

# The Evolution of Very-Low-Calorie Diets: An Update and Meta-analysis

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### Abstract

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**Objective:** Very-low-calorie diets (VLCDs), providing <800 kcal/d, have been used since the 1970s to induce rapid weight loss. Previous reviews of the literature have disagreed concerning the relative efficacy of VLCDs vs. conventional low-calorie diets (LCDs) for achieving long-term weight loss.

**Research Methods and Procedures:** We sought to update findings on the clinical use, safety, and efficacy of VLCDs and to perform a meta-analysis of randomized trials that compared the long-term efficacy of LCDs and VLCDs. Original research articles were retrieved by a Medline search and from prior reviews of VLCDs. Trials were included only if they were randomized comparisons of LCDs and VLCDs and included a follow-up assessment at least 1 year after maximum weight loss. Data were abstracted by both authors regarding: duration of VLCD, total length of treatment, attrition, short- and long-term weight loss, changes in weight-related comorbidities, and adverse effects.

**Results:** Six randomized trials were found that met inclusion criteria. VLCDs, compared with LCDs, induced significantly greater short-term weight losses ( $16.1 \pm 1.6\%$  vs.  $9.7 \pm 2.4\%$  of initial weight, respectively;  $p = 0.0001$ ) but similar long-term losses ( $6.3 \pm 3.2\%$  vs.  $5.0 \pm 4.0\%$ , respectively;  $p > 0.2$ ). Attrition was similar with VLCD and LCD regimens.

**Discussion:** VLCDs did not produce greater long-term weight losses than LCDs. In the United States, the use of liquid meal replacements as part of a 1000 to 1500 kcal/d diet may provide an effective and less expensive alternative to VLCDs. In Europe, VLCDs are used with less intensive medical supervision than in the United States, which reduces the cost of this approach.

**Key words:** diet, reducing; energy intake; weight loss; very-low-calorie diet; meta-analysis

### Introduction

Very-low-calorie diets (VLCDs)<sup>1</sup> reached the height of their popularity in the United States in 1988 when Oprah Winfrey announced to her television audience that she had lost 67 pounds by consuming a liquid diet. Interest in this approach declined sharply in 1990 when Winfrey reported that she had regained her lost weight and would “never diet again.” Despite these market ups and downs, >200,000 Americans used VLCDs in 2004 (personal communication, J. LaRosa, Marketdata Enterprises, July 20, 2005). Similarly, an estimated 67,800 months’ supply of VLCD products was sold in the European Union in 2000 (1). In addition, three recent reviews concluded that VLCDs are associated with greater long-term weight losses than are conventional reducing diets (2–4).

This article updates a prior review of the use of VLCDs (5) and presents a meta-analysis of randomized trials that compared the long-term efficacy of VLCDs with low-calorie diets (LCDs) comprised of conventional foods. The review concludes by examining the use of meal replacement plans that have evolved from VLCDs over the past decade.

### VLCDs: An Overview

An expert panel convened by the National Heart, Lung, and Blood Institute (NHLBI) defined VLCDs as diets providing fewer than 800 kcal/d (6), the same definition used

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<sup>1</sup> Nonstandard abbreviations: VLCD, very-low-calorie diet; LCD, low-calorie diet; NHLBI, National Heart, Lung, and Blood Institute; REE, resting energy expenditure; SD, standard deviation; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>.

by a recent European expert panel (1). The diets are designed to produce rapid weight loss while preserving lean body mass. This is accomplished by providing large amounts of dietary protein, typically 70 to 100 g/d or 0.8 to 1.5 g protein/kg ideal body weight (5,7). Protein may be obtained from a milk-, soy-, or egg-based powder, which is mixed with water and consumed as a liquid diet. Such diets may provide up to 80 g carbohydrate/d and 15 g fat/d, and they include 100% of the recommended daily allowance for essential vitamins and minerals. Alternatively, protein may be obtained from a protein-sparing modified fast, consisting of servings of lean meat, fish, and fowl (8,9). The modified fast must be supplemented with a multivitamin and 2 to 3 g/d potassium. Both diets require patients to drink 2 L/d non-caloric fluids (5). The two approaches produce comparable short-term weight losses (10). Thus, the choice of diet may be left to patient preference. Some investigators severely restrict carbohydrate to induce ketosis, which is thought to reduce hunger (8–10). However, comparable hunger ratings have been reported with ketotic and non-ketotic VLCDs (11).

