.66 to 0.92)
Logue et al,[141] 2005	Individual (24)	329	-1.4 (3.2)	336	-0.9 (3.4)	-0.52 (-1.02 to -0.02)
Luley et al,[79] 2014	Individual (12)	58	-7.3 (6.3)	60	-2.7 (6.5)	-4.50 (-7.40 to -1.70)
Ma et al,[80] 2013	Group (15)	79	-6.3 (8.0)	81	-2.4 (0.1)	-3.90 (-5.66 to -2.14)
Marrero et al,[81] 2016	Group (12)	94	-5.5 (6.1)	81	-0.2 (6.2)	-5.30 (-7.14 to -3.46)
Martin et al,[83] 2008	Individual (6)	68	-1.4 (3.7)	69	-0.2 (3.6)	-1.22 (-2.64 to 0.20)
Mensink et al,[142] 2003	Individual (24)	40	-3.1 (3.8)	48	-0.2 (3.5)	-2.90 (-4.43 to -1.37)
Moore et al,[85] 2003	Individual (12)	279	-0.5 (NR)	286	-0.9 (NR)	1.00 (-1.90 to 3.90)
Morgan et al,[86] 2011	Technology (3)	34	-5.3 (6.4)	31	-3.1 (6.4)	-2.20 (-5.50 to 1.05)
Nakade et al,[88] 2012	Mixed (12)	115	-4.5 (4.4)	111	0.1 (5.8)	-4.60 (-5.94 to -3.26)
Nanchahal et al,[89] 2012	Individual (9)	103	-2.4 (5.6)	114	-1.3 (5.1)	-0.70 (-2.17 to 0.76)
Nicklas et al,[91] 2014	Technology (12)	36	-2.8 (6.1)	39	0.5 (5.9)	-3.30 (-6.00 to -0.60)
Nilsen et al,[144] 2011	Group (18)	93	-2.5 (9.6)	89	-3.0 (10.1)	0.50 (-2.37 to 3.37)
O'Brien et al,[138] 2017	Group (12)	30	-4.0 (3.9)	28	0.8 (4.0)	-4.80 (-7.30 to -2.20)
Pacanowski and Levitsky,[93] 2015	Technology (12)	81	-2.1 (5.6)	67	-0.4 (4.4)	-1.70 (-3.31 to -0.09)
Patrick et al,[95] 2011	Technology (12)	217	-0.9 (7.1)	224	-0.2 (6.9)	-0.69 (-1.52 to 0.14)
Penn et al,[97] 2009	Individual (60)	51	-2.3 (NR)	51	0.0 (NR)	-2.50 (-4.20 to 0.70)
Phelan et al,[147] 2017	Mixed (12)	174	-3.2 (5.7)	193	-0.9 (5.7)	-2.30 (-3.50 to -1.10)
Puhkala et al,[100] 2015	Individual (12)	47	-3.4 (6.6)	48	0.7 (3.9)	-4.00 (-6.20 to -1.90)
Rock et al,[103] 2007	Individual (12)	35	-6.6 (10.2)	35	-0.7 (5.5)	-5.90 (-9.74 to -2.06)
Rock et al,[102] 2015	Mixed (24)	297	-5.3 (6.8)	288	-1.2 (6.7)	-4.10 (-5.19 to -3.01)
Rodriguez-Critobal et al,[146] 2017	Group (24)	283	-1.8 (6.7)	302	-1.3 (1.7)	-0.50 (-1.54 to 0.54)
Rosas et al,[104] 2015	Mixed (24)	84	-1.4 (4.9)	41	-0.7 (4.8)	-0.70 (-2.49 to 1.09)
Ross et al,[105] 2012	Individual (24)	249	-2.4 (5.4)	241	-0.9 (5.6)	-1.56 (-2.53 to -0.59)
Shapiro et al,[107] 2012	Technology (12)	81	-1.7 (5.4)	89	-1.0 (4.3)	-0.62 (-2.10 to 0.86)
Stevens et al,[115] 1993	Group (18)	293	-3.8 (6.1)	235	0.1 (4.0)	-3.90 (-4.77 to -3.03)
Stevens et al,[116] 2001	Group (36)	545	-2.0 (5.8)	551	0.7 (4.2)	-2.70 (-3.30 to -2.10)
Svetkey et al,[117] 2015	Mixed (24)	120	-3.6 (NR)	123	-2.3 (NR)	-1.33 (-3.19 to 0.53)
Thomas et al,[139] 2017	Technology (12)	91	-1.6 (4.9)	86	-1.2 (5.0)	-0.40 (-1.85 to 1.05)
Tsai et al,[121] 2010	Individual (12)	22	-2.3 (4.2)	25	-1.1 (4.0)	-1.20 (-3.56 to 1.16)
Tuomilehto et al,[122] 2001	Individual (48)	256	-4.2 (5.1)	250	-0.8 (3.7)	-3.40 (-4.18 to -2.62)
von Gruenigen et al,[126] 2012	Mixed (12)	41	-3.0 (8.8)	34	1.4 (11.1)	-4.60 (-5.80 to -3.50)
Wadden et al,[127] 2011	Individual (24)	131	-3.4 (6.9)	130	-2.3 (6.8)	-1.10 (-2.76 to 0.56)
Whelton et al,[143] 1998	Mixed (28)	294	-4.7 (2.6)	291	-1.1 (2.2)	-3.60 (-3.99 to -3.21)
Wing et al,[131] 1998	Group (24)	30	-7.4 (9.7)	29	-0.3 (4.5)	-7.10 (-10.94 to -3.26)
Wylie-Rosett et al,[132] 2001	Mixed (12)	194	-3.4 (7.3)	97	-1.0 (5.6)	-2.36 (-3.87 to -0.84)
Overall (I^2 = 90.0%, P < .001)						-2.39 (-2.86 to -1.93)



