

The Role of Weight Management in the Treatment of Adult Obstructive Sleep Apnea

An Official American Thoracic Society Clinical Practice Guideline

David W. Hudgel, Sanjay R. Patel, Amy M. Ahasic, Susan J. Bartlett, Daniel H. Bessesen, Melisa A. Coaker, P. Michelle Fiander, Ronald R. Grunstein, Indira Gurubhagavatula, Vishesh K. Kapur, Christopher J. Lettieri, Matthew T. Naughton, Robert L. Owens, Jean-Louis D. Pepin, Henri Tuomilehto, and Kevin C. Wilson; on behalf of the American Thoracic Society Assembly on Sleep and Respiratory Neurobiology

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Background: Overweight/obesity is a common, reversible risk factor for obstructive sleep apnea severity (OSA). The purpose of this guideline is to provide evidence-based recommendations for the management of overweight/obesity in patients with OSA.

Methods: The Grading of Recommendations, Assessment, Development and Evaluation approach was used to evaluate the literature. Clinical recommendations were formulated by a panel of pulmonary, sleep medicine, weight management, and behavioral science specialists.

Results: Behavioral, pharmacological, and surgical treatments promote weight loss and can reduce OSA severity, reverse common comorbidities, and improve quality of life, although published studies have methodological limitations. After considering the quality of evidence, feasibility, and acceptability of these interventions, the panel made a strong recommendation that patients with OSA who are overweight or obese be treated with comprehensive lifestyle

intervention consisting of 1) a reduced-calorie diet, 2) exercise or increased physical activity, and 3) behavioral guidance. Conditional recommendations were made regarding reduced-calorie diet and exercise/increased physical activity as separate management tools. Pharmacological therapy and bariatric surgery are appropriate for selected patients who require further assistance with weight loss.

Conclusions: Weight-loss interventions, especially comprehensive lifestyle interventions, are associated with improvements in OSA severity, cardiometabolic comorbidities, and quality of life. The American Thoracic Society recommends that clinicians regularly assess weight and incorporate weight management strategies that are tailored to individual patient preferences into the routine treatment of adult patients with OSA who are overweight or obese.

Keywords: obstructive sleep apnea; obesity; comprehensive lifestyle intervention; weight-loss medications; bariatric surgery

Contents	Peer Review	OSA Who Are Overweight or Obese?; and Question 3: Should Both a Reduced-Calorie Diet and Exercise/Increased Physical Activity Be Recommended (Rather Than a Reduced-Calorie Diet Alone) to Patients with OSA Who Are Overweight or Obese?
Overview	Results	
Summary of Recommendations	Question 1: Should a Reduced-Calorie Diet Be Recommended (Rather Than No Diet) to Patients with OSA Who Are Overweight or Obese?	
Introduction	Question 2: Should Exercise/Increased Physical Activity Be Recommended (Rather Than No Exercise) to Patients with	
Methods		
Panel Composition		
Questions		
Literature Search		
Evidence Synthesis		
Recommendations		
Manuscript Preparation		

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ORCID IDs: 0000-0003-3148-723X (D.W.H.); 0000-0002-9142-5172 (S.R.P.); 0000-0001-9755-2490 (S.J.B.); 0000-0002-3579-9292 (P.M.F.); 0000-0001-6682-5812 (R.R.G.); 0000-0002-5417-1097 (V.K.K.); 0000-0001-7950-2908 (C.J.L.); 0000-0003-2734-0841 (M.T.N.); 0000-0002-6515-6204 (R.L.O.); 0000-0003-4429-2263 (K.C.W.).

Correspondence and requests for reprints should be addressed to David W. Hudgel, M.D., 10103 Beaver Dam Crescent, Box 186, Grand Bend, ON, N0M 1T0, Canada. E-mail: dgern@thoracic.org.

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Question 4: Should a Comprehensive Lifestyle Intervention (i.e., a Program That Includes a Reduced-Calorie Diet, Exercise/ Increased Physical Activity, and Behavioral Counseling) Be Recommended (Rather Than No Weight-Loss Intervention) to Patients with OSA Who Are Overweight or Obese?; and Question 5: Should a Comprehensive Lifestyle Intervention (i.e., a Program That Includes a Reduced-Calorie Diet,

Exercise/Increased Physical Activity, and Behavioral Counseling) Be Recommended (Rather Than a Reduced-Calorie Diet Alone) to Patients with OSA Who Are Overweight or Obese? Question 6: Should Weight-Loss Medications Be Recommended (Rather Than Comprehensive Lifestyle Intervention Alone) to Patients with OSA Who Are Overweight or Obese and Who Have Been Unsuccessful in Losing Weight with Lifestyle Intervention?

Question 7: Should Bariatric Surgery Be Recommended (Rather Than Comprehensive Lifestyle Intervention Alone) to Patients with OSA Who Are Overweight or Obese and Who Have Been Unsuccessful in Losing Weight with Lifestyle Intervention?

Discussion

**What Others Are Saying
Putting It All Together
Future Research
Conclusions**

Overview

Although previously developed guidelines on the treatment of adult obstructive sleep apnea (OSA) recommended weight loss for patients who are overweight or obese, detailed analyses of the impact of weight-loss therapies on OSA and its sequelae, as well as recommendations on specific weight management strategies, were not provided. The purpose of this clinical practice guideline is to 1) review the evidence of the impact of weight-loss interventions on OSA severity, quality of life, and associated comorbidities and 2) provide specific recommendations for weight management in adult patients with OSA who are overweight or obese, as defined as a body mass index (BMI) greater than or equal to 25 kg/m². A panel of sleep and pulmonary physicians, weight management experts, and behavioral scientists developed seven therapy-related questions, reviewed the relevant literature, and used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to summarize the outcomes and shortcomings of the literature. On the basis of this analysis, evidence-based recommendations were made for the management of overweight/obesity in adults with OSA.

The following questions were developed for the evidence-based review:

Question 1: Should a reduced-calorie diet be recommended (rather than no diet) to patients with OSA who are overweight or obese?

Question 2: Should exercise/increased physical activity be recommended (rather than no exercise) to patients with OSA who are overweight or obese?

Question 3: Should both a reduced-calorie diet and exercise/increased physical activity be recommended (rather than a reduced-calorie diet alone) to patients with OSA who are overweight or obese?

Question 4: Should a comprehensive lifestyle intervention (i.e., a program that includes a reduced-calorie diet, exercise/increased physical activity, and behavioral counseling) be recommended (rather than no weight-loss intervention) to patients with OSA who are overweight or obese?

Question 5: Should a comprehensive lifestyle intervention (i.e., a program that includes a reduced-calorie diet, exercise/increased physical activity, and behavioral counseling) be recommended (rather than a reduced-calorie diet alone) to patients with OSA who are overweight or obese?

Question 6: Should weight-loss medications be recommended (rather than comprehensive lifestyle intervention alone) to patients with OSA who are overweight or obese and who have been unsuccessful in losing weight with lifestyle intervention?

Question 7: Should bariatric surgery be recommended (rather than comprehensive lifestyle intervention alone) to patients with OSA who are overweight or obese and who have been unsuccessful in losing weight with lifestyle intervention?

Summary of Recommendations

- For patients with OSA who are overweight or obese (i.e., BMI \geq 25 kg/m²):
 - We **recommend** participation in a comprehensive lifestyle intervention program that includes a reduced-calorie diet, exercise/increased physical activity, and behavioral counseling rather than no program (strong recommendation, very low certainty in the estimated effects).
 - We **suggest** participation in a comprehensive lifestyle intervention program that includes a reduced-calorie diet, exercise/increased physical activity, and behavioral counseling rather than a program that includes only a reduced-calorie diet, with or without exercise/increased physical activity (conditional recommendation, very low certainty in the estimated effects).
 - We **suggest** participation in a reduced-calorie diet (with or without exercise/increased physical activity) rather than no diet (conditional recommendation, very low certainty in the estimated effects).
 - We **suggest** exercise/increased physical activity rather than no exercise or increased physical activity (conditional recommendation, very low certainty in the estimated effects).
- For patients with OSA with a BMI greater than or equal to 27 kg/m², whose weight has not improved despite participating in a comprehensive weight-loss lifestyle program, and who have

no contraindications including no active cardiovascular disease, we **suggest** an evaluation for antiobesity pharmacotherapy (conditional recommendation, very low certainty in the estimated effects).

- For patients with OSA with a BMI greater than or equal to 35 kg/m², whose weight has not improved despite participating in a comprehensive weight-loss lifestyle intervention program, and who have no contraindications, we **suggest** referral for bariatric surgery evaluation (conditional recommendation, very low certainty in the estimated effects).

Note: In recommending weight management strategies for patients with OSA who are overweight or obese, it is recommended that clinicians discuss options and involve patients in shared decision-making, considering their values and preferences (*see* DISCUSSION section below).

Introduction

The relationship between weight gain and the development and worsening of OSA is well established (1–4). Furthermore, obesity and OSA are complexly intertwined because obesity is an aggravating factor for many of the known metabolic and cardiovascular comorbidities of OSA (5, 6). Published guidelines for the management of OSA acknowledge obesity as an exacerbating factor for OSA and mention weight loss as an adjunctive therapeutic tool (7–10). However, none provides detailed recommendations about how to achieve weight loss. Perhaps because of the absence of specific clinically relevant recommendations, weight-loss strategies have not been implemented systematically in the routine care of patients with OSA who are overweight or obese.

To address this knowledge gap, the American Thoracic Society (ATS) commissioned a panel of pulmonary and sleep medicine specialists, weight management experts, behavioral scientists, and patients to summarize the relevant evidence and make recommendations regarding weight-loss interventions in the care of patients with OSA who are overweight or obese. Overweight was defined as a BMI of 25.0–29.9 kg/m² (or, in some studies, BMI of 27.0–29.9 kg/m²) and obesity, which can be further subdivided

into grade I obesity (BMI, 30.0–34.9 kg/m²), grade II obesity (BMI, 35.0–39.9 kg/m²), and grade III obesity (BMI, ≥40.0 kg/m²). The cutoffs used in various regions of the world for categorizing people as overweight or obese may be different based on ethnic and/or racial differences defining the risks for weight-related disorders in different populations.

Methods

This clinical practice guideline was developed in accordance with ATS policies and procedures.

Panel Composition

The project was proposed by the chair and co-chair through the ATS Sleep and Respiratory Neurobiology Assembly and was approved by the ATS Board of Directors. Potential panelists were identified by the chair and co-chair on the basis of their expertise in sleep-disordered breathing, weight management, and/or behavioral science. All potential panelists disclosed their conflicts of interest to the ATS. Panelists determined to have no substantial conflicts of interest were “approved without limitation,” whereas those with potential conflicts of interest that were considered manageable were “approved with management,” allowing participation in discussions about the evidence but not in the formulation of recommendations related to their conflicts of interest. Potential panelists whose conflicts of interest were deemed not manageable were disqualified. The final guideline panel consisted of 20 members: a chair, a co-chair, 10 additional experts in sleep-disordered breathing, 1 expert in weight management, 1 behavioral scientist, 3 patients, 1 lead methodologist, and 2 medical librarians. One sleep-disordered breathing expert and one librarian served as additional methodologists.

Questions

The chair and co-chair and lead methodologist drafted key clinical questions in a PICO (population, intervention, comparator, and outcome) format. The questions were then discussed, modified, and approved by the full guideline panel. Outcomes that might be affected by each of the interventions were numerically rated (from 1 to 7) according to their importance. The evidence was assessed only for outcomes whose average rating fell into the “important” or “critical” categories. The primary outcomes evaluated were quality of life, mortality, weight loss, change in OSA severity, resolution of OSA,

cardiovascular events or stroke, major and minor adverse events, daytime sleepiness, other OSA-related symptoms, sexual function, and glycemic control. Three individuals with OSA were consulted to obtain a patient perspective about the appropriateness of these questions and the most relevant clinical outcomes.