We note that the definition of a VLCD is arbitrary. A 700 kcal/d diet, for example, would induce a relatively modest energy deficit in a short, sedentary woman with a resting energy expenditure (REE) of 1100 kcal/d. In contrast, a 1200 kcal/d diet would induce a substantial energy deficit in a tall man with an REE of 2500 kcal/d. The man would seem to have a greater risk of adverse metabolic effects (described later), even though technically he was prescribed an LCD and the woman a VLCD. Thus, an alternative definition of a VLCD is a diet that provides <50% of an individual's predicted REE (12).

### *Clinical Use of VLCDs*

In the United States, VLCDs are generally used as part of a comprehensive intervention that includes medical monitoring and a program of lifestyle modification. Care is provided by a physician, often in conjunction with a dietitian, psychologist, and/or exercise physiologist (5,6,13). Treatment, including the cost of the VLCD, is typically \$1800 to \$2200 for the first 12 weeks, during the period of rapid weight loss (14). An additional 12 to 14 weeks of refeeding (in which conventional foods are reintroduced) and weight stabilization bring total costs for 6 months to \$3000 to \$3500 (5).

In European Union nations, VLCDs are frequently used with less medical supervision than provided in the United States (1,15,16). In most countries, diet products can be purchased over-the-counter or from a pharmacist without a prescription (except in France). As recommended by the SCOOP-VLCD report, prepared by an expert European panel, consumers may use a VLCD as a sole source of nutrition for 3 weeks before seeking medical supervision (1). (SCOOP refers to Scientific Co-Operation on Questions

Relating to Food.) The report, however, also states that persons with obesity-related conditions should consult their physician before starting a VLCD. Thus, although physicians may be involved in identifying appropriate persons for treatment with a VLCD and for providing medical monitoring after the first 3 weeks, they do not have the same gatekeeping role as their U.S. counterparts. Rossner and Torgerson (17) have reviewed the Swedish experience with VLCDs and concluded that such programs can be provided largely by dietitians and nurses, lessening the need for physician involvement. We note that some companies in the United States sell VLCDs directly to consumers (14), whom they tell to consult with their physician before dieting. However, medically unsupervised use of these diets falls outside the guidelines recommended by expert panels in the United States.

### *Safety*

VLCDs are considered safe and effective when used by appropriately selected individuals under careful medical supervision (5). The diets are designed for patients with a BMI  $\geq 30$  kg/m<sup>2</sup>, a group at increased risk of cardiovascular morbidity and mortality and that also may derive the most benefit from substantial weight loss. In the United States, all candidates for a VLCD are expected to undergo a history and physical examination to determine medical and behavioral contraindications to treatment, as described in previous reviews (5,7). As noted previously, a similar recommendation applies in Europe to individuals who have significant comorbidities (1).

Patients in medically supervised VLCD programs in the U.S. are monitored by a physician approximately every 2 weeks during the period of rapid weight loss (i.e., 1.5 to 2.5 kg/wk). During this time, they are at increased risk of gallstones, cold intolerance, hair loss, headache, fatigue, dizziness, volume depletion (with electrolyte abnormalities), muscle cramps, and constipation (5,15,16,18). These side effects are usually mild and easily managed.

Cholelithiasis has been studied in detail (19–25). In an early study, gallstones developed in 25% of patients during 8 weeks of VLCD, and 6% of patients eventually required cholecystectomy (19). In a second trial, asymptomatic gallstones occurred in ~12% of patients within 6 months of starting a VLCD, and approximately one-half of these individuals eventually became symptomatic, requiring cholecystectomy (20). The risk of cholelithiasis can be decreased by administration of ursodeoxycholic acid (21,22), including a moderate amount of fat in the diet (23,24), and limiting the rate of weight loss to 1.5 kg/wk (25).

In Europe, VLCDs apparently have not been associated with a higher than expected rate of cholelithiasis. This has been attributed to the inclusion of at least 7 grams of fat in meal replacement regimens sold in Europe, as reported by Festi et al. (23).

Unsupervised use of VLCDs can result in serious complications, including death (18,26). The great majority of fatalities related to VLCDs occurred in the 1970s when dieters consumed products that contained low-quality protein (i.e., hydrolyzed collagen) and were deficient in vitamins and minerals. Of 60 persons who died in the United States, most developed cardiac complications after a loss of ~30% of initial weight, achieved in an average of 4 months. No deaths were reported in persons who dieted for 8 weeks or fewer (for a full review of this issue, see 26–28).