NR indicates not reported.

Figure 4. Pooled Analysis of Risk of Developing Diabetes in Behavior-Based Weight Loss Interventions Compared With Controls (Key Question 2)

Source	Planned Follow-up, mo	No. With Diabetes/Total (%)		Risk Ratio (95% CI)
		Intervention	Control	
Ackermann et al,[25] 2015	12	26/220 (11.8)	24/226 (10.6)	1.11 (0.66-1.88)
Bhopal et al,[36] 2014	36	12/81 (15.0)	17/82 (21.0)	0.71 (0.36-1.40)
Katula et al,[71] 2011	12	2/135 (1.5)	7/138 (5.1)	0.29 (0.06-1.38)
Knowler et al,[73] 2002	36[a]	92/638 (14.4)	190/657 (28.9)	0.50 (0.40-0.62)
Luley et al,[79] 2014	12	1/58 (1.7)	3/60 (5.0)	0.34 (0.04-3.22)
Ma et al,[80] 2013	15	1/79 (1.3)	1/81 (1.2)	1.03 (0.07-16.11)
Penn et al,[97] 2009	60	5/51 (9.8)	11/51 (21.6)	0.45 (0.20-1.20)
Tuomilehto et al,[122] 2001	108[b]	106/265 (40.0)	140/257 (54.5)	0.73 (0.61-0.88)
Wing et al,[131] 1998	24	5/32 (15.6)	2/29 (6.9)	2.27 (0.48-10.79)
Overall (I^2 = 49.2%, P = .046)				0.67 (0.51-0.89)



[a] Actual follow-up range, 12 to 55 months.

[b] Actual follow-up range, 0 to 192 months.

In the 3 trials large enough to examine differences in musculoskeletal issues between groups, results were mixed.[25,73,105]

Almost all medication trials reported adverse events. Weight loss medications were associated with more adverse events than placebo, which was associated with higher dropout rates for adverse events in the medication groups than in the placebo groups. However, serious adverse events were not generally more common in participants randomized to medications. There are multiple potential harms required by the FDA to be listed on weight loss medication labels, but these harms have not been well evaluated in the trials included in this review.

Discussion

The summary of evidence is shown in **Table 3**. Behavior-based weight loss interventions were associated with more weight loss, and behavior-based weight loss maintenance interventions were associated with less weight regain, than control conditions over 12 to 18 months. The degree of weight loss in the current review is slightly smaller but consistent in magnitude with the 2011 review on this topic. Although addressed in fewer trials, weight loss or weight loss maintenance interventions lasting up to 36 months reported significantly greater weight loss or weight loss maintenance in the intervention participants compared with control participants. Weight loss estimates were consistent and precise over time; however, pooled analyses showed considerable statistical heterogeneity, reflecting heterogeneity in intervention groups and differences in populations, settings, and designs. Using various modes of intervention delivery (group, individual, mixed, technology-based, and print-based), trials were generally designed to help participants achieve or maintain a 5% or greater weight loss through a combination of dietary changes and increased physical activity.