Literature Search

The published literature was searched in the following databases: MEDLINE, Excerpta Medica Database (Embase), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, Cochrane Central Database of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), NHS Economic Evaluations Database, Database of Abstracts of Reviews of Effectiveness (DARE), and Health Technology Assessment (HTA) Database. Search strategies consisted of controlled vocabulary terms (such as Medical Subject Headings), keyword terms, and phrases. Conceptual sets included 1) OSA and obesity and 2) OSA and weight-loss interventions (e.g., drug therapy or surgery or exercise therapy or nutritional therapy or diet), which were combined using Boolean “OR.” Filters were used as needed to narrow the search results according to study design. Searches were not limited by publication date or language, and databases were searched from date of inception to search date. Searching was conducted in July and August 2015 and then updated in February 2017 and February 2018. Gray literature searches consisted of searching Gray Matters (11), ClinicalTrials.gov (12), the World Health Organization’s International Clinical Trials Registry Platform (13), and the bibliographic databases on the websites of select organizations. These resources are itemized in the online supplement.

Evidence Synthesis

The lead methodologist (A.M.A.) reviewed all publications retrieved from the literature searches for relevance, initially screening on the basis of title and/or abstract and then reviewing the full text of potentially relevant publications, as were the included and excluded studies lists of related systematic reviews. Published abstracts were used if they contained data on at least one of our outcomes of interest. Findings from relevant publications were extracted into structured data tables. Only randomized trials were

extracted. Duplicate data abstraction was not mandated. When data from individual studies were amenable to pooling, the random effects model of DerSimonian and Laird as implemented in the Cochrane Collaboration Review Manager, version 5.3, was used to pool results across studies (14, 15). Relative risk (RR) was used to report the results for dichotomous outcomes, and the mean difference (MD) was used to report the results for continuous outcomes, each with an accompanying 95% confidence interval (CI). Statistical heterogeneity of the pooled results was measured using the I^2 and chi-square tests, considering an I^2 value greater than or equal to 50% or a chi-square $P \leq 0.05$ to indicate significant heterogeneity. Results from the meta-analyses are provided in the evidence tables in the online supplement.

We used the GRADE approach to assess certainty in the estimated effects (i.e., the quality of evidence) for each intervention on each outcome of interest (16). The lead methodologist created evidence profiles using the Guideline Development Tool (17), which categorized the overall certainty in the evidence into one of four levels: high, moderate, low, or very low. Each level represents the certainty in the accuracy of the estimated effects for a specific intervention. The full guideline panel reviewed the evidence profiles and provided input and feedback.

Recommendations

The guideline panel met at the 2016 ATS International Conference in San Francisco

and several subsequent conference calls to discuss the evidence profiles and develop recommendations to answer each PICO question using the Evidence to Decision framework (18, 19). No relevant data could be identified for two of the initial PICO questions, so these were dropped from further consideration. These questions were as follows: 1) Should both a reduced-calorie diet and exercise/increased physical activity be recommended (rather than exercise alone) to patients with OSA who are overweight or obese? and 2) Should weight-loss medications be recommended to patients with OSA who are overweight or obese (rather than no weight-loss intervention)?

The panelists made decisions about whether to recommend for or against an intervention on the basis of the balance of desirable consequences (benefits) and undesirable consequences (burdens, adverse effects), quality of evidence, cost and cost-effectiveness, feasibility, and acceptability to patients (i.e., patient values and preferences). Using the GRADE approach, the panelists rated each recommendation as either “strong” or “conditional.” The meanings of “strong” and “conditional” recommendations are described in Table 1, and the methods employed are summarized in Table 2. All recommendations were formulated and graded by discussion and consensus; voting was never required.

Manuscript Preparation

The initial draft of the manuscript was written by the chair and co-chair and lead methodologist with major contributions from

task force members for certain sections. All members of the guideline panel reviewed the manuscript; comments were addressed by the chair and co-chair, and the revised manuscript was redistributed to the full panel for further review. Revision and full-panel review occurred twice. Once the manuscript was approved by the full panel, it was submitted for external peer review. Evidence tables are provided in the online supplement.

Peer Review

External peer review was organized and overseen by the ATS Documents Editor. Comments from the reviewers were collated into a single decision letter and sent to the chair. The manuscript was subsequently revised by the panel according to feedback received from the peer reviewers. After several cycles of review and revisions, the manuscript was deemed satisfactory and sent to the ATS Board of Directors for further review and final approval.

Results

Question 1: Should a Reduced-Calorie Diet Be Recommended (Rather Than No Diet) to Patients with OSA Who Are Overweight or Obese?

Summary of the evidence from non-OSA literature. The NIH/NHLBI Guideline on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults conducted a meta-analysis of 34 randomized controlled trials (RCTs), finding a strong and

Table 1. Implications of Strong and Conditional Recommendations

	Strong Recommendation	Conditional Recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful in helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.
For policy makers	The recommendation can be adopted as policy in most situations, including for use as performance indicators.	Policy making will require substantial debate and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

Table 2. Summary of Guideline Development Methods

Activity	Yes	No
Panel assembly included experts for relevant clinical and nonclinical disciplines	X	
Included a methodologist with appropriate expertise (documented expertise in conducting systematic reviews to identify the evidence base and the development of evidence-based recommendations)	X	
Included an individual who represents the views of patients and society at large	X	
Literature review performed in collaboration with librarian	X	
Searched multiple electronic databases; reviewed reference lists of retrieved articles	X	
Evidence synthesis applied prespecified inclusion and exclusion criteria	X	
Evaluated included studies for sources of bias	X	
Used GRADE to describe quality of evidence	X	
Generation of recommendations used GRADE to rate the strength of recommendations	X	

Definition of abbreviation: GRADE = Grading of Recommendations, Assessment, Development and Evaluation.

consistent effect of reduced-calorie diets consisting of approximately 1,000–1,200 kcal/d in inducing weight loss (20). Of the studies lasting 6 months or more, mean weight loss with a reduced-calorie diet was about 8% of body weight compared with control. The American Heart Association/American College of Cardiology (AHA/ACC) guidelines group conducted a review of three trials comparing low-fat with low-carbohydrate diets and five trials comparing high-protein with low-protein diets, finding no difference in weight loss between diets after controlling for the amount of caloric deficit (21). Similarly, studies of reduced-carbohydrate diets, low-glycemic load diets, Mediterranean-style diets, and vegan diets all suggested no benefit of one diet over another for weight loss after adjusting for caloric intake.

Summary of the evidence from OSA-specific literature. Our literature search identified two randomized trials and an abstract that evaluated the effect of weight loss in people with OSA (22–24); the abstract reported on a study in progress and did not include sufficient data for analysis (22). The trials were not pooled, because, other than weight change, they reported different outcomes.

The earlier trial randomly assigned 23 moderately obese patients with snoring and excessive daytime sleepiness to either caloric restriction to induce weight loss of 0.5 kg/wk

or no dietary changes (23). Baseline sleep studies were performed, and then the patients were followed until body weight had decreased 5% in the weight-loss group and had stabilized in the control group. Repeat sleep studies were then performed. Follow-up ranged from 5 to 8 months.

Patients in the weight-loss group had a larger decrease in their apnea index during non-REM sleep than patients in the control group (MD, 30.3 fewer events/h; 95% CI, 1.9 to 58.7 fewer events/h). There were also differences between the groups that did not reach statistical significance, including weight loss (MD, 11.0 kg more in the weight-loss group; 95% CI, 39.5 more to 17.5 kg less), apnea index during REM sleep (MD, 19.4 fewer events/h in the weight-loss group; 95% CI, 50.7 fewer to 11.9 more events/h), and mean oxygen saturation as measured by pulse oximetry during non-REM sleep (3.4% less desaturation in weight-loss group; 95% CI, 11.2% less to 4.4% more desaturation) and REM sleep (7.2% less desaturation in the weight-loss group; 95% CI, 20.0% less desaturation to 5.7% more desaturation).

A later trial randomly assigned 29 patients with OSA to follow a reduced-calorie diet (–800 kcal/d) or to make no dietary changes for 4 months (24). Patients in the weight-loss group had a larger decrease in their BMI (MD, 2.0 kg/m² lower; 95% CI, 3.4–0.5 kg/m² lower),

neck circumference (MD, 0.8 cm smaller; 95% CI, 0.1–1.5 cm smaller), and apnea–hypopnea index (AHI) (7.35 fewer events/h; 95% CI, 0.8 to 13.9 fewer events/h) than patients in the control group. The weight-loss group also had non–statistically significant greater weight loss (MD, 6.0 kg more weight loss; 95% CI, 16.7 kg more to 4.7 kg less weight loss).

When taking these studies together, we found that patients randomized to a dietary intervention had non–statistically significant greater weight loss than control individuals (MD, 6.6 kg more weight loss; 95% CI, 16.7 kg more weight loss to 3.4 less weight loss). Neither trial reported on quality of life, daytime sleepiness, other OSA-related symptoms, cardiovascular events, mortality, or adverse events. The panel’s confidence in the estimated effects was very low because both trials were small with a serious risk of bias due to the absence of blinding and high dropout rates.

Conclusions. In patients with OSA who are overweight or obese, a weight-loss program focusing on reduced-calorie diet alone was associated with decreases in BMI, neck circumference, and OSA severity. Adverse effects were not reported. The panel judged that the benefits of a weight-loss program focusing on diet outweigh the risks, burdens, and costs, but the panel’s confidence was tempered by its very low certainty in the estimated effects.

Recommendation. For patients with OSA who are overweight or obese, we **suggest** a reduced-calorie diet (with or without exercise/increased physical activity) rather than no diet (conditional recommendation, very low certainty in the estimated effects).

Question 2: Should Exercise/ Increased Physical Activity Be Recommended (Rather Than No Exercise) to Patients with OSA Who Are Overweight or Obese?; and Question 3: Should Both a Reduced-Calorie Diet and Exercise/Increased Physical Activity Be Recommended (Rather Than a Reduced-Calorie Diet Alone) to Patients with OSA Who Are Overweight or Obese?

Summary of the evidence from non-OSA literature. The NIH/NHLBI review evaluated studies that assessed the impact of increased physical activity, typically aerobic activities (20). Twelve randomized trials found that increased physical activity had a

modest impact on weight loss; 10 of 12 studies reported a weight loss that averaged 2.4% of baseline weight, whereas 2 of 12 studies reported a weight gain compared with control. Two meta-analyses found that when combined with diet, exercise led to greater weight loss than diet alone in studies lasting more than 1 year, but this improvement did not occur in shorter-duration studies (25, 26). These data suggest that increased physical activity may play a greater role in prevention of weight regain than in increasing weight loss *per se*. However, aerobic exercise is associated with other advantages, such as producing a clinically significant reduction in blood pressure (27, 28). In a meta-analysis of 47 randomized clinical trials, mean reduction in blood pressure was 6 mm Hg systolic and 5 mm Hg diastolic in patients with hypertension and 2 mm Hg systolic and 1 mm Hg diastolic in normotensive individuals (28).

Summary of the evidence from OSA-specific literature. We identified 10 randomized trials that compared either exercise versus no exercise or exercise plus reduced-calorie diet versus diet alone in patients with OSA; 8 of the trials were published manuscripts (29–36), and 2 were abstracts (37, 38). One abstract did not include enough data to be pooled with other trials and thus was not considered further (38). Two trials were not pooled with other studies because the populations and interventions differed significantly from other included trials; specifically, both trials looked at patients with cardiac disease but did not specifically enroll overweight and/or obese patients, and they included patients with central or mixed sleep apnea (34, 36).

All other trials enrolled sedentary patients with OSA who were overweight or obese. In the majority of trials, patients had moderate to severe OSA (AHI, ≥ 15 events/h) (29, 30, 32, 33), although one trial enrolled patients with mild OSA (AHI, 5–14 events/h) (31), and one trial did not indicate the severity of OSA (37). Three trials specified a maximum allowable BMI for enrollment, which ranged from 30 to 40 kg/m² (30, 32, 33). The exercise training groups received a variety of training approaches, including aerobic only (31, 33), aerobic plus resistance (29, 30, 32, 34), or unspecified individualized exercise training (37), which ranged from 4 weeks to 6 months in duration. One three-armed study protocol randomized patients to exercise under normoxic versus hypoxic

conditions or to control (35). Data from the hypoxic arm of this study was not considered, because this was not an exercise intervention of interest *a priori*. Control groups were highly variable and included no exercise or standard care (31, 34, 37), “healthy” diet (32), stretching only (29), education (30), or continuous positive airway pressure (CPAP) or oral appliance therapy (32). One study used CPAP in both the intervention and control groups (33).