The SCOOP-VLCD report (1) noted that there have been no documented deaths attributable to VLCDs since their inclusion in the early 1980s of high-quality proteins (i.e., milk, egg, or soy). Nonetheless, in the United States, there were six reports of death during this time in persons who consumed the Cambridge Diet (which provided 330 kcal/d at the time) (26). Observational data clearly can lead to different conclusions about the safety of a product because of differences in the way the product is used (e.g., duration of use) or in the populations that use it (e.g., lean vs. obese individuals). As used in European Union nations, for example, dexfenfluramine appeared to be safe, whereas in the United States, where dexfenfluramine and fenfluramine were used for longer periods than in Europe, these medications were found to be associated with valvular heart disease (29). Thus, although VLCDs seem to be safe when consumed for brief periods without medical supervision, long-term unsupervised use of a VLCD could be associated with significant health complications (as could any hypocaloric, reducing diet).

### *Efficacy of VLCDs for Weight Loss*

Most evaluations of VLCDs have consisted of single-site case series conducted at academic medical centers or in individual physician practices. Most studies found that patients who completed a comprehensive VLCD program (that included lifestyle modification) generally lost 15% to 25% of initial weight in 3 to 4 months (2,3,15,16,30–32). Attrition in these programs typically ranged from 25% to 50% during the first 3 to 6 months, and patients generally regained 40% to 50% of lost weight 1 to 2 years after treatment, in the absence of follow-up care (30–32).

The NHLBI expert panel did not recommend the use of VLCDs over LCDs providing 1000 to 1500 kcal/d of conventional foods (6). The panel's conclusion was based on data from randomized trials that showed no differences in long-term weight losses between VLCDs and LCDs, principally because of greater weight regain after VLCDs (6).

Despite this expert panel's conclusion, the majority of individual randomized trials showed slightly larger long-term weight losses for persons prescribed VLCDs. Anderson and colleagues, in a meta-analysis of long-term studies, concluded that VLCDs were associated with greater long-term weight reductions than LCDs (2). The studies included

in that review, however, were mostly case series, and the meta-analysis did not account for the possibility of differential attrition among patients consuming either a LCD or a VLCD. Astrup and Rossner (3), in a qualitative review of several studies, also concluded that the larger initial weight losses induced by VLCDs were associated with greater long-term weight losses. Their conclusion assumed that patients participated in a weight maintenance intervention that included lifestyle modification. In addition, the European SCOOP-VLCD report noted that long-term weight losses may be greater after larger initial reductions in weight (1). Given the conflicting conclusions of these reviews, we performed a meta-analysis of randomized trials that compared VLCDs and LCDs to determine whether combining study results would reveal any incremental long-term benefit of VLCDs.

## **Research Methods and Procedures**

### *Data Sources and Study Selection*

A Medline search from 1966 to the present was performed using multiple combinations of the MeSH terms reducing diet, obesity, energy intake, and weight loss. Bibliographies of relevant articles and one quantitative review (2) and three recent qualitative reviews (3,15,16) were also searched for additional references. We selected only randomized controlled trials that compared VLCDs and LCDs and included at least a 1-year follow-up assessment after maximum initial weight loss was achieved. An exception was made for a study by Wing et al. (33), in which patients consumed a VLCD for two separate 12-week periods during a year. We used weight loss after the second 12-week trial. Studies that used weight loss medication were excluded.

VLCDs were defined as diets providing <800 kcal/d and LCDs as those providing 800 to 1800 kcal/d. Over 1000 titles or abstracts were examined, including 16 original research papers that included long-term comparisons of VLCDs and LCDs. Of these 16 reports, 14 were randomized trials. Of the 14 randomized studies, seven were excluded because they did not include a 1-year follow-up assessment (after maximum weight loss) (34–40). An eighth study was excluded because both VLCD and LCD patients were treated concomitantly with weight loss medication (ephedrine and caffeine) (41). Thus, six studies were included in the meta-analysis (Figure 1) (33,42–46). Two additional studies were identified that included long-term follow-up comparisons of LCD and VLCD programs (47,48). However, neither of these studies was a randomized trial, as was determined by contacting the investigators. There were no disagreements between the two authors regarding inclusion/exclusion of individual trials.