As in the previous review, behavior-based weight loss interventions were associated with a decreased risk of progressing from prediabetes to type 2 diabetes at up to 36 months of follow-up. Other intermediate- and longer-term health outcomes were infrequently reported, and in those studies reporting such outcomes, most were underpowered. Adverse events of behavior-based interventions were sparsely reported, but no serious harms were related to interventions.

FDA-approved weight loss medications (liraglutide, lorcaserin, naltrexone and bupropion, orlistat, and phentermine-topiramate) were associated with more weight loss and weight loss maintenance and a decreased incidence of progression to type 2 diabetes compared with placebo at up to 48 months of follow-up. Although weight loss medication studies reported improvements on obesity-specific QOL measures, comparative scores were often missing, and differences were small and of unclear significance. Although rates of serious adverse events were low and generally similar between groups, participants randomized to medications experienced more adverse events, resulting in higher withdrawal rates, compared with those in the placebo groups. The medication evidence was limited by the small number of trials for each medication, methodological variability, missing data regarding dispersion, poor follow-up, and limited applicability (given that participants had to meet narrowly defined inclusion criteria).

Intentional weight loss among individuals who have obesity may lead to a small decrease in mortality risk, although the observational literature is conflicting, especially for men and for individuals without obesity-related comorbidities.[161-163] The literature is limited on the effects of intentional weight loss on other outcomes (eg, cardiovascular disease and cancer).[164,165] In the context of sparse direct trial evidence on health outcomes, observational evidence does not suggest that intentional weight loss among those who are overweight, especially those with BMIs less than 28, is associated with decreased mortality.[166-170] Individuals who undergo bariatric surgery experience significant improvements in diabetes,[171,172] sleep apnea,[172,173] QOL,[174] depression,[175] and pain and physical function,[176] although data on long-term health outcomes such as mortality, cardiovascular disease, and cancer are still lacking. The amount of weight loss that occurs with weight loss surgery, however, is much greater than what can usually be achieved with behavior-based weight loss interventions and there are metabolic changes that occur after surgery, independent of weight loss, that could contribute to improvements in health outcomes after surgery.[177]

Table 2. Weight Loss Results in All Medication-Based Weight Loss and Medication-Based Weight-Loss Maintenance Randomized Clinical Trials, by Drug (Key Question 2) (18 Trials; n = 22 972)