Measured outcomes of interest included weight, AHI, daytime sleepiness, sleep quality, mortality, and adverse events (see Table E1 in the online supplement). When the trials were pooled, exercise did not cause weight loss, whether measured by body weight (MD, +2.1 kg; 95% CI, –4.3 to +8.6 kg), BMI (MD, –0.04 kg/m²; 95% CI, –1.7 to +1.6 kg/m²), or neck circumference (MD, +0.4 cm; 95% CI, –1.5 to +2.4 cm). There were also no changes in the AHI (MD, –0.8 events/h; 95% CI, –13.4 to +11.8 events/h), mortality, daytime sleepiness, or adverse events. The only change among the pooled outcomes was an improvement in sleep quality as measured by the Pittsburgh Sleep Quality Index (MD, –2.7; 95% CI, –4.3 to –1.0); this change was smaller than what is generally considered important (i.e., the minimal clinically important difference is ≥ 3) (39), and absolute postintervention mean values were still indicative of poor sleep (40). In single trials, exercise decreased serum glucose (30) and improved depression, fatigue, vigor, vitality, and physical functioning (29). The panel’s confidence in these estimated effects was very low because the trials were small with a serious risk of bias due to the absence of blinding and short durations of follow-up.

Conclusions. For patients with OSA who are overweight or obese, short-term increases in exercise/increased physical activity did not produce clinically significant weight loss or improvement in OSA severity, although they were associated with a minimal improvement in sleep quality. It is well known, however, that exercise/increased physical activity may lead to an improvement in general health, including blood pressure. The panel judged that the benefits of exercise/increased physical activity likely outweigh the risks and burdens in most patients with OSA who are overweight or obese if one considers benefits beyond OSA-specific outcomes. The panel also believed that diet and

exercise are likely complementary, with the former inducing weight loss and improving OSA severity and the latter improving general well-being. The panel’s certainty was tempered by its very low confidence in the estimated effects and its recognition that the majority of evidence was derived from studies that compared exercise with no exercise rather than exercise plus diet with diet alone.

Recommendation. For patients with OSA who are overweight or obese, we **suggest** exercise/increased physical activity rather than no exercise/increased physical activity, regardless of whether a reduced-calorie diet is added (conditional recommendation, very low certainty in the estimated effects).

Question 4: Should a Comprehensive Lifestyle Intervention (i.e., a Program That Includes a Reduced-Calorie Diet, Exercise/Increased Physical Activity, and Behavioral Counseling) Be Recommended (Rather Than No Weight-Loss Intervention) to Patients with OSA Who Are Overweight or Obese?; and Question 5: Should a Comprehensive Lifestyle Intervention (i.e., a Program That Includes a Reduced-Calorie Diet, Exercise/Increased Physical Activity, and Behavioral Counseling) Be Recommended (Rather Than a Reduced-Calorie Diet Alone) to Patients with OSA Who Are Overweight or Obese?

Summary of the evidence from non-OSA literature. The NIH/NHLBI review identified four randomized trials evaluating the addition of behavioral therapy to other weight-loss interventions (20). Three of the four trials found the addition of a behavioral intervention increased the amount of weight lost at the end of the intervention or at 1 year. However, follow-up 5 years after cessation of the behavioral intervention found no long-term difference in weight, suggesting that behavioral interventions need to be maintained to minimize weight regain. A comparison of different behavioral strategies found no clear benefit of one strategy over another, but it showed that the use of multimodal strategies and greater intensity of therapy predicted greater weight loss. The AHA/ACC guidelines identified 10 randomized trials evaluating a high-intensity comprehensive lifestyle intervention combining behavioral therapy,

reduced-calorie diet, and exercise/ increased physical activity with a minimum of 14 in-person sessions with a trained interventionist over the initial 6 months (41). Overall, lifestyle intervention produced weight loss of about 8 kg at both 6 and 12 months, which was significantly greater than the usual care or no intervention arm. The most common behavioral strategy used was self-monitoring, but problem solving, stimulus control, and relapse prevention were also commonly incorporated. High-intensity interventions (≥ 14 visits over 6 mo) were associated with greater weight loss than moderate-intensity (6–12 visits over 6 mo) or low-intensity (< 6 visits over 6 mo) lifestyle interventions.

Summary of the evidence from OSA-specific literature. Our literature search identified nine randomized trials that compared a reduced-calorie diet plus behavioral modification with no intervention in patients with OSA who were overweight or obese (42–50). Some of the trials incorporated exercise (supervised or unsupervised) as part of the intervention (44, 46, 48–50). One additional study was identified that examined a behavioral intervention specifically aimed at increasing fruit and vegetable consumption added to dietary advice aimed at weight loss versus dietary advice alone (51). Data from this study were not analyzed further, owing to the specific nature of the behavioral intervention, which was outside the scope of the panel's interventions of interest. No other studies were found comparing a comprehensive lifestyle intervention with reduced-calorie diet alone. Four trials included at least some overweight patients (BMI, ≥ 25 kg/m²) (42, 48–50), five enrolled only patients whose BMI was greater than or equal to 30 kg/m² (43–47), and three set upper limits of 40 kg/m² or 45 kg/m² on the allowable BMI (46, 48, 49). One trial enrolled only patients with mild sleep apnea (AHI, 5–15 events/h) (49), one trial enrolled patients with an AHI greater than or equal to 10 events/h (43), five trials enrolled patients with an AHI greater than or equal to 15 events/h (42, 44, 46, 47, 50), and two trials allowed OSA of all severities (45, 48). Among diets, five trials included meal substitution (43, 46–49), and four did not (42, 44, 45, 50). Behavioral interventions were wide ranging and included various combinations of self-determination, goal setting, stimulus

control, self-monitoring, self-regulation, group support, problem solving, and relapse prevention. The trials' durations ranged from 9 weeks to 12 months.

Measured outcomes of interest included change in weight or other measures of weight loss, change in AHI, resolution of OSA, daytime sleepiness, quality of life, other OSA symptoms, glycemic control, adverse events, and mortality. Comprehensive lifestyle interventions improved multiple outcomes (Table E2). These programs induced weight loss when any meal substitution was included in the dietary intervention (change in weight: MD, -11.6 kg; 95% CI, -17.8 to -5.3 kg; change in BMI: MD, -4.1 kg/m²; 95% CI, -6.3 to -2.0 kg/m²). Weight loss was not significant in the absence of meal substitution (change in weight: MD, -0.8 kg; 95% CI, -3.0 to $+1.5$ kg; change in BMI: MD, -1.9 kg/m²; 95% CI, -4.9 to $+1.2$ kg/m²). Similarly, weight loss was observed in interventions that included exercise/increased physical activity compared with control (change in weight: MD, -9.0 kg; 95% CI, -10.5 to -7.4 kg; change in BMI: MD, -3.2 kg/m²; 95% CI, -4.1 to -2.3 kg/m²), whereas weight loss was not significant in studies that did not include exercise (change in weight: MD, -7.2 kg; 95% CI, -19.9 to $+5.6$ kg; change in BMI: MD, -3.4 kg/m²; 95% CI, -7.7 to $+0.9$ kg/m²). There was considerable heterogeneity and inconsistency among studies without an exercise intervention. Comprehensive lifestyle interventions were associated with reduced OSA severity (change in AHI: MD, -8.5 events/h; 95% CI, -10.8 to -6.3 events/h) and reduced daytime sleepiness as measured by the Epworth Sleepiness Scale (ESS) (MD, -2.4 points; 95% CI, -5.4 to -0.5 points).

Several other outcomes were not pooled, because they were reported from only a single trial. These included increased resolution of OSA (defined as AHI < 5 events/h at end of study) (57.1% vs. 30.6%; RR, 1.87; 95% CI, 1.06–3.31), reduced snoring as measured by the Snore Outcomes Survey (MD, 7.2 points; 95% CI, 1.4 to 13.1 points), and reduced neck circumference (MD, -1.3 cm; 95% CI, -1.9 to -0.8 cm). No deaths were reported in any of the trials. There was no difference in reported serious or any adverse events. The impact of comprehensive lifestyle interventions on quality of life and glucose control was uncertain owing to inconsistent

results. Notably, the decrease in AHI correlated with the magnitude of weight loss (43, 48, 50).

The beneficial effects of comprehensive lifestyle modification were further supported by two randomized trials that were published after completion of our evidence synthesis. One trial compared comprehensive lifestyle modification with general advice to lose weight (52), and the other compared lifestyle modification with three education sessions to discuss diet and exercise in individuals who were overweight and had OSA (53). In both trials, individuals who received the comprehensive lifestyle modification had a larger decrease in their AHI.

The panel's confidence in the estimated effects ranged from very low to moderate, depending on the outcome. Reasons for the panel's diminished confidence included imprecision due to small sample size and few events, as well as risk of bias due to lack of blinding, short durations of follow-up, failure to describe concealment, failure to adequately describe randomization procedures, and high dropout rates.

Conclusions. Comprehensive lifestyle interventions that combine reduced-calorie diet (especially meal substitution), exercise/increased physical activity, and behavioral modifications are associated with numerous desirable consequences, including weight loss, reductions in OSA severity, and improvement in daytime sleepiness in patients with OSA who are overweight or obese. They may also decrease neck circumference, reduce snoring, and lead to resolution of OSA. Moreover, comprehensive lifestyle interventions have no significant demonstrable harm and, therefore, minimal undesirable consequences. As a result, the panel was certain that the balance of desirable to undesirable consequences of a comprehensive lifestyle intervention greatly exceeds the balance for no intervention, because there is no reason to expect benefits from no intervention. The panel was less certain that the balance of desirable to undesirable consequences of a comprehensive lifestyle intervention exceeds the balance for a reduced-calorie diet, but they believed that it was likely. The panel's lack of certainty was due to the absence of any controlled studies comparing comprehensive lifestyle intervention with reduced-calorie diets in

patients with OSA and, therefore, the need to inform the recommendation with indirect evidence from the general obese population.

Recommendations.

- For patients with OSA who are overweight or obese, we **recommend** participation in a comprehensive lifestyle intervention program that includes a reduced-calorie diet, exercise/increased physical activity, and behavioral counseling rather than no program (**strong** recommendation, very low certainty in the estimated effects).
- For patients with OSA who are overweight or obese, we **suggest** participation in a comprehensive lifestyle intervention program that includes a reduced-calorie diet, exercise/increased physical activity, and behavioral counseling rather than a program that includes only a reduced-calorie diet, with or without exercise/increased physical activity (**conditional** recommendation, very low certainty in the estimated effects).

Question 6: Should Weight-Loss Medications Be Recommended (Rather Than Comprehensive Lifestyle Intervention Alone) to Patients with OSA Who Are Overweight or Obese and Who Have Been Unsuccessful in Losing Weight with Lifestyle Intervention?

Summary of the evidence from non-OSA

literature. All recent authoritative guidelines agree that among patients who are unable to achieve or sustain weight loss through a comprehensive lifestyle intervention, consideration should be given to adjunctive pharmacotherapy if their BMI is greater than or equal to 30 kg/m² or their BMI is greater than or equal to 27 kg/m² with weight-related comorbidities (such as OSA), unless otherwise contraindicated (16, 17).

We conducted a systematic review to identify studies assessing the effects of U.S. Food and Drug Administration–approved weight-loss medications. These agents included phentermine, orlistat, lorcaserin, liraglutide, naltrexone/bupropion, and phentermine/topiramate extended release (ER). Our initial search was limited to studies that specifically enrolled patients with OSA; it yielded only three studies (54–56), one of which was published only

as an abstract that did not report enough data for analysis (56). Two additional studies that specifically did not enroll patients with OSA gave some OSA-related outcome data (57, 58). Thus, our search was expanded to include studies that did not specifically recruit patients with OSA. Forty-six additional RCTs were identified across the six medications of interest, although one trial of naltrexone/bupropion was excluded from analysis because it was stopped early owing to breach of confidentiality (59). The majority of the additional studies were conducted with orlistat (57, 58, 60–81). In addition, four studies of liraglutide (82–85), two studies of phentermine/topiramate (86, 87), three studies of lorcaserin (88–90), four studies of naltrexone/bupropion (91–94), and eight studies measuring the effects of phentermine (95–102) were identified. All of the phentermine studies were published between 1969 and 1981 and generally did not meet current standards for reporting of randomized trial methods and data, thus limiting meaningful analysis of results. A summary of the findings of these studies is represented in Table 3.