For the six studies selected, data were extracted for: length of treatment with VLCD, total length of therapy, attrition, short- and long-term weight loss as a percentage of

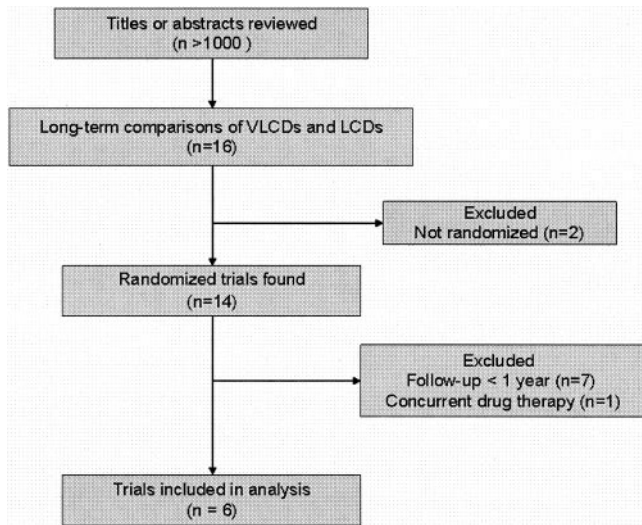


Figure 1: Flowchart for conducting the literature review.

initial weight, and changes in obesity-related comorbidities. Data were extracted independently by both authors and then compared for any discrepancies.

**Statistical Analyses**

Differences between the two dietary regimens in both short- and long-term weight loss were computed as: (percentage of initial weight lost for VLCD) – (percentage of initial weight lost for LCD). Analyses using weight loss in kilograms also were conducted and yielded the same statistical conclusions. Differences in attrition also were computed as: (VLCD – LCD). Given the varying lengths of follow-up, attrition was standardized as the percentage of the sample that dropped out per month. In one trial (42), there were three treatment groups, but data were analyzed only for the two groups that received the same behavioral counseling with and without VLCD. This was done to assess the true incremental effect of a VLCD when added to a standard behavioral intervention. All data were subjected to heterogeneity testing using the Q statistic (49). Heterogeneity was found for most comparisons; thus, a random effects model was used (50). Regression analysis was used to test for associations between study characteristics and the between-group difference in weight loss. All analyses were conducted using Stata version 8.2 SE (Stata Corporation, College Station, TX).

**Data Imputation**

In one study, the standard deviations (SDs) of the long-term weight losses were not given (43). Thus, using the other five studies, we calculated the SD as a percentage of the mean weight loss. We then used this percentage to impute an SD for the study with missing data.

**Results**

**Sample**

The six randomized controlled trials were published between 1989 and 1997 (33,42–46). Four of the studies were conducted in the U.S., one in Sweden, and one in multiple countries (i.e., Sweden, Norway, and Denmark). Individual level data were not available from these studies. Therefore, although the combined number of participants in these trials was 314, the *N* for our analysis was 6.

As shown in Table 1, the majority of studies enrolled patients with a BMI of 35 to 40 kg/m<sup>2</sup>. Two studies enrolled only women (42,45), and two other trials enrolled only patients with type 2 diabetes (33,44). Participants were prescribed VLCDs for 8 to 24 weeks, and the total length of treatment ranged from 6 to 26 months. Three studies used liquid meal replacements (43,45,46), one used a protein-sparing modified fast (42), and two studies used a combination of the two approaches (33,44). In three studies, patients were provided with exercise goals, which consisted of daily walking (33,42,43). For the LCD group, all six studies prescribed hypocaloric diets comprised of conventional foods, with energy goals ranging from 1000 to 1800 kcal/d.

**Attrition**

Attrition per month across the six studies was 0.8 ± 0.7% for the VLCD group and 0.9 ± 0.4% for the LCD group (*p* > 0.2). Overall attrition in the six studies was 22.3% for VLCD groups (range, 14.6% to 40.7%) and 22.6% for LCD groups (range, 0% to 51.9%) over a mean of 29 ± 18 months.