Source	Follow-up		Dose	Intervention			Control			Between-Group Difference in Mean Change, kg (95% CI)[a]	Study-Reported *P* Value
	Planned, mo	No. (%)		No.	Baseline Weight, Mean (SD) kg	Mean (95% CI) Change, kg	No.	Baseline Weight, Mean (SD) kg	Mean (95% CI) Change, kg		
Liraglutide											
Astrup et al,[31] 2012	12	121 (63.1)	3.0 mg/d	93	97.5 (13.8)	−7.8 (NR)	98	97.3 (12.3)	−2.0 (NR)	−5.80 (−8.00to−3.70)	<.0001
Pi-Sunyer et al,[99] 2015	13	2589 (69.4)	3.0 mg/d	2437	106.2 (21.2)	−8.4 (−8.7 to−8.1)	1225	106.2 (21.7)	−2.8 (−3.2to−2.4)	−5.60 (−6.00to−5.10)	<.001
le Roux et al,[160] 2017	36[b]	1865 (50.0)	3.0 mg/d	1472	107.5 (21.6)	−6.5 (−6.9 to−6.1)	738	107.9 (21.8)	−2.0 (−2.5to−1.5)	−4.60 (−5.30to−3.90)	<.0001
Lorcaserin Hydrochloride											
Fidler et al,[51] 2011	12	1778 (55.5)	10 mg ×2/d	1561	100.3 (15.7)	−5.8 (−6.1 to−5.5)[c]	1541	100.8 (16.2)	−2.9 (−3.2to−2.6)[c]	−2.90 (NR)[c]	<.001
Smith et al,[113] 2010	12	1581 (49.7)	10 mg ×2/d	1538	100.4 (16.0)	−5.8 (−6.2 to−5.4)	1499	99.7 (15.9)	−2.2 (−2.4to−2.0)	−3.60 (−4.04to−3.16)	<.001
Naltrexone HCL-Bupropion HCL											
Apovian et al,[28] 2013	13	805 (53.8)	16/180 mg ×3/d	702	100.3 (16.6)	−6.2 (−6.6 to−5.8)[c]	456	99.2 (15.9)	−1.3 (−1.9to−0.7)[c]	NR	<.001
Greenway et al,[57] 2010	13	697 (59.9)	16/180 mg ×3/d	471	99.7 (15.9)	−6.1 (−6.7 to−5.5)[c]	511	99.5 (14.3)	−1.4 (−2.0to−0.8)[c]	NR	<.0001
Orlistat											
Broom et al,[38] 2002	12	347 (65.3)	120 mg ×3/d	259	100.9 (20.5)	−5.8 (−6.8 to−4.8)	263	101.8 (19.8)	−2.3 (−3.1to−1.5)	−3.50 (−4.79to−2.21)	<.0001
Davidson et al,[45] 1999	12	591 (66.3)	120 mg ×3/d	657	100.7 (15.4)	−8.8 (−9.5 to−8.0)	223	100.6 (13.4)	−5.8 (−7.1to−4.5)	−2.95 (−4.45to−1.45)	<.001
Derosa et al,[48] 2003	12	48 (96.0)	120 mg ×3/d	25	94.2 (9.8)	−8.6 (−9.0 to−8.2)	23	95.3 (10.2)	−7.6 (−7.9to−7.3)	−1.00 (−1.49to−0.51)	NR
Finer et al,[52] 2000	12	139 (61.0)	120 mg ×3/d	110	97.9 (12.9)	−3.3 (NR)[c]	108	98.4 (15.0)	−1.3 (NR)[c]	−1.99 (−3.60to−0.38)[c]	.016
Hauptman et al,[59] 2000	12	427 (67.2)	120 mg ×3/d	210	100.5 (14.2)	−7.9 (−9.1 to−6.8)	212	101.8 (14.6)	−4.1 (−5.2to−3.0)	−3.80 (−5.37to−2.23)	.001
			60 mg ×3/d	213	100.4 (14.6)	−7.1 (−8.1 to−6.0)	212	101.8 (14.6)	−4.1 (−5.2to−3.0)	−2.94 (−4.46to−1.42)	.001
	18	NR	120 mg ×3/d	210	100.5 (14.2)	−6.2 (−7.4 to−5.0)	212	101.8 (14.6)	−2.9 (−4.0to−1.8)	−3.29 (−4.94to−1.64)	.001
			60 mg ×3/d	213	100.4 (14.6)	−5.8 (−6.8 to−4.8)	212	101.8 (14.6)	−2.9 (−4.0to−1.8)	−2.85 (−4.36to−1.34)	.001
	24	328 (51.7)	120 mg ×3/d	210	100.5 (14.2)	−5.0 (−6.5 to−3.6)	212	101.8 (14.6)	−1.6 (−2.9to−0.4)	−3.37 (−5.25to−1.49)	.001
			60 mg ×3/d	213	100.4 (14.6)	−4.5 (−5.7 to−3.3)	212	101.8 (14.6)	−1.6 (−2.9to−0.4)	−2.81 (−4.51to−1.11)	.001
Krempf et al,[74] 2003	12	478 (68.7)	120 mg ×3/d	346	97.0 (16.7)	−6.3 (−7.3 to−5.3)[c]	350	97.5 (16.8)	−3.3 (−4.3to−2.3)[c]	NR	<.0001
	18	425 (61.1)		346	97.0 (16.7)	−5.3 (−6.3 to−4.3)[c]	350	97.5 (16.8)	−2.4 (−3.4to−1.4)[c]	NR	<.0001
Lindgärde,[77] 2000	12	376 (85.9)	120 mg ×3/d	190	96.1 (13.7)	−5.6 (−6.3 to−4.9)	186	95.9 (13.5)	−4.3 (−5.1to−3.5)	−1.30 (−2.43to−0.17)	<.05
Phentermine-Topiramate Extended Release											
Rössner et al,[106] 2000	12	524 (71.9)	120 mg ×3/d	242	96.7 (13.8)	−9.4 (−10.2to−8.6)	237	97.7 (14.6)	−6.4 (−7.3to−5.5)	−3.00 (−4.17to−1.83)	<.001
			60 mg ×3/d	239	99.1 (14.3)	−8.5 (−9.4 to−7.6)	237	97.7 (14.6)	−6.4 (−7.3to−5.5)	−2.10 (−3.36to−0.84)	<.001
	24	435 (59.7)	120 mg ×3/d	242	96.7 (13.8)	−7.4 (−8.3 to−6.5)	237	97.7 (14.6)	−4.3 (−5.2to−3.4)	−3.10 (−4.40to−1.80)	<.001
			60 mg ×3/d	239	99.1 (14.3)	−6.6 (−7.7 to−5.5)	237	97.7 (14.6)	−4.3 (−5.2to−3.4)	−2.30 (−3.71to−0.89)	.005
Sjöström et al,[111] 1998	12	544 (79.1)	120 mg ×3/d	343	99.1 (NR)	−10.3 (NR)	340	99.8 (NR)	−6.1 (NR)	−4.20 (NR)	<.001
Swinburn et al,[119] 2005	12	269 (79.4)	120 mg ×3/d	170	103.3 (17.8)	−4.7 (−5.9 to−3.5)	169	106.9 (17.8)	−0.9 (−1.5to−0.3)	−3.80 (−5.12to−2.48)	.001
Torgerson et al,[120] 2004	12	2746 (83.1)	120 mg ×3/d	1640	110.4 (16.3)	−10.6 (NR)	1637	110.6 (16.5)	−6.2 (NR)	−4.40 (NR)	<.001
	48	1414 (42.8)	120 mg ×3/d	1640	110.4 (16.3)	−5.8 (NR)	1637	110.6 (16.5)	−3.0 (NR)	−2.70 (NR)[c]	<.001
Gadde et al,[54] 2011	13	1723 (69.3)	15/92 mg/d	981	103.0 (17.6)	−10.2 (−10.8to−9.7)[c]	979	103.3 (18.1)	−1.4 (−2.0to−0.8)[c]	NR	<.0001
			7.5/46 mg/d	488	102.6 (18.2)	−8.1 (−8.9 to−7.4)[c]	979	103.3 (18.1)	−1.4 (−2.0to−0.8)[c]	NR	<.0001