The duration of these studies ranged from 20 to 56 weeks. Combined, these trials included over 30,000 patients, more than half of whom received medications. The overall quality of the included studies was low because the existing data were generated largely by manufacturer-funded trials and/or limited by high dropout rates (30–50% in most studies). In addition, there was significant variability regarding the effect of these medications on weight loss. Across studies, the use of weight-loss medications was associated with greater reductions in body weight than placebo, diet, or lifestyle modifications alone.

In general, an increased incidence of adverse cardiovascular events was not identified in these studies. However, we note that most trials excluded patients with known cardiovascular disease, and trial durations were most commonly 6–12 months. Both factors likely limited the ability to identify incident cardiovascular events during these trials.

Summary of the evidence from OSA-specific literature. Our literature search identified three studies of patients with OSA that evaluated the effects of phentermine/topiramate ER (54), liraglutide (55), or orlistat (56). Two additional studies of orlistat were identified

that did not specifically enroll patients with OSA but reported outcomes related to OSA specifically (57, 58).

ORLISTAT. One study correlated weight loss due to orlistat with minimal reductions in CPAP pressures (<1 cm H₂O). However, no measures regarding the impact on AHI or somnolence were conducted, and no comparisons with placebo or no treatment were made (56).

A randomized trial conducted by the European Orlistat Obesity Study Group compared orlistat with placebo over a 2-year period in obese patients (57). Both arms of the trial received a hypocaloric diet during the first year and a weight maintenance diet during the second year. Orlistat improved quality of life among those with apneas, but its effect on the AHI was not measured.

In a similar randomized trial comparing orlistat with placebo over a 2-year period in obese patients, by Sjöström and colleagues found that the use of orlistat to promote weight loss resulted in improved vitality among patients with OSA, as measured by the 36-item Short Form Health Survey (58). Again, both arms of the trial received a hypocaloric diet during the first year and a weight maintenance diet during the second year. Use of orlistat improved vitality among patients with OSA, as measured by the 36-item Short Form Health Survey; however, there were no improvements in other health status domains, and the trial did not measure the AHI or other sleep-related outcomes.

LIRAGLUTIDE. In the SCALE (Satiety and Clinical Adiposity—Liraglutide Evidence in Nondiabetic and Diabetic Individuals) trial, 359 obese patients (BMI, >30 kg/m²), who had at least moderate OSA (AHI, ≥15 events/h) and were not using positive airway pressure, were randomly assigned to receive either liraglutide plus both diet and exercise or placebo plus both diet and exercise for 32 weeks in a double-blind, multicenter study (55). Liraglutide decreased body weight (MD, −4.9 kg; 95% CI, −6.2 to −3.7 kg; BMI: MD, −1.6 kg/m²; 95% CI, −2.0 to −1.2 kg/m²), neck circumference (MD, −0.8 cm; 95% CI, −1.2 to −0.3 cm), and AHI (MD, −6.1 events/h; 95% CI, −11.0 to −1.2 events/h). The decrease in AHI correlated with the amount of weight lost. Improvements in some measures of quality of life, as well as decreases in blood pressure and serum lipid concentrations, were also

Table 3. Studies of Weight-Loss Medications

Medication	No. of Studies Reviewed/No. of Subjects	Follow-up (Range)	Effect on Weight [Mean (95% CI) Difference in kg, or as Specified]	No. of Studies with OSA as Outcome/No. of Subjects	Effect on OSA [Mean (95% CI) Difference in AHI, or as Specified]	No. of Studies with QOL Outcome
Phentermine	8 studies/169 D, 171 C	12 d to 24 wk	-2.1 (-3.1 to -1.0)	0 studies	No data	No data
Orlistat	25 studies/6,831 D, 6,388 C	26 wk to 3 yr	-2.9 (-3.5 to -2.3)	3 studies	12 patients on CPAP had reduction in pressure of 0.55 cm H ₂ O	2 studies mention improvement in OSA QOL, but minimal data provided
Lorcaserin	3 studies/3,447 D, 3,441 C	52 wk	-2.9 (-3.4 to -2.5)	0 studies	No data	3 studies, minimal improvement in IWQoL-Lite
Liraglutide 3 mg	5 studies/3,341 D, 1,924 C	20 to 68 wk	-4.7 (-5.7 to -3.7)	1 study/176 D, 179 C	-6.1 (-11.4 to -0.8)	1 study, modest improvement in IWQoL-Lite
Naltrexone/bupropion	4 studies/2,489 D, 1,432 C	56 wk	-4.5 (-5.0 to -3.9)	0 studies	No data	3 studies, modest improvement in IWQoL-Lite
Phentermine/topiramate ER	3 studies/1,515 D, 1,516 C	28 to 56 wk	-8.7% (-9.7% to -7.7%)	1 study/22 D, 23 C	-14.9 (-26.5 to -3.3)	1 study, improvement in SF-36

Definition of abbreviations: AHI = apnea-hypopnea index; C = control; CI = confidence interval; CPAP = continuous positive airway pressure; D = drug; ER = extended release; IWQoL-Lite = Impact of Weight on Quality of Life-Lite instrument; OSA = obstructive sleep apnea; QOL = quality of life; SF-36 = 36-Item Short Form Health Survey.

noted among those taking liraglutide. Changes in daytime somnolence did not differ between the groups. No deaths were reported in this trial.

PHENTERMINE-TOPIRAMATE ER. In a randomized, double-blind, placebo-controlled, single-center trial, 45 obese patients (BMI, 30–40 kg/m²) with moderate OSA (AHI, ≥15 events/h) who refused or could not tolerate positive airway pressure therapy and who did not have cardiac disease (i.e., active coronary artery disease, heart failure, valvulopathy, uncontrolled hypertension, or life-threatening arrhythmias) were randomly assigned to receive either phentermine/topiramate ER plus weight-loss counseling ($n = 22$) or placebo ($n = 23$) plus weight-loss counseling for 28 weeks (54). Subjects were counseled to decrease dietary intake by 500 kcal/d and encouraged to increase walking exercise.

At 28 weeks, those receiving phentermine/topiramate ER experienced greater weight loss (MD, -6.5 kg; 95% CI, -3.0 to -10.0 kg), improvement in AHI (MD, -14.9 events/h; 95% CI, -3.0 to -26.8 events/h), and improvement in sleep quality (Pittsburgh Sleep Quality Index score, +3 units vs. +1 unit; $P = 0.04$). The decrease in AHI correlated with the amount of weight lost ($n = 43$; $r = 0.52$; $P = 0.003$). Those receiving phentermine/topiramate ER also had mild improvement in their general health perception score, blood pressure, and serum lipid concentrations compared with those receiving placebo. Both groups had slight improvement in daytime somnolence and a mild increase in pulse rate that did not differ between groups. No deaths were reported in the trial. Approximately 50% of drug-treated subjects experienced dry mouth, and approximately 25% had dysgeusia without such symptoms in control individuals. Diet- and exercise-related changes were not measured.

Conclusions. Limited randomized trial data support the idea that the addition of a weight-loss medication to a behavioral weight-loss program (i.e., reduced-calorie diet, exercise/increased physical activity, and behavioral counseling) improves sleep quality, OSA severity, and possibly other OSA-related outcomes. Available medications vary in their efficacy and side effect profiles. The panel weighed the potential benefits versus risks and determined that the addition of a weight-loss medication may be worthwhile for

individuals without contraindications who are not improving despite participation in a comprehensive lifestyle intervention weight-loss program. The panel's certainty in its judgment was diminished because the potential desirable and undesirable consequences were finely balanced, and its confidence in the estimated effects on which it relied to make its judgment was low.

The reason for limiting this recommendation to patients who do not have active cardiovascular disease is the persistent uncertainty about the safety of phentermine, phentermine/topiramate ER, lorcaserin, and naltrexone/bupropion in patients with underlying cardiovascular disease or seizure disorder, as well as in those receiving antidepressant therapy. On one hand, these agents may increase heart rate and myocardial oxygen demand, which, in theory, could have negative consequences in such patients. On the other hand, liraglutide has been shown to be cardioprotective in doses administered for type 2 diabetes mellitus (103). Providers treating overweight or obese patients with OSA should be knowledgeable about these medications, including their indications, risks, and potential benefits.

Recommendation. For patients with OSA with a BMI greater than or equal to 27 kg/m², who have not lost sufficient weight despite participating in a comprehensive lifestyle weight management program and have no contraindications or active cardiovascular disease, we **suggest** an evaluation for potential antiobesity pharmacotherapy (conditional recommendation, very low certainty in the estimated effects).

REMARKS. "Active cardiovascular disease" refers to a myocardial infarction or cerebrovascular accident within the past 6 months, uncontrolled hypertension, life-threatening arrhythmias, or decompensated congestive heart failure.

Question 7: Should Bariatric Surgery Be Recommended (Rather Than Comprehensive Lifestyle Intervention Alone) to Patients with OSA Who Are Overweight or Obese and Who Have Been Unsuccessful in Losing Weight with Lifestyle Intervention?

Summary of the evidence from non-OSA literature. RCTs in obese populations not selected for OSA have established that

weight loss, glycemic control, resolution of diabetes, and improvements in quality of life are greater with bariatric procedures than nonsurgical interventions and that gastric bypass surgery has greater effects than gastric banding (41, 104).

In our initial literature search, only two RCTs were identified that compared bariatric surgery with no surgery in overweight/obese patients with OSA (105, 106). Thus, we expanded our search to include RCTs of bariatric surgery versus no surgery in overweight/obese patients not specifically identified as having OSA. A total of 13 additional RCTs comparing a range of procedures, including gastric banding, sleeve gastrectomy, gastric bypass, and biliopancreatic diversion, were identified (107–119). One of these studies was published only as an abstract that did not report sufficient data for analysis, and thus it was not considered further (119).

Studies that evaluated gastric banding found greater weight loss among those who underwent gastric banding than in control individuals (MD, -15.2 kg; 95% CI, -20.4 to -10.0 kg). The difference in weight loss was even larger among those who underwent gastric bypass than in control individuals (MD, -29.4 kg; 95% CI, -40.8 to -18.0 kg). Similarly, when gastric bypass was combined with biliopancreatic diversion and gastric sleeve procedures, patients who received surgery lost weight compared with nonsurgical control individuals (MD, -27.1 kg; 95% CI, -34.5 to -19.7 kg). Weight loss was not the only effect; bariatric surgery improved glycemic control according to HbA1c concentrations (MD, -1.6%; 95% CI, -2.0% to -1.2%), and the resolution of diabetes was nine times more likely with bariatric surgery (RR, 9.6; 95% CI, 5.3 to 17.3). No deaths were observed in any of the trials. Bariatric surgery resulted in a greater frequency of serious adverse events relative to medical management (23.3% vs. 13.8%; RR, 0.95; 95% CI, 0.87–1.03), but this difference was not statistically significant.

Summary of the evidence from OSA-specific literature. Two RCTs were identified that specifically enrolled patients with OSA. Both trials compared gastric banding with comprehensive lifestyle intervention in patients with OSA and a BMI greater than or equal to 35 kg/m² who were also being treated with positive airway pressure (105, 106). Assessed outcomes

included body weight, OSA severity, daytime sleepiness, quality of life, blood pressure, HbA1c, and adverse events (Table E3).

When the trials were pooled, gastric banding decreased body weight (MD, -11.0 kg; 95% CI, -20.8 to -1.3 kg) more than comprehensive lifestyle intervention; however, OSA severity was not significantly improved (MD, -3.3 events/h; 95% CI, -13.6 to $+7.1$ events/h). There was no difference in the rate of OSA resolution when those who underwent gastric banding were compared with control individuals (20.8% vs. 13.6%; RR, 1.5; 95% CI, 0.4–5.7) in the only study that assessed this outcome (106). There was a trend toward improved sleepiness as assessed by the ESS in one study (MD, -2.4 points; 95% CI, -5.1 to $+0.3$ points). Serious adverse event rates were similar in both studies. No deaths were reported, and one patient had a surgical complication that required reoperation (105).