**Short-Term Weight Loss**

Participants in the VLCD and LCD arms of the studies lost a mean of 16.1 ± 1.6% and 9.7 ± 2.4% of initial weight, respectively. The mean difference of 6.4 ± 2.7% was highly significant (*p* = 0.0001), revealing the short-term superiority of the VLCD regimen, which was prescribed for a mean of 12.7 ± 6.4 weeks. Figure 2 shows the difference in weight loss between groups (i.e., VLCD – LCD) for each of the six studies. Five of the six studies reported data for completers only, whereas one study used an intention-to-treat analysis, with the last observation carried forward for dropouts. Our analysis is based on the data provided in the reports. (We did not have access to the raw data to reexamine the findings using a last-observation-carried forward or baseline-carried forward analysis.)

**Long-Term Weight Loss**

At follow-up assessment, which ranged from 1 to 5 years (mean = 1.9 ± 1.6 years) after completing the VLCD, mean weight losses in the VLCD and LCD groups were 6.3 ± 3.2% and 5.0 ± 4.0% of initial weight, respectively. As shown in Figure 3, the difference between groups was 1.3 ±

**Table 1.** Summary of results for the six randomized trials that compared a VLCD with an LCD

Study	Treatment regimen	N	BMI (kg/m <sup>2</sup> )	Treatment duration (weeks)	Maximal mean weight loss ± SD (percentage initial weight)	Follow-up weight loss ± SD (percentage initial weight)	Attrition (percentage per month)
Ryttig et al. (43)*	1. LCD, 1600 kcal/d, 112 weeks + BT	27	37.6	112	Week 8: 6.2 ± 4.1	26 Months: 4.7 ± 7.3 (n = 16)	26 months: 1.6
	2. VLCD, 420 kcal/d, 8 weeks + LCD 104 weeks + BT	54	37.7	112	Week 8: 16.7 ± 6.3	26 Months: 5.1 ± 8.5 (n = 26)	26 Months: 2
Torgerson et al. (46)†	1. LCD, 1200 to 1800 kcal/d, 104 weeks + BT	55	40.5	104	Week 26: 7.3 ± 6.0	24 Months: 5.4 ± 8.1 (n = 45)	24 Months: 0.8
	2. VLCD, 456 to 608 kcal/d, 12 weeks + LCD 92 weeks + BT	58	40.2	104	Week 26: 14.6 ± 9.0	24 Months: 7.9 ± 12.3 (n = 45)	24 Months: 0.9
Wadden et al. (42)‡	1. LCD, 1200 kcal/d, 26 weeks + BT	22	39.4 (both groups)	26	Week 26: 12.3 ± 6.2	66 Months: +2.9 ± 1.7 (n = 16)	66 Months: 0.4
	2. VLCD, 400 to 500 kcal/d, 8 weeks + LCD 18 weeks + BT	31		26	Week 26: 15.8 ± 6.3	66 Months: +0.8 ± 2.4 (n = 23)	66 Months: 0.4
Wadden et al. (45)	1. LCD, 1200 kcal/d, 78 weeks + BT	21	38.8	78	Week 26: 11.2 ± 5.9	18 months: 11.5 ± 7.8 (n = 17)	18 months: 1.1
	2. VLCD, 420 kcal/d, 16 weeks + LCD 62 weeks + BT	28	40.0	78	Week 26: 19.9 ± 8.9	18 months: 10.1 ± 9.3 (n = 23)	18 months: 1
Wing et al. (44)	1. LCD, 1000 to 1500 kcal/d, 20 weeks + BT	19	38.1	72	Week 20: 9.7 ± 4.1	18 months: 6.5 ± 6.6 (n = 16)	18 months: 0.9
	2. VLCD, 400 kcal/d, 8 weeks + LCD 12 weeks + BT	17	37.3	72	Week 20: 18.2 ± 9.3	18 months: 8.4 ± 9.0 (n = 17)	18 months: 0
Wing et al. (33)	1. LCD, 1000 to 1200 kcal/d, 50 weeks + BT	48	38.3	50	Week 50: 9.7 ± 10.8	24 months: 5.3 ± 7.3 (n = 41)	24 months: 0.6
	2. VLCD, 400 to 500 kcal/d, for two 12-week trials + LCD 26 weeks + BT	45	37.4	50	Week 50: 13.4 ± 9.7	24 months: 6.8 ± 7.6 (n = 38)	24 months: 0.7

VLCD, very-low-calorie diet; LCD, low-calorie diet; SD, standard deviation; BT, behavior therapy.

\* Groups 2 and 3 from the original study were combined in the analysis; both groups consumed an LCD after 8 weeks of VLCD, with one group including meal replacements in their diet. The SDs for long-term weight loss were imputed, as described in the text.