Abbreviation: NR, not reported.

[a] Study-reported adjusted between-group difference in mean change reported if available; otherwise, calculated unadjusted between-group difference.

[b] Individuals with prediabetes at baseline only.

[c] Least squares mean.

Table 3. Summary of Evidence, by Key Question and Intervention Type

Intervention	No. of Studies (No. of Observations)	Summary of Findings	Consistency and Precision[a,b]	Other Limitations	Strength of Evidence	Applicability
KQ1: Health Outcomes						
Behavior-based weight loss	18 RCTs (9543)	All-cause mortality: 4 trials reported no differences between groups at up to 16-y follow-up CVD: 2 trials reported no between-group differences in incidence of CVD events after 3 and 10 y of follow-up QOL: 15 trials reported no consistent effects at ≥1 y follow-up	Reasonably consistent Imprecise	Few trials reported CVD morbidity or CVD- or all-cause-related mortality with longer-term follow-up or sufficient power to detect differences QOL variably measured, and few trials reported absolute values Reporting bias undetected	Low for benefit	Trials reporting all-cause mortality and CVD events were limited to adults with obesity with prediabetes or prehypertension
Behavior-based weight loss maintenance	2 RCTs (366)	QOL: No consistent effects of maintenance interventions on QOL after 1- to 2-y follow-up	Inconsistent Imprecise	No trials reported health outcomes beyond QOL QOL data limited and poorly reported Reporting bias undetected	Insufficient	Design of trials was mixed, with 1 including a weight loss intervention for all participants within the trial and the other recruiting participants after ≥5% weight loss in the past year Trials represented a general, unselected population with BMIs ≥30 (in trial with weight loss before study entry) to ≥35 (in trial with weight loss as part of study)[c]
Medication-based weight loss	10 RCTs (17 315)	CVD: 2 trials reported few events in either group QOL: 10 trials generally reported improved QOL scores in participants randomized to medications vs placebo	Reasonably consistent Imprecise	Number of CVD events low, with insufficient power to detect differences Trials with high dropout rates and QOL absolute values not reported in 4 of 10 trials In studies with value, differences were small and of unclear clinical significance No reporting bias suspected	Low for benefit	Trials were of highly selected populations with multiple exclusions relevant to health outcomes (eg, history of serious medical conditions, cardiovascular events, psychiatric illness)
Medication-based weight loss maintenance	0					
KQ2: Weight Outcomes						
Behavior-based weight loss	79 RCTs (24 101)	Pooled results of 67 trials indicated greater weight loss from behavior-based weight loss interventions vs control conditions at 12-18 mo (mean difference in weight change, −2.39 kg [95% CI, −2.86 to −1.93]; 67 trials [n = 22 065]; I^2 = 90.0%) Mean absolute changes in weight ranged from −0.5 kg (1.1 lb) to −9.3 kg (20.5 lb) among intervention participants and from 1.4 kg (3.1 lb) to −5.6 (12.3 lb) among control participants Weight change at follow-up beyond 12-18 mo not as well reported but found consistent, although generally attenuated, effects over time Heterogeneity within each individual intervention group, confounded with differences in the populations, settings, and trial quality, make it nearly impossible to disentangle what variables might be driving larger effects A meta-analysis of 38 trials reported that intervention participants had a 1.94× greater probability of losing 5% of their initial weight vs control groups over 12-18 mo (RR, 1.94 [95% CI, 1.70 to 2.22]; 38 trials [n = 12 231]; I^2 = 67.2%), which translated into an NNT of 8	Reasonably consistent Reasonably precise	Few trials reported baseline cardiovascular risk status of participants Very few trials reported differences in weight change at longer follow-up (eg, ≥2 y) or after a period of no intervention to examine maintenance of effects Considerable statistical heterogeneity in all pooled analyses No reporting bias suspected	Moderate for benefit	Majority took place in United States in community-based or research settings Few included primary care involvement Interventions were highly variable in delivery mode but used similar behavior change strategies and messages Most interventions were 1-2 y in duration, and more than one-third were group-based interventions Half of trials represented an unselected population eligible for participation based on BMI; the remaining half recruited adults who were overweight or had obesity and at high cardiovascular risk (prediabetes, hypertension, high-normal blood pressure, the metabolic syndrome) Median BMI, 33.4 across trials; median age, 50.3 y[c]