These findings are supported by a randomized trial that was published after completion of our evidence synthesis. The trial compared gastric banding with positive airway pressure therapy in patients with severe OSA (AHI, ≥ 30 events/h) and a BMI of 35 – 45 kg/m² (120). Similar to the trials above, gastric banding had a greater effect on weight loss, but not on OSA-related outcomes, when compared with an alternative intervention. Specifically, only patients who underwent gastric banding had a significant decrease in their BMI (from a mean of 39.1 to 35.7 kg/m²; $P < 0.05$) and weight (from a mean of 115.4 kg to 106.7 kg; $P < 0.05$), and both groups had significant reductions in AHI and excessive daytime sleepiness compared with baseline. The reduction in AHI was greater among those who received positive airway pressure at 9 months but similar in the two groups by 18 months. The reduction in excessive daytime sleepiness was similar in the two groups at both 9 and 18 months.

Conclusions. Gastric banding does not appear to reduce OSA severity to a greater degree than lifestyle interventions alone or positive pressure therapy alone. However, bariatric surgery in those patient groups not defined as having OSA with a BMI greater than or equal to 35 kg/m² added to comprehensive lifestyle intervention decreases weight, improves glycemic control, and increases resolution of diabetes compared with lifestyle interventions alone.

Severe adverse events are uncommon. There are no randomized trial data available for other bariatric procedures in OSA, but weight loss overall was less after gastric banding than after other bariatric procedures. We did not perform our own cost analysis; however, an assessment of cost-effectiveness for the British National Health Service found that bariatric surgery was cost-effective in comparison to nonsurgical treatment in patients with a BMI greater than or equal to 35 kg/m² (121). Similarly, a more recent review by the Canadian Agency for Drugs and Technologies in Health found that over a lifetime, bariatric surgery was more cost-effective than conventional treatment in patients with morbid obesity (122).

The panel concluded that, taken together, for patients with a BMI greater than or equal to 35 kg/m² who have failed a comprehensive lifestyle intervention program for weight loss, bariatric surgery should be considered, based on patient preferences because the benefits likely outweigh the risks and burdens in most patients with OSA if one considers benefits beyond OSA-specific outcomes.

Of note, discussion about bariatric surgery with their sleep provider is welcomed by a substantial proportion of patients with OSA who are obese (123). The panel limited this recommendation to those with severe obesity (BMI, ≥ 35 kg/m²) because studies of bariatric surgery in OSA have been limited to this group.

Recommendation. For patients with OSA with a BMI greater than or equal to 35 kg/m² whose weight has not improved despite participating in a comprehensive lifestyle intervention program for weight loss, and who have no contraindications, we **suggest** referral for bariatric surgery evaluation (conditional recommendation, very low certainty in the estimated effects).

Discussion

What Others Are Saying

Weight loss in OSA. Our recommendations extend those offered in other OSA treatment guidelines. The American College of Physicians recommends that patients with OSA who are overweight or obese be encouraged to lose weight on the basis of three trials of comprehensive lifestyle intervention, but they did not address

pharmacological therapy or bariatric surgery (7). The American Academy of Sleep Medicine (8, 10) and the Canadian Thoracic Society (9) recommend educating patients on the relationship between excess weight and OSA, and they recommend weight loss for patients with OSA who are overweight or obese, but they provide no recommendations regarding specific strategies to achieve weight loss beyond consideration of bariatric surgery. For example, the 2015 American Academy of Sleep Medicine quality-of-care measures for management of OSA in adults recommend two quality metrics related to weight management: measuring weight at every clinical visit and annual discussion with a healthcare provider on weight status (124).

However, no assessment or recommendations regarding the content of the discussion on excess weight is suggested. Our recommendations are consistent with those of major obesity management guidelines in recommending comprehensive lifestyle intervention with three components—reduced-calorie diet, exercise/increased physical activity, and behavioral guidance—because these three components offer the greatest potential for a successful behavioral approach to the treatment of overweight/obesity (16–18).

Weight loss in diabetes. Multicenter randomized trials have shown that weight loss, usually induced by comprehensive lifestyle intervention, prevents the development of type 2 diabetes mellitus in high-risk groups and improves glycemic control in those with type 2 diabetes (125–127). With the weight loss accomplished by bariatric surgery, diabetes has been shown to improve dramatically if not resolve (128). In an OSA subgroup of the Look AHEAD (Action for Health in Diabetes) study of subjects with diabetes, weight loss resulted in improvement of diabetes and improvement in OSA severity, which remained stable despite a weight regain of nearly 50% after 4 years (129). Although a reduction in cardiovascular events was not demonstrated overall, a clinically important improvement in cardiovascular risk was found in the subgroup losing at least 10% of initial weight (130). Given the strong evidence that weight loss prevents and ameliorates type 2 diabetes mellitus, many diabetes centers have developed evidence-based weight-loss programs. As a result, clinicians

caring for patients with OSA who are overweight or obese potentially may gain from the knowledge and experience of their diabetology colleagues, enrolling their patients in weight-loss programs at diabetes centers, or duplicating those programs in sleep centers.

Putting It All Together

Weight loss is consistently associated with improvement in OSA severity, regardless of how the weight loss is achieved. Additional benefits of weight loss may include actual resolution of OSA, improvement or prevention of type 2 diabetes mellitus, decreased blood pressure, and improved quality of life. Behavioral approaches to weight loss have essentially no risk, whereas pharmacological and surgical therapies have mild to moderate risks. Taken together, weight loss should be a goal of all clinicians who take care of overweight or obese patients with OSA. However, there are some basic factors to be considered that potentially may enhance the clinician’s approach to patients with OSA who are overweight or obese.

Diagnosis of overweight/obesity and discussion of this state with patients.

Although most clinicians recognize the overweight or obese state in their patients and are aware of the benefits of weight loss, many of these patients do not carry the diagnosis of overweight or obesity. As a result, a weight management program is often not initiated (131, 132). Furthermore, even when the need for weight loss is discussed, evidence suggests that physicians fail to recommend the most effective interventions when counseling on weight-loss strategies (133). Terminology when discussing the diagnosis of being overweight or obese is important. Patients are generally accepting of the discussion, except for some morbidly obese individuals (134, 135). Descriptors such as “weight problem” and “excess weight” are preferred by patients over “fatness,” “excess fat,” “large size,” “obesity,” and “heaviness” (136, 137). The term “adiposity-based chronic disease,” or ABCD, has been devised to remove any “judgmental” aspect related to the term “obesity” (138).

Treatment of overweight/obesity. We concur with the NIH/NHLBI weight management guideline which states that the clinician should first assess the “reasons and motivation for weight reduction; previous history of successful

and unsuccessful weight-loss attempts; family, friends, and work-site support; the patient’s understanding of the causes of obesity and how obesity contributes to several diseases; attitude toward physical activity; capacity to engage in physical activity; time availability for weight-loss intervention; and financial considerations” (139). Discussing weight-loss approaches may yield positive results, as illustrated by a study which found that overweight and obese patients were more likely to participate in a weight-loss program if they were referred to a specific program than if they were simply advised to lose weight; moreover, the individuals who were referred to a weight-loss program lost more than twice as much weight as those who were simply advised to lose weight (140). These findings have been confirmed by another study and a meta-analysis (141, 142). Thus, open and nonjudgmental communication between the clinician and the patient with OSA about being overweight or obese, followed by specific referral to a successful weight management program, has the potential not only to improve OSA severity but also to reduce cardiometabolic and other weight-related risks and diseases and improve quality of life.

Specific recommendations of the components of a successful comprehensive lifestyle intervention for weight loss have been reviewed in the NIH/NHLBI and AHA/ACC guidelines, and key details are provided in Tables 4–6 (20, 41). The key feature of a successful diet is creating an energy deficit by restricting caloric intake. The specific type of diet used to generate that deficit does not seem important from a weight-loss standpoint and so should be tailored to patient preference. Increased physical activity alone is minimally effective

in generating weight loss, but it is essential for long-term weight maintenance. At least 150 min/wk of moderate-intensity aerobic activity is recommended during the weight-loss period, but increasing physical activity to 200–300 min/wk in the long term may minimize weight regain. The focus of behavioral intervention is goal setting and attainment, cognitive restructuring, reducing cues to eat, and long-term adherence to diet and physical activity recommendations. A key aspect of its success is self-monitoring of diet, activity, and weight. Frequency of contact for lifestyle interventions is important. Interventions implemented for less than 1 month do not produce weight loss consistently, and high-intensity interventions (≥ 14 sessions over 6 mo) produce greater weight loss than low- or moderate-intensity interventions. Once weight loss is achieved, monthly maintenance sessions can forestall or minimize weight regain in the long term.

In addition to lifestyle interventions, we also agree with a guideline developed by the American Association of Clinical Endocrinologists and the American College of Endocrinology, which states, “Patients who are overweight or obese and have obstructive sleep apnea should be treated with weight-loss therapy that includes lifestyle interventions and additional modalities as needed, including phentermine-topiramate extended release or bariatric surgery; the weight-loss goal should be at least 7 to 11% of total body weight or more” (143), although we do not advocate for a specific weight-loss medication. A comprehensive program that combines a reduced-calorie diet, exercise, and counseling should be prescribed as soon as the patient is willing to begin (41, 139). Clinicians caring for

Table 4. Specific Advice for Diet as Part of a Comprehensive Weight-Loss Intervention*

Key aspect of successful diet is reduction in caloric intake

Options for doing so include:

- General recommendation for 1,200–1,500 kcal/d for women and 1,500–1,800 kcal/d for men
- Reducing caloric intake by 500–1,000 kcal/d

No specific dietary composition (e.g., low fat, low carbohydrate, high protein) proven to be more successful for weight loss

Tailor diet composition to patient preference to maximize adherence

*Recommendations taken from Reference 41.

Table 5. Specific Advice for Exercise/Physical Activity as Part of a Comprehensive Weight-Loss Intervention*

Increased aerobic activity (e.g., brisk walking) for ≥ 150 min/wk
 Avoid ambulatory conveniences such as elevators when possible
 Tailor activity to patient preference to maximize adherence
 In the long term, increase physical activity to 200–300 min/wk to minimize weight regain

*Recommendations taken from Reference 41.

these patients need to have knowledge of locally available comprehensive lifestyle intervention programs that combine diet, exercise, and behavior modification. Several commercial programs have proven successful and are accessible in most geographic regions (144, 145).

Even though patients may be referred to an external program, it is important for the clinician caring for patients with OSA to follow and continue to encourage these patients in their weight management efforts. In talking about overweight/obesity with patients, the clinician might consider using the 5-A framework that is used during smoking cessation: assess, advise, agree, assist, and arrange (146). Motivational interviewing techniques may also be helpful (147–149). As an alternative to external referral, clinicians might consider providing weight management services within their own practices. Many large sleep centers employ cognitive behavioral therapy practitioners for treatment of insomnia who may be able to apply their behavioral expertise in developing on-site weight-loss programs.

In addition to face-to-face weight management, the Internet has enabled the development of several online weight-loss programs. Randomized trials suggest that online feedback and counseling enhance weight loss, although the trials are too heterogeneous to be pooled into a single estimate (150–152). Broad societal changes such as nutritional labeling and sugar taxes are underway (153), but they are progressing quite slowly.

Cost-effectiveness. In a cost-effectiveness analysis in the United

Kingdom, participation in a successful external weight management program was more cost-effective than an in-house program (154). The analysis predicted that such programs could reduce diabetes mellitus prevalence by 20% and cardiovascular disease incidence by 5%.

Overweight/obesity is a chronic disease that results from the complex interplay of genetic, physiological, social, psychological, behavioral, and environmental causes. The overweight/obesity state is challenging for individuals to address and benefits most from long-term therapies reviewed above and from support. After initial weight loss, long-term management is ideal. Patients who lose weight as part of a comprehensive lifestyle intervention should be encouraged to remain engaged in long-term weight maintenance programs to minimize weight regain and related comorbidities, including OSA.