† Weight loss and its SD were estimated from the figure in the manuscript.

‡ As described in the text, only Groups 2 and 3 were compared to evaluate the effect of VLCD when added to maximal therapy.

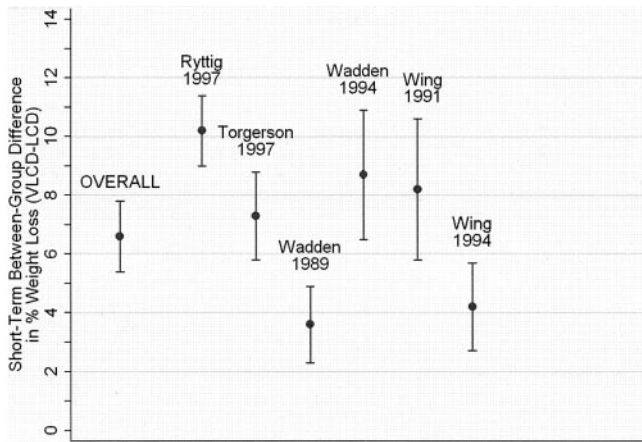


Figure 2: Differences between the VLCD and LCD groups (i.e., VLCD – LCD) in short-term percentage reduction in initial weight. All values are mean ± standard error. Results shown are from references 33 and 42 to 46.

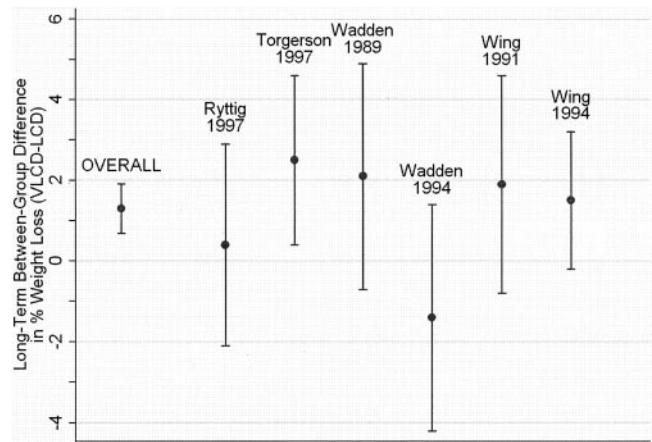


Figure 3: Differences between the VLCD and LCD groups (i.e., VLCD – LCD) in the long-term percentage reduction in initial weight. All values are mean ± standard error. Results shown are from references 33 and 42 to 46.

5.1%, which was not statistically significant ( $p > 0.2$ ). VLCD and LCD patients regained 62% and 41% of lost weight, respectively.

#### Changes in Weight-Related Comorbidities

Four studies assessed changes in comorbid conditions at long-term follow-up (33,43–45). In a study by Wing et al. (44), participants in both dietary groups began treatment with a hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) value of 10.4%. At Week 72 (1 year after a 20-week program), a decrease of 1.2 percentage points was observed in VLCD patients, compared with an increase of 1.4 points in the LCD group ( $p = 0.01$ ). This difference in HbA<sub>1c</sub> was observed despite comparable weight losses in the two groups of 8.4% and 6.5%, respectively, at Week 72. (Changes in lipids in the two groups did not differ significantly.) A second study, however, by the same investigators, failed to replicate the difference in glycemic control at a 2-year follow-up (33). HbA<sub>1c</sub> increased by 0.1 and 0.2 percentage points in the VLCD and LCD groups, respectively, with weight losses of 6.8% and 5.3%. There also were no significant differences between groups in changes in lipids or systolic blood pressure (33). Diastolic blood pressure fell by 8 mm Hg in the VLCD group, compared with a 3 mm Hg reduction in the LCD group ( $p = 0.03$ ), but this finding was not observed in the first study by Wing et al. (44). Rytting et al. (43) found no significant changes within groups in glycemic control, blood pressure, or lipids for either group at 2 years, despite weight losses of 5.1% and 4.7% for the VLCD and LCD groups, respectively. Wadden et al. (45) reported greater decreases in binge eating among LCD- as compared with VLCD-treated patients, with similar weight losses at long-term follow-up. Changes in cardiovascular disease risk factors were not measured.