(continued)

Table 3. Summary of Evidence, by Key Question and Intervention Type (continued)

Intervention	No. of Studies (No. of Observations)	Summary of Findings	Consistency and Precision[a,b]	Other Limitations	Strength of Evidence	Applicability
Behavior-based weight loss maintenance	9 RCTs (2701)	Pooled results of 8 trials indicated greater weight loss maintenance from behavior-based maintenance interventions vs control conditions at 12-18 mo (mean difference, −1.59 kg [3.5 lb] [95% CI, −2.38 to −0.79]; 8 trials [n = 1408]; I^2 = 26.8%) Eight of the 9 trials reported that both intervention and control participants regained weight over 12-18 mo of maintenance, with the intervention participants experiencing less weight regain; the remaining trial noted that both groups continued to lose weight, with no differences between groups	Reasonably consistent Reasonably precise	Only 3 trials provided data beyond 18-mo follow-up No reporting bias suspected	Moderate for benefit	Design of trials was mixed, with some including a weight loss intervention for all participants within the trial (6 trials) and the others recruiting participants after documented or self-reported weight loss Majority took place in United States in community-based or research settings, and few included primary care involvement; all but 1 of the trials represented a general, unselected population Mean BMI at enrollment in weight loss phase, 34.2; median age, 49.2 y[c]
Medication-based weight loss	20 RCTs (25 742)	Trials indicated greater weight loss from weight loss medications vs placebo at 12-18 mo (mean or LSM difference in weight change between medication and placebo ranged from −1.0 to −5.8 kg [2.2-12.8 lb]; no meta-analysis conducted) Absolute changes in weight ranged from mean or LSM of −3.3 to −10.6 kg [7.3-23.4 lb] among medication participants and from −0.9 to −7.6 kg [2.0-16.8 lb] among placebo participants over 12-18 mo Medication participants had a 1.2× to 3.9× greater probability of losing 5% of their initial weight vs placebo participants over 12-18 mo	Reasonable consistent Imprecise	Trials generally had low follow-up (10 trials with ≥35% attrition) and most were of short duration (≤13-mo follow-up) Limited data reporting (eg, only report LSMs, no between-group difference in mean change or variability around difference) Very few trials reported differences in weight change at longer follow-up (eg, ≥2 y) or after a period of no intervention to examine maintenance of effects No reporting bias suspected	Low for benefit	One-half took place in the United States, with the majority occurring in academic, research, or specialty care settings Few included primary care involvement; nearly one-half had run-in periods to assess medication adherence Most interventions were 1-2 y in duration Median BMI, 36.1; median age, 45 y[c]
Medication-based weight loss maintenance	3 RCTs (1273)	Trials indicate greater weight loss maintenance in medication vs placebo participants over 12 to 36 mo (mean difference ranged from −0.6 to −3.5; no meta-analysis conducted) Absolute changes ranged from weight loss of 6.3 kg (14.0 lb) to gain of 5.1 kg (11.2 lb) among medication participants vs gain of 0.1 to 7.1 kg (0.2-15.7 lb) among placebo participants	Reasonably consistent Imprecise	Trials generally had low follow-up (23%-30% attrition or NR) and were of short duration (2 trials of only 12- to 13-mo duration) No reporting bias suspected	Insufficient	All were conducted in research clinics in the United States, Canada, and Scandinavia Participants were required to lose 5% to 8% of baseline weight before randomization Median BMI at baseline, 35.6; median age, 46.2 y[c]
KQ2: Intermediate Outcomes						
Behavior-based weight loss	22 RCTs (9135)	Incident diabetes (13 trials [n = 4095]): Absolute cumulative incidence of diabetes at up to 3-y follow-up ranged from 0%-15% in intervention and 0%-28.9% in control group DPP and Finnish DPS found statistically significant lower incidence of developing diabetes at 3-9 y; no other trial found between-group differences, but trials generally had smaller sample sizes and shorter follow-up Other intermediate outcomes: Prevalence of hypertension, the metabolic syndrome, use of CVD medications, and estimated 10-y risk of CVD were sparsely reported Limited evidence from larger trials for reduced prevalence of hypertension and use of CVD medications; limited and mixed results for the metabolic syndrome and 10-y CVD risk	Reasonably consistent Imprecise	Intermediate health outcomes were not well reported Small size and short duration of many studies limited power to detect differences in intermediate outcomes in majority of studies No reporting bias suspected	Moderate for benefit (incident diabetes) Low for benefit (other interme-diate outcomes)	All but 1 trial reporting incident diabetes were limited to adults with prediabetes