Future Research

Our analysis of the applicable literature suggests that OSA can be improved with weight loss and even resolved in some cases, although the quality of the evidence is modest and there is still much work to be done. Small sample sizes, short study durations, high dropout rates, and a lack of blinding were common methodological weaknesses identified. In addition, many studies evaluated individuals incidentally noted to have OSA rather than patients presenting for OSA treatment. Similarly, many studies failed to evaluate outcomes relevant to patients with OSA. Resolution of these study design defects is not easy to accomplish, but we anticipate that their

identification will aid investigators in the design of future studies in this area. The panel encourages further research into the behavioral, pharmacological, and surgical treatment of excess weight, not only as adjunctive therapy but also as a potential primary treatment of OSA in patients who are overweight or obese. Specific research questions that the panel believes should be a high priority for future research include the following:

- What is the impact of weight-loss interventions in OSA populations on
 - patient-related outcomes related to OSA?
 - discontinuation of primary OSA therapy?
 - cardiometabolic comorbidities that commonly coexist with OSA?
- In which OSA populations can weight-loss intervention be used as primary treatment for OSA?
- In which subgroups of patients with OSA are weight-loss interventions most effective?
- How do weight-loss interventions provided as adjunctive therapy impact the effectiveness of second-line OSA treatments (e.g., positional therapy, mandibular advancement devices, upper airway surgery)?
- What is the safety of pharmacologic weight-loss interventions in the setting of cardiovascular diseases that commonly coexist with OSA?
- What is the efficacy and acceptability of sleeve gastrectomy and gastric bypass surgery to treat OSA?
- How can weight-loss interventions be feasibly incorporated into routine OSA care?
- What is the relative effectiveness of simultaneous behavioral support for weight loss and CPAP adherence compared with each alone?
- What is the long-term effect of the typical weight regain seen with weight-loss interventions on OSA-related outcomes?

Conclusions

Despite evidence that weight loss can reduce OSA severity, weight management is still not a mainstay of OSA treatment in that existing clinical practice guidelines (7–9, 143) and a recent NIH symposium (155) make only cursory reference to the benefits of weight management and do not offer specific therapeutic recommendations regarding how to achieve weight loss. However, our

Table 6. Specific Advice for Behavioral Counseling as Part of a Comprehensive Weight-Loss Intervention*

At least 14 sessions (individual or group) over the first 6 mo
 Monthly booster sessions (in person or by phone) after the first 6 mo
 Regular self-monitoring of food intake, physical activity, and weight
 If in-person programs are not feasible, consider Internet-based programs

*Recommendations taken from Reference 41.

guideline demonstrates that clinicians caring for patients with OSA who are overweight or obese should view excess weight as a major potentially modifiable contributing factor to OSA severity and

engage in health education and shared decision-making with patients about evidence-based strategies to address excess weight. When indicated, discussion should include participation in a comprehensive

lifestyle modification program and, if needed, exploration of additional options such as pharmacotherapy or bariatric surgery, based on patient preferences and needs. ■

This official guideline was prepared by an *ad hoc* subcommittee of the ATS Assembly on Sleep and Respiratory Neurobiology.

Members of the subcommittee are as follows:

DAVID W. HUDGEL, M.D., F.R.A.C.P. (*Chair*)¹
 SANJAY R. PATEL, M.D., M.S. (*Co-Chair*)²
 AMY M. AHASIC, M.D., M.P.H.^{3*}
 SUSAN J. BARTLETT, PH.D.^{4‡}
 DANIEL H. BESSESEN, M.D.^{5‡}
 MELISA A. COAKER, M.A., M.D.^{6‡}
 P. MICHELLE FIANDER, M.A., M.L.I.S.^{7§}
 RONALD R. GRUNSTEIN, M.B., M.D., PH.D.^{8‡}
 INDIRA GURUBHAGAVATULA, M.D., M.P.H.^{9‡}
 VISHESH K. KAPUR, M.D., M.P.H.^{10‡}
 CHRISTOPHER J. LETTIERI, M.D.^{11‡}
 MATTHEW T. NAUGHTON, M.D., F.R.A.C.P.^{12‡}
 ROBERT L. OWENS, M.D.^{13‡}
 JEAN-LOUIS D. PEPIN, M.D., PH.D.^{14‡}
 HENRI TUOMILEHTO, M.D., PH.D.^{15‡}
 KEVIN C. WILSON, M.D.^{16,17§}

Iowa; ⁷University of Utah, Salt Lake City, Utah; ⁸Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia; ⁹University of Pennsylvania Perelman School of Medicine, Corporal Michael Crescenz VA Medical Center, Philadelphia, Pennsylvania; ¹⁰University of Washington, Seattle, Washington; ¹¹U.S. Army, Uniformed Services University, Washington, DC; ¹²Monash University, Melbourne, Australia; ¹³University of California, San Diego, California; ¹⁴CHU de Grenoble, Grenoble, France; ¹⁵University of East Finland, Helsinki, Finland; ¹⁶American Thoracic Society, New York, New York; and ¹⁷Boston University, Boston, Massachusetts.

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*Lead methodologist.

‡Panel member.

§Additional methodologists.

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References

- Schwartz AR, Gold AR, Schubert N, Stryzak A, Wise RA, Permutt S, *et al.* Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis* 1991;144:494–498.
- Newman AB, Foster G, Givelber R, Nieto FJ, Redline S, Young T. Progression and regression of sleep-disordered breathing with changes in weight: the Sleep Heart Health Study. *Arch Intern Med* 2005;165:2408–2413.
- Redline S, Schluchter MD, Larkin EK, Tishler PV. Predictors of longitudinal change in sleep-disordered breathing in a nonclinic population. *Sleep* 2003;26:703–709.
- Peppard PE, Ward NR, Morrell MJ. The impact of obesity on oxygen desaturation during sleep-disordered breathing. *Am J Respir Crit Care Med* 2009;180:788–793.
- Rimm EB, Stampfer MJ, Giovannucci E, Ascherio A, Spiegelman D, Colditz GA, *et al.* Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. *Am J Epidemiol* 1995;141:1117–1127.
- Ford ES, Cooper RS. Risk factors for hypertension in a national cohort study. *Hypertension* 1991;18:598–606.
- Qaseem A, Holty JE, Owens DK, Dallas P, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Management of obstructive sleep apnea in adults: A clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2013;159:471–483.
- Epstein LJ, Kristo D, Strollo PJ Jr, Friedman N, Malhotra A, Patil SP, *et al.*; Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 2009;5:263–276.
- Fleetham J, Ayas N, Bradley D, Ferguson K, Fitzpatrick M, George C, *et al.*; CTS Sleep Disordered Breathing Committee. Canadian Thoracic Society guidelines: diagnosis and treatment of sleep disordered breathing in adults. *Can Respir J* 2006;13:387–392.
- Morgenthaler TI, Kapen S, Lee-Chiong T, Alessi C, Boehlecke B, Brown T, *et al.*; Standards of Practice Committee; American Academy of Sleep Medicine. Practice parameters for the medical therapy of obstructive sleep apnea. *Sleep* 2006;29:1031–1035.
- Grey matters: a practical tool for searching health-related grey literature. Ottawa, ON, Canada: Canadian Agency for Drugs and Technologies in Health (CADTH); 2015.
- NIH, National Library of Medicine. ClinicalTrials.gov [accessed 2017 Feb 10]. Available from: <https://www.clinicaltrials.gov/>.
- World Health Organization (WHO). International Clinical Trials Registry Platform [accessed 2017 Feb 10]. Available from: <http://apps.who.int/trialsearch/>.
- Review Manager (RevMan) [computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–188.

16. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, *et al.* GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011;64:401–406.
17. GRADEpro GDT: GRADEpro Guideline Development Tool [software]. McMaster University; 2015 (developed by Evidence Prime, Inc.).
18. Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, *et al.*; ATS Documents Development and Implementation Committee. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med* 2006;174:605–614.
19. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, *et al.* GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol* 2013;66:719–725.
20. National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. *Obes Res* 1998;6(Suppl 2):51S–209S. [Published erratum appears in *Obes Res* 1998;6:464.]
21. Apovian CM, Aronne LJ. The 2013 American Heart Association/American College of Cardiology/The Obesity Society guideline for the management of overweight and obesity in adults: what is new about diet, drugs, and surgery for obesity? *Circulation* 2015;132:1586–1591.
22. Haddank K, Paul T, Sen M, Ferguson KA. A randomized controlled trial evaluating the effectiveness of a weight loss strategy in overweight and obese patients with obstructive sleep apnea (OSA) [abstract]. *Sleep Med* 2006;7(Suppl 2):S73–S74.
23. Smith PL, Gold AR, Meyers DA, Haponik EF, Bleecker ER. Weight loss in mildly to moderately obese patients with obstructive sleep apnea. *Ann Intern Med* 1985;103:850–855.
24. Fernandes JF, Araújo LdaS, Kaiser SE, Sanjuliani AF, Klein MR. The effects of moderate energy restriction on apnoea severity and CVD risk factors in obese patients with obstructive sleep apnoea. *Br J Nutr* 2015;114:2022–2031.
25. Wu T, Gao X, Chen M, van Dam RM. Long-term effectiveness of diet-plus-exercise interventions vs. diet-only interventions for weight loss: a meta-analysis. *Obes Rev* 2009;10:313–323.
26. Johns DJ, Hartmann-Boyce J, Jebb SA, Aveyard P; Behavioural Weight Management Review Group. Diet or exercise interventions vs combined behavioral weight management programs: a systematic review and meta-analysis of direct comparisons. *J Acad Nutr Diet* 2014;114:1557–1568.
27. Fagard RH. Physical fitness and blood pressure. *J Hypertens Suppl* 1993;11:S47–S52.
28. Kelley GA, Kelley KA, Tran ZV. Aerobic exercise and resting blood pressure: a meta-analytic review of randomized, controlled trials. *Prev Cardiol* 2001;4:73–80.
29. Kline CE, Crowley EP, Ewing GB, Burch JB, Blair SN, Durstine JL, *et al.* The effect of exercise training on obstructive sleep apnea and sleep quality: a randomized controlled trial. *Sleep* 2011;34:1631–1640.
30. Desplan M, Mercier J, Sabaté M, Ninot G, Prefaut C, Dauvilliers Y. A comprehensive rehabilitation program improves disease severity in patients with obstructive sleep apnea syndrome: a pilot randomized controlled study. *Sleep Med* 2014;15:906–912.
31. Sengul YS, Ozalevli S, Oztura I, Itil O, Baklan B. The effect of exercise on obstructive sleep apnea: a randomized and controlled trial. *Sleep Breath* 2011;15:49–56.
32. Barros Schütz TC, Cunha TCA, Moura-Guimaraes T, Luz GP, Ackel-D'Elia C, da Silva Alves E, *et al.* Comparison of the effects of continuous positive airway pressure, oral appliance and exercise training in obstructive sleep apnea syndrome. *Clinics (São Paulo)* 2013;68:1168–1174.
33. Ackel-D'Elia C, da Silva AC, Silva RS, Truksinas E, Sousa BS, Tufik S, *et al.* Effects of exercise training associated with continuous positive airway pressure treatment in patients with obstructive sleep apnea syndrome. *Sleep Breath* 2012;16:723–735.
34. Servantes DM, Pelcerman A, Salvetti XM, Salles AF, de Albuquerque PF, de Salles FC, *et al.* Effects of home-based exercise training for patients with chronic heart failure and sleep apnoea: a randomized comparison of two different programmes. *Clin Rehabil* 2012;26:45–57.
35. González-Muniesa P, Lopez-Pascual A, de Andrés J, Lasa A, Portillo MP, Arós F, *et al.* Impact of intermittent hypoxia and exercise on blood pressure and metabolic features from obese subjects suffering sleep apnea-hypopnea syndrome. *J Physiol Biochem* 2015;71:589–599.
36. Mendelson M, Lyons OD, Yadollahi A, Inami T, Oh P, Bradley TD. Effects of exercise training on sleep apnoea in patients with coronary artery disease: a randomised trial. *Eur Respir J* 2016;48:142–150.
37. Fanfulla F, Taurino AE, D'Artavilla Lupo N, Piran M, Scalvini S, Fracchia C. CPAP use and weight control in obese OSA patient improves by a tele-assistance program [abstract]. Presented at the European Respiratory Society 18th Annual Congress. October 4–8, 2008, Berlin, Germany.
38. Karlsen T, Nes BM, Tjonna AE, Engstrom M, Stoylen A, Wisloff U, *et al.* Aerobic interval exercise training improves the apnea-hypopnea index and self-reported sleepiness in obstructive sleep apnea patients [abstract]. *Eur Heart J* 2014;35(Suppl):730.
39. Buysse DJ, Germain A, Moul DE, Franzen PL, Brar LK, Fletcher ME, *et al.* Efficacy of brief behavioral treatment for chronic insomnia in older adults. *Arch Intern Med* 2011;171:887–895.
40. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
41. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, *et al.*; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Obesity Society. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation* 2014;129(25, Suppl 2):S102–S138.
42. Igelström H, Emtner M, Lindberg E, Åsenlöf P. Tailored behavioral medicine intervention for enhanced physical activity and healthy eating in patients with obstructive sleep apnea syndrome and overweight. *Sleep Breath* 2014;18:655–668.
43. Nerfeldt P, Nilsson BY, Uddén J, Rössner S, Friberg D. Weight reduction improves nocturnal respiration in obese sleep apnoea patients—a randomized controlled pilot study. *Obes Res Clin Pract* 2008;2:119–124.
44. Moss J, Tew GA, Copeland RJ, Stout M, Billings CG, Saxton JM, *et al.* Effects of a pragmatic lifestyle intervention for reducing body mass in obese adults with obstructive sleep apnoea: a randomised controlled trial. *Biomed Res Int* 2014;2014:102164.
45. Hood MM, Corsica J, Cvengros J, Wyatt J. Impact of a brief dietary self-monitoring intervention on weight change and CPAP adherence in patients with obstructive sleep apnea. *J Psychosom Res* 2013;74:170–174.
46. Chirinos JA, Gurubhagavatula I, Teff K, Rader DJ, Wadden TA, Townsend R, *et al.* CPAP, weight loss, or both for obstructive sleep apnea. *N Engl J Med* 2014;370:2265–2275.
47. Johansson K, Neovius M, Lagerros YT, Harlid R, Rössner S, Granath F, *et al.* Effect of a very low energy diet on moderate and severe obstructive sleep apnoea in obese men: a randomised controlled trial. *BMJ* 2009;339:b4609.
48. Foster GD, Borradaile KE, Sanders MH, Millman R, Zammit G, Newman AB, *et al.*; Sleep AHEAD Research Group of Look AHEAD Research Group. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. *Arch Intern Med* 2009;169:1619–1626.
49. Tuomilehto HP, Seppä JM, Partinen MM, Peltonen M, Gylling H, Tuomilehto JO, *et al.*; Kuopio Sleep Apnea Group. Lifestyle intervention with weight reduction: first-line treatment in mild obstructive sleep apnea. *Am J Respir Crit Care Med* 2009;179:320–327.
50. Ng SSS, Chan RSM, Woo J, Chan TO, Cheung BHK, Sea MMM, *et al.* A randomized controlled study to examine the effect of a lifestyle modification program in OSA. *Chest* 2015;148:1193–1203.
51. Svendsen M, Blomhoff R, Holme I, Tonstad S. The effect of an increased intake of vegetables and fruit on weight loss, blood pressure and antioxidant defense in subjects with sleep related breathing disorders. *Eur J Clin Nutr* 2007;61:1301–1311.