#### Adverse Events

No study reported any serious adverse events attributable to the VLCD. No symptomatic cholelithiasis was reported among VLCD participants in any of the trials. Rytting et al. reported mild reversible alopecia in 35% of VLCD patients, compared with 2% of LCD participants (43). In the first study by Wing et al. (44), an increase in uric acid was seen in the VLCD group, although no patients developed clinical symptoms of gout. In the second study by Wing (33), transient cold intolerance, constipation, and alopecia were common in the VLCD group.

#### Study Characteristics and Weight Loss

The difference between groups in weight loss (i.e., VLCD – LCD) was not associated with the length of time the VLCD was used or with the total length of therapy. This was true for both short- and long-term weight loss. Even within the VLCD group, duration of VLCD use and total length of therapy were not associated with greater weight loss. There also were no associations between demographic variables, such as BMI or gender, and the difference between groups in weight loss. There were no differences in weight loss for the two studies that received partial support from industry, as compared with the four studies that were not industry-funded.

### Discussion

This meta-analysis of six studies showed that VLCDs induced significantly greater short-term weight losses than LCDs but comparable long-term changes in weight. The equivalence of long-term losses was attributable to greater weight regain among the VLCD-treated patients. The present findings support the conclusion of the NHLBI ex-

pert panel that VLCDs not be recommended in lieu of LCDs comprised of conventional foods (6). The strength of the present conclusion resides in the examination of studies that directly compared VLCDs and LCDs, in head-to-head trials, rather than extrapolating across investigations, in which only one or the other diet was used (2). Results of this analysis should resolve the conflicting conclusions of prior reviews (1–5). We note that the present findings represent a best case scenario for both dietary approaches because data were provided for treatment completers only in five of six studies. Also, the relative absence of adverse events reported in VLCD participants in these six trials (particularly that no patient developed symptomatic cholelithiasis) may have been attributable to lack of detailed assessment.

The short-term weight losses clearly favored the use of VLCDs. Thus, these diets potentially would be a more attractive option if there were effective methods of maintaining lost weight. Several studies have addressed this issue using medications or behavioral weight maintenance counseling. Apfelbaum et al. (51) showed that, after 4 initial weeks of a VLCD, during which patients lost 7.6 kg, those randomized to 1 year of treatment with sibutramine achieved a cumulative loss of 12.8 kg at the end of this time, compared with a loss of 7.1 kg for placebo-treated individuals ( $p = 0.004$ ). Mathus-Vliegen (52) prescribed a VLCD for 3 months, which induced an initial weight loss of 15.2 kg. Participants were then randomly assigned to sibutramine (10 mg/d) or placebo for an additional 15 months. At month 18, patients in the sibutramine group maintained a loss of 10.7 kg, compared with 8.5 kg for those prescribed placebo ( $p < 0.008$ ). Thus, sibutramine slowed but did not prevent weight regain after a 15-kg loss. A study that combined the use of a VLCD with dexfenfluramine revealed similar findings. Patients lost 15% of initial weight in the first 6 months but maintained a loss of only 10% at 1 year, despite remaining on medication the entire time (53). Dexfenfluramine was removed from the market in 1997 because of its association with valvulopathy (54). Further studies are needed of medications on the horizon, such as rimonabant (55), to determine whether they can sustain the 15% to 25% reductions in initial weight achieved with VLCDs.

Several studies have investigated the benefits of behavioral weight maintenance therapy after the period of rapid weight loss with a VLCD. Such treatment provides weekly or biweekly group meetings, training in relapse prevention, and encouragement to adhere to diet and exercise recommendations. In a non-randomized study, patients with extreme obesity who attended weekly small group meetings for 2 years maintained a loss of 15.2% at the end of this time, after losing a maximum of 27.3% (32). In a randomized trial, patients who lost 11.9 kg in 6 months by consuming a 1200 kcal/d diet of conventional foods maintained a loss of 12.2 kg a year later while attending 39 group behavioral maintenance sessions (45). In contrast, persons

who lost 21.5 kg (during the first 6 months) by adhering to a VLCD maintained a loss of only 10.9 kg, despite receiving the same 39 maintenance sessions. Poor maintenance of weight loss was also observed in a follow-up trial in which patients, after a loss of ~20 kg, received biweekly maintenance sessions combined with either placebo or sertraline (56). An additional randomized trial showed that VLCD-treated patients who lost 14.8 kg regained 50% to 80% of lost weight 18 months after the end of treatment and did not benefit from individualizing