(continued)

Table 3. Summary of Evidence, by Key Question and Intervention Type (continued)

Intervention	No. of Studies (No. of Observations)	Summary of Findings	Consistency and Precision[a,b]	Other Limitations	Strength of Evidence	Applicability
Behavior-based weight loss maintenance	0					
Medication-based weight loss	6 RCTs (13 256)	Incident diabetes (3 trials [n = 9484]): Absolute cumulative incidence of diabetes at up to 4-y follow-up ranged from 0%-6% in medication and 1%-11% in placebo groups, which were statistically different for most drugs Other intermediate outcomes: 4 trials reported mixed results for use of lipid-lowering and antihypertensive medications, prevalence of the metabolic syndrome, and 10-y CVD risk score	Reasonably consistent[d] Imprecise	Trials generally had high dropout rates No reporting bias suspected	Insufficient	21%-67% of participants had prediabetes
Medication-based weight loss maintenance	1 RCT (309)	Incident diabetes: Absolute cumulative incidence of diabetes at 3-y follow-up was 5% in medication and 11% in placebo groups, which was statistically different	NA (1 trial)	Only 1 trial with 35% dropout No reporting bias suspected	Insufficient	26% of participants had prediabetes
KQ3: Harms						
Behavior-based weight loss and weight loss maintenance	30 RCTs (12 824)	There were no serious harms related to the interventions, and most trials noted no differences between groups in the rates of adverse events, including cardiovascular events In the 3 trials large enough to examine musculoskeletal issues between groups, results were mixed	Reasonably consistent Precise	Harms sparsely reported for included trials Few details provided about how harms were recorded and specific events that occurred Did not include observational evidence on harms related to intentional weight loss No reporting bias suspected[e]	Low for harm	Applicable to US primary care population
Medication-based weight loss and weight loss maintenance	33 RCTs and 2 observational studies (239 428)	Serious adverse events were relatively uncommon and generally similar between groups Participants randomized to medications experienced more adverse events, which was associated with higher dropout rates in the medication groups than in the placebo groups	Reasonably consistent Imprecise	Few conducted statistical testing of differences between groups; harms listed on labels not well evaluated No reporting bias suspected	Moderate for harm	Highly selected group chosen for low risk of serious adverse events

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DPP, Diabetes Prevention Program; DPS, Diabetes Prevention Study; LSM, least squares mean; NA, not applicable; NNT, number needed to treat; NR, not reported; QOL, quality of life; RCT, randomized clinical trial; RR, risk ratio.