52. Igelström H, Åsenlöf P, Emtner M, Lindberg E. Improvement in obstructive sleep apnea after a tailored behavioural sleep medicine intervention targeting healthy eating and physical activity: a randomised controlled trial. *Sleep Breath* [online ahead of print] 8 Dec 2017; DOI: 10.1007/s11325-017-1597-z.
53. Shechter A, Foster GD, Lang W, Reboussin DM, St-Onge MP, Zammit G, *et al.*; Sleep Ahead Research Group of the Look Ahead Research Group. Effects of a lifestyle intervention on REM sleep-related OSA severity in obese individuals with type 2 diabetes. *J Sleep Res* 2017; 26:747–755.
54. Winslow DH, Bowden CH, DiDonato KP, McCullough PA. A randomized, double-blind, placebo-controlled study of an oral, extended-release formulation of phentermine/topiramate for the treatment of obstructive sleep apnea in obese adults. *Sleep* 2012;35:1529–1539.
55. Blackman A, Foster GD, Zammit G, Rosenberg R, Aronne L, Wadden T, *et al.* Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. *Int J Obes* 2016;40: 1310–1319.
56. Petersen MC, Qvist J. Weight loss in obese patients with severe OSAS decreases neck circumference and lowers level of CPAP pressure - a trial of dietary intervention with or without lipase inhibition therapy [abstract]. *Sleep Med* 2003;4(Suppl 1):S36.
57. Rössner S, Sjöström L, Noack R, Meinders AE, Noseda G; European Orlistat Obesity Study Group. Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. *Obes Res* 2000;8:49–61.
58. Sjöström L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppeschaar HP, *et al.*; European Multicentre Orlistat Study Group. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. *Lancet* 1998;352:167–172.
59. Nissen SE, Wolski KE, Prcela L, Wadden T, Buse JB, Bakris G, *et al.* Effect of naltrexone-bupropion on major adverse cardiovascular events in overweight and obese patients with cardiovascular risk factors: a randomized clinical trial. *JAMA* 2016;315:990–1004.
60. Bakris G, Calhoun D, Egan B, Hellmann C, Dolker M, Kingma I. Orlistat improves blood pressure control in obese subjects with treated but inadequately controlled hypertension. *J Hypertens* 2002;20: 2257–2267.
61. Berne C; Orlistat Swedish Type 2 Diabetes Study Group. A randomized study of orlistat in combination with a weight management programme in obese patients with type 2 diabetes treated with metformin. *Diabet Med* 2005;22:612–618.
62. Broom I, Wilding J, Stott P, Myers N; UK Multimorbidity Study Group. Randomised trial of the effect of orlistat on body weight and cardiovascular disease risk profile in obese patients: UK Multimorbidity Study. *Int J Clin Pract* 2002;56:494–499.
63. Van Gaal LF, Broom JI, Enzi G, Toplak H; Orlistat Dose-Ranging Study Group. Efficacy and tolerability of orlistat in the treatment of obesity: a 6-month dose-ranging study. *Eur J Clin Pharmacol* 1998;54: 125–132.
64. Davidson MH, Hauptman J, DiGirolamo M, Foreyt JP, Halsted CH, Heber D, *et al.* Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA* 1999;281:235–242.
65. Derosa G, Maffioli P, Salvadeo SA, Ferrari I, Gravina A, Mereu R, *et al.* Comparison of orlistat treatment and placebo in obese type 2 diabetic patients. *Expert Opin Pharmacother* 2010;11:1971–1982.
66. Derosa G, Mugellini A, Ciccarelli L, Fogari R. Randomized, double-blind, placebo-controlled comparison of the action of orlistat, fluvastatin, or both an anthropometric measurements, blood pressure, and lipid profile in obese patients with hypercholesterolemia prescribed a standardized diet. *Clin Ther* 2003;25:1107–1122.
67. Finer N, James WP, Kopelman PG, Lean ME, Williams G. One-year treatment of obesity: a randomized, double-blind, placebo-controlled, multicentre study of orlistat, a gastrointestinal lipase inhibitor. *Int J Obes Relat Metab Disord* 2000;24:306–313.
68. Hanefeld M, Sachse G. The effects of orlistat on body weight and glycaemic control in overweight patients with type 2 diabetes: a randomized, placebo-controlled trial. *Diabetes Obes Metab* 2002;4: 415–423.
69. Hauptman J, Lucas C, Boldrin MN, Collins H, Segal KR. Orlistat in the long-term treatment of obesity in primary care settings. *Arch Fam Med* 2000;9:160–167.
70. Hill JO, Hauptman J, Anderson JW, Fujioka K, O'Neil PM, Smith DK, *et al.* Orlistat, a lipase inhibitor, for weight maintenance after conventional dieting: a 1-y study. *Am J Clin Nutr* 1999;69:1108–1116.
71. Hollander PA, Elbein SC, Hirsch IB, Kelley D, McGill J, Taylor T, *et al.* Role of orlistat in the treatment of obese patients with type 2 diabetes: a 1-year randomized double-blind study. *Diabetes Care* 1998;21:1288–1294.
72. Krempf M, Louvet JP, Allanic H, Miloradovich T, Joubert JM, Attali JR. Weight reduction and long-term maintenance after 18 months treatment with orlistat for obesity. *Int J Obes Relat Metab Disord* 2003;27:591–597.
73. Lindgärde F. The effect of orlistat on body weight and coronary heart disease risk profile in obese patients: the Swedish Multimorbidity Study. *J Intern Med* 2000;248:245–254.
74. Miles JM, Leiter L, Hollander P, Wadden T, Anderson JW, Doyle M, *et al.* Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin. *Diabetes Care* 2002;25:1123–1128.
75. Richelsen B, Tonstad S, Rössner S, Toubro S, Niskanen L, Madsbad S, *et al.* Effect of orlistat on weight regain and cardiovascular risk factors following a very-low-energy diet in abdominally obese patients: a 3-year randomized, placebo-controlled study. *Diabetes Care* 2007;30:27–32.
76. Swinburn BA, Carey D, Hills AP, Hooper M, Marks S, Proietto J, *et al.* Effect of orlistat on cardiovascular disease risk in obese adults. *Diabetes Obes Metab* 2005;7:254–262.
77. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004; 27:155–161.
78. Cocco G, Pandolfi S, Rousson V. Sufficient weight reduction decreases cardiovascular complications in diabetic patients with the metabolic syndrome. *Heartdrug* 2005;5:68–74.
79. Guy-Grand B, Drouin P, Eschwège E, Gin H, Joubert JM, Valensi P. Effects of orlistat on obesity-related diseases - a six-month randomized trial. *Diabetes Obes Metab* 2004;6:375–383.
80. Kelley DE, Bray GA, Pi-Sunyer FX, Klein S, Hill J, Miles J, *et al.* Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care* 2002;25:1033–1041.
81. Poston WS, Haddock CK, Pinkston MM, Pace P, Reeves RS, Karakoc N, *et al.* Evaluation of a primary care-oriented brief counselling intervention for obesity with and without orlistat. *J Intern Med* 2006; 260:388–398.
82. Astrup A, Rössner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, *et al.*; NN8022-1807 Study Group. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet* 2009;374:1606–1616.
83. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, *et al.*; SCALE Obesity and Prediabetes NN8022-1839 Study Group. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med* 2015;373:11–22.
84. Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, *et al.*; NN8022-1923 Investigators. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes* 2013;37: 1443–1451.
85. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjøth TV, *et al.*; NN8022-1922 Study Group. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE Diabetes randomized clinical trial. *JAMA* 2015;314:687–699.
86. Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiers ML, Najarian T, *et al.* Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity (Silver Spring)* 2012;20:330–342.
87. Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiers ML, *et al.* Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated

- comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011;377:1341-1352.
88. O'Neil PM, Smith SR, Weissman NJ, Fidler MC, Sanchez M, Zhang J, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. *Obesity (Silver Spring)* 2012;20:1426-1436.
 89. Smith SR, Weissman NJ, Anderson CM, Sanchez M, Chuang E, Stubbe S, et al.; Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) Study Group. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med* 2010;363:245-256.
 90. Fidler MC, Sanchez M, Raether B, Weissman NJ, Smith SR, Shanahan WR, et al.; BLOSSOM Clinical Trial Group. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. *J Clin Endocrinol Metab* 2011;96:3067-3077.
 91. Wadden TA, Foreyt JP, Foster GD, Hill JO, Klein S, O'Neil PM, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity (Silver Spring)* 2011;19:110-120.
 92. Apovian CM, Aronne L, Rubino D, Still C, Wyatt H, Burns C, et al.; COR-II Study Group. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity (Silver Spring)* 2013;21:935-943.
 93. Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, et al.; COR-I Study Group. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2010;376:595-605.
 94. Hollander P, Gupta AK, Plodkowski R, Greenway F, Bays H, Burns C, et al.; COR-Diabetes Study Group. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care* 2013;36:4022-4029.
 95. Brightwell DR, Naylor CS. Effects of a combined behavioral and pharmacological program on weight loss. *Int J Obes* 1979;3:141-148.
 96. Campbell CJ, Bhalla IP, Steel JM, Duncan LJ. A controlled trial of phentermine in obese diabetic patients. *Practitioner* 1977;218:851-855.
 97. Langlois KJ, Forbes JA, Bell GW, Grant GF Jr. A double-blind clinical evaluation of the safety and efficacy of phentermine hydrochloride (Fastin) in the treatment of exogenous obesity. *Curr Ther Res Clin Exp* 1974;16:289-296.
 98. Sonka J, Límanová Z, Zbírková A, Kratochvíl O. Effects of diet, exercise and anorexigenic drugs on serum thyroid hormones. *Endokrinologie* 1980;76:351-356.
 99. Sproule BC. Double-blind trial of anorectic agents. *Med J Aust* 1969;1:786.
 100. Truant AP, Olon LP, Cobb S. Phentermine resin as an adjunct in medical weight reduction: a controlled, randomized, double-blind prospective study. *Curr Ther Res Clin Exp* 1972;14:726-738.
 101. Wise PJ. Clinical experience with a new dosage form of phentermine hydrochloride. *Obes Bariatr Med* 1975;4:102-105.
 102. Willims RA, Foulsham BM. Weight reduction in osteoarthritis using phentermine. *Practitioner* 1981;225:231-232.
 103. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:311-322.
 104. Colquitt JL, Pickett K, Loveman E, Frampton GK. Surgery for weight loss in adults. *Cochrane Database Syst Rev* 2014;(8):CD003641.
 105. Dixon JB, Schachter LM, O'Brien PE, Jones K, Grima M, Lambert G, et al. Surgical vs conventional therapy for weight loss treatment of obstructive sleep apnea: a randomized controlled trial. *JAMA* 2012;308:1142-1149.
 106. Feigel-Guiller B, Drui D, Dimet J, Zair Y, Le Bras M, Fuertes-Zamorano N, et al. Laparoscopic gastric banding in obese patients with sleep apnea: a 3-year controlled study and follow-up after 10 years. *Obes Surg* 2015;25:1886-1892.
 107. Dixon JB, O'Brien PE, Playfair J, Chapman L, Schachter LM, Skinner S, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *JAMA* 2008;299:316-323.
 108. Ikramuddin S, Korner J, Lee WJ, Connett JE, Inabnet WB, Billington CJ, et al. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. *JAMA* 2013;309:2240-2249.
 109. Liang Z, Wu Q, Chen B, Yu P, Zhao H, Ouyang X. Effect of laparoscopic Roux-en-Y gastric bypass surgery on type 2 diabetes mellitus with hypertension: a randomized controlled trial. *Diabetes Res Clin Pract* 2013;101:50-56.
 110. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaiconelli A, Leccesi L, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med* 2012;366:1577-1585.
 111. O'Brien PE, Dixon JB, Laurie C, Skinner S, Proietto J, McNeil J, et al. Treatment of mild to moderate obesity with laparoscopic adjustable gastric banding or an intensive medical program: a randomized trial. *Ann Intern Med* 2006;144:625-633.
 112. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med* 2012;366:1567-1576.
 113. Wentworth JM, Playfair J, Laurie C, Ritchie ME, Brown WA, Burton P, et al. Multidisciplinary diabetes care with and without bariatric surgery in overweight people: a randomised controlled trial. *Lancet Diabetes Endocrinol* 2014;2:545-552.
 114. Courcoulas AP, Goodpaster BH, Egleton JK, Belle SH, Kalarchian MA, Lang W, et al. Surgical vs medical treatments for type 2 diabetes mellitus: a randomized clinical trial. *JAMA Surg* 2014;149:707-715.
 115. Halperin F, Ding SA, Simonson DC, Panosian J, Goebel-Fabbri A, Wewalka M, et al. Roux-en-Y gastric bypass surgery or lifestyle with intensive medical management in patients with type 2 diabetes: feasibility and 1-year results of a randomized clinical trial. *JAMA Surg* 2014;149:716-726.
 116. Mingrone G, Greco AV, Giancaterini A, Scarfone A, Castagneto M, Pugeat M. Sex hormone-binding globulin levels and cardiovascular risk factors in morbidly obese subjects before and after weight reduction induced by diet or malabsorptive surgery. *Atherosclerosis* 2002;161:455-462.
 117. Parikh M, Chung M, Sheth S, McMacken M, Zahra T, Saunders JK, et al. Randomized pilot trial of bariatric surgery versus intensive medical weight management on diabetes remission in type 2 diabetic patients who do NOT meet NIH criteria for surgery and the role of soluble RAGE as a novel biomarker of success. *Ann Surg* 2014;260:617-622; discussion 622-624.
 118. Reis LO, Favaro WJ, Barreiro GC, de Oliveira LC, Chaim EA, Fregonesi A, et al. Erectile dysfunction and hormonal imbalance in morbidly obese male is reversed after gastric bypass surgery: a prospective randomized controlled trial. *Int J Androl* 2010;33:736-744.
 119. Heindorff H, Hougaard K, Larsen PN. Laparoscopic adjustable gastric banding increases weight loss compared to dietary treatment: a randomized study [abstract]. *Obes Surg* 1997;7:300-301.
 120. Bakker JP, Tavakkoli A, Rueschman M, Wang W, Andrews R, Malhotra A, et al. Gastric banding surgery versus continuous positive airway pressure for obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med* 2018;197:1080-1083.
 121. Picot J, Jones J, Colquitt JL, Gospodarevskaya E, Loveman E, Baxter L, et al. The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation. *Health Technol Assess* 2009;13(41).
 122. Canadian Agency for Drugs and Technologies in Health (CADTH). Bariatric surgical procedures for obese and morbidly obese patients: a review of comparative clinical and cost-effectiveness, and guidelines. Ottawa, ON, Canada: CADTH; 2014.
 123. Dudley KA, Tavakkoli A, Andrews RA, Seiger AN, Bakker JP, Patel SR. Interest in bariatric surgery among obese patients with obstructive sleep apnea. *Surg Obes Relat Dis* 2015;11:1146-1151.

124. Aurora RN, Collop NA, Jacobowitz O, Thomas SM, Quan SF, Aronsky AJ. Quality measures for the care of adult patients with obstructive sleep apnea. *J Clin Sleep Med* 2015;11:357–383.
125. Williamson DA, Rejeski J, Lang W, Van Dorsten B, Fabricatore AN, Toledo K; Look AHEAD Research Group. Impact of a weight management program on health-related quality of life in overweight adults with type 2 diabetes. *Arch Intern Med* 2009;169:163–171.
126. Lindström J, Peltonen M, Eriksson JG, Ilanne-Parikka P, Aunola S, Keinänen-Kiukaanniemi S, et al.; Finnish Diabetes Prevention Study (DPS). Improved lifestyle and decreased diabetes risk over 13 years: long-term follow-up of the randomised Finnish Diabetes Prevention Study (DPS). *Diabetologia* 2013;56:284–293.
127. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403.
128. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrenbach K, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA* 2004;292:1724–1737.
129. Kuna ST, Reboussin DM, Borradaile KE, Sanders MH, Millman RP, Zammit G, et al.; Sleep AHEAD Research Group of the Look AHEAD Research Group. Long-term effect of weight loss on obstructive sleep apnea severity in obese patients with type 2 diabetes. *Sleep* 2013;36:641–649A.
130. Gregg EW, Jakicic JM, Blackburn G, Bloomquist P, Bray GA, Clark JM, et al.; Look AHEAD Research Group. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol* 2016;4:913–921.
131. Ahn S, Smith ML, Ory MG. Physicians' discussions about body weight, healthy diet, and physical activity with overweight or obese elderly patients. *J Aging Health* 2012;24:1179–1202.
132. Tork S, Meister KM, Uebele AL, Hussain LR, Kelley SR, Kerlakian GM, et al. Factors influencing primary care physicians' referral for bariatric surgery. *JLS* 2015;19:e2015.00046.
133. Phelan S, Nallari M, Darroch FE, Wing RR. What do physicians recommend to their overweight and obese patients? *J Am Board Fam Med* 2009;22:115–122.
134. Koball AM, Mueller PS, Craner J, Clark MM, Nanda S, Kebede EB, et al. Crucial conversations about weight management with healthcare providers: patients' perspectives and experiences. *Eat Weight Disord* 2018;23:87–94.
135. Lewis KH, Gudzone KA, Fischer H, Yamamoto A, Young DR. Racial and ethnic minority patients report different weight-related care experiences than non-Hispanic Whites. *Prev Med Rep* 2016;4:296–302.
136. Volger S, Vetter ML, Dougherty M, Panigrahi E, Egner R, Webb V, et al. Patients' preferred terms for describing their excess weight: discussing obesity in clinical practice. *Obesity (Silver Spring)* 2012;20:147–150.
137. Strømme M, Bakken IJ, Andenæs E, Klöckner CA, Mårvik R, Kulseng B, et al. Obese, fat, or just overweight? *Tidsskr Nor Laegeforen* 2015;135:1732–1736.
138. Mechanick JI, Hurley DL, Garvey WT. Adiposity-based chronic disease as a new diagnostic term: the American Association of Clinical Endocrinologists and American College of Endocrinology position statement. *Endocr Pract* 2017;23:372–378.
139. Schuster RJ, Tasosa J, Terwoord NA. Translational research—implementation of NHLBI Obesity Guidelines in a primary care community setting: the Physician Obesity Awareness Project. *J Nutr Health Aging* 2008;12:764S–769S.
140. Aveyard P, Lewis A, Tearne S, Hood K, Christian-Brown A, Adab P, et al. Screening and brief intervention for obesity in primary care: a parallel, two-arm, randomised trial. *Lancet* 2016;388:2492–2500.
141. Pool AC, Kraschnewski JL, Cover LA, Lehman EB, Stuckey HL, Hwang KO, et al. The impact of physician weight discussion on weight loss in US adults. *Obes Res Clin Pract* 2014;8:e131–e139.
142. Rose SA, Poynter PS, Anderson JW, Noar SM, Conigliaro J. Physician weight loss advice and patient weight loss behavior change: a literature review and meta-analysis of survey data. *Int J Obes* 2013;37:118–128.
143. Garvey WT, Mechanick JI, Brett EM, Garber AJ, Hurley DL, Jastreboff AM, et al.; Reviewers of the AACE/ACE Obesity Clinical Practice Guidelines. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract* 2016;22(Suppl 3):1–203.
144. Jolly K, Lewis A, Beach J, Denley J, Adab P, Deeks JJ, et al. Comparison of range of commercial or primary care led weight reduction programmes with minimal intervention control for weight loss in obesity: Lighten Up randomised controlled trial. *BMJ* 2011;343:d6500.
145. Gudzone KA, Doshi RS, Mehta AK, Chaudhry ZW, Jacobs DK, Vakil RM, et al. Efficacy of commercial weight-loss programs: an updated systematic review. *Ann Intern Med* 2015;162:501–512.
146. Whitlock EP, Orleans CT, Pender N, Allan J. Evaluating primary care behavioral counseling interventions: an evidence-based approach. *Am J Prev Med* 2002;22:267–284.
147. Young MD, Collins CE, Callister R, Plotnikoff RC, Doran CM, Morgan PJ. The SHED-IT weight loss maintenance trial protocol: a randomised controlled trial of a weight loss maintenance program for overweight and obese men. *Contemp Clin Trials* 2014;37:84–97.
148. Simpson SA, McNamara R, Shaw C, Kelson M, Moriarty Y, Randell E, et al. A feasibility randomised controlled trial of a motivational interviewing-based intervention for weight loss maintenance in adults. *Health Technol Assess* 2015;19(50).
149. Webber KH, Tate DF, Quintiliani LM. Motivational interviewing in internet groups: a pilot study for weight loss. *J Am Diet Assoc* 2008;108:1029–1032.
150. Collins CE, Morgan PJ, Hutchesson MJ, Callister R. Efficacy of standard versus enhanced features in a web-based commercial weight-loss program for obese adults, part 2: randomized controlled trial. *J Med Internet Res* 2013;15:e140.
151. Neve M, Morgan PJ, Jones PR, Collins CE. Effectiveness of web-based interventions in achieving weight loss and weight loss maintenance in overweight and obese adults: a systematic review with meta-analysis. *Obes Rev* 2010;11:306–321.
152. Blomfield RL, Collins CE, Hutchesson MJ, Young MD, Jensen ME, Callister R, et al. Impact of self-help weight loss resources with or without online support on the dietary intake of overweight and obese men: the SHED-IT randomised controlled trial. *Obes Res Clin Pract* 2014;8:e476–e487.
153. Dharmasena S, Capps O Jr. Intended and unintended consequences of a proposed national tax on sugar-sweetened beverages to combat the U.S. obesity problem. *Health Econ* 2012;21:669–694.
154. Brown M, McPherson K. Computer modelling the health and economic outcomes of the Weight Watchers GP referral scheme [abstract]. *Obes Facts* 2009;2(Suppl 2):115.
155. Parthasarathy S, Carskadon MA, Jean-Louis G, Owens J, Bramoweth A, Combs D, et al. Implementation of sleep and circadian science: recommendations from the Sleep Research Society and National Institutes of Health workshop. *Sleep* 2016;39:2061–2075.