[a] Consistency defined as the degree to which contributing studies estimate the same direction of effect (ie, consistently suggest benefit or harm). Consistency can be rated as reasonably consistent, inconsistent, or not applicable.

[b] Precision is defined as the degree to which contributing studies estimate the same magnitude of effect (ie, precisely suggest the magnitude of benefit or harm). Precision can be rated as reasonably precise, imprecise, or not applicable.

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

[d] Data for incident diabetes are consistent, but data for CVD are inconsistent.

[e] Suspected in 1 case for a behavior-based maintenance trial.

Limitations

This review had several limitations. First, tertiary prevention studies were excluded if they specifically focused on persons with conditions for which weight loss is considered as part of disease management (eg, diabetes, polycystic ovarian syndrome), and studies of surgery or nonsurgical devices were excluded because these studies were considered outside the scope of primary care–relevant interventions.

Second, the review did not include continuous intermediate outcomes (eg, continuous measures of blood pressure, cholesterol levels, glucose levels); rather, it focused on specific diseases or risk factors (eg, diabetes, hypertension).

Third, data were pooled across a body of literature that was heterogeneous with respect to demographic characteristics, interventions, and settings. The considerable statistical heterogeneity (I^2 > 85%) indicates that the pooled results should be interpreted with caution and confidence interval estimates should be primarily used to understand the magnitude of effects. Across the trials, there were large standard deviations relative to the mean change, suggesting that some adults showed fairly large reductions in weight, some showed no or modest changes, and some gained weight.

Fourth, given the heterogeneity among intervention groups and differences in populations and settings, it was not possible to identify if particular intervention variables (ie, number of sessions, in-person vs remote, group- vs individual-based) were more effective. To fully address this would require examination of comparative effectiveness studies (which were specifically excluded in this review). However, the consistency seen across specific interventions and across various subgroups (albeit with a wide range in effect sizes) suggests that benefits are likely dependent on individual, social, and environmental factors rather than specific intervention characteristics.

Fifth, although weight loss interventions (both behavior-based and medication-based) were associated with short-term weight loss, there remains a paucity of data on what happens long term. Only a limited number of trials reported follow-up beyond 24 months, and in most of those, ongoing weight loss or maintenance sessions, medication use, or both occurred throughout follow-up. Survey data suggest that a minority of individuals are successful at long-term weight loss maintenance.[178,179]

Sixth, there was also a paucity of data on long-term health outcomes. While it appears that weight loss interventions can reduce diabetes incidence, larger trials with longer-term follow-up are required to understand the full benefits of these interventions on health outcomes and whether those effects are long-lasting. Additionally, there were few data on patient-centered outcomes such as QOL and psychological outcomes such as weight stigmatization,[180] eating disorders,[181-183] and weight fluctuation ("yo-yo" dieting).[184-186]

Seventh, many of the trials, especially those examining weight loss medications, may have been biased by high attrition; nearly half of the studies had attrition of 35% of more. Studies with high attrition were included because early discontinuation was likely a result of the intervention (ie, adverse effects, lack of weight loss, time commitments) and not necessarily design flaws. Although it was required that trials use multiple imputation methods or procedures for accounting for missing data, imputing such large amounts of data might have led to biased comparisons in unknown directions.

Eighth, almost all studies relied on BMI to identify their populations. Although long-term health risks increase with increasing BMI, the precise BMI at which increased risk occurs—and the strength of the relationship—appears to vary by race/ethnicity, age, and personal or lifestyle factors.[187-213] Participants generally fell into the overweight and obese categories, and results were not reliably stratified by BMI. It was therefore not possible to make conclusions about whether the health effects of weight loss interventions varied according to baseline BMI category, age, and race/ethnicity. Future trials should examine the effects of weight loss interventions in diverse populations stratified by BMI as well as emerging classification systems, which include assessment of physical, mental, and functional health to characterize obesity severity.[214,215]

Conclusions

Behavior-based weight loss interventions with or without weight loss medications were associated with more weight loss and a lower risk of developing diabetes than control conditions. Weight loss medications, but not behavior-based interventions, were associated with higher rates of harms. Long-term weight and health outcomes data, as well as data on important subgroups, were limited.

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Concept and design: LeBlanc, Patnode, Webber, O'Connor.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: LeBlanc, Webber, Redmond, Rushkin.
Critical revision of the manuscript for important intellectual content: LeBlanc, Patnode, Webber, O'Connor.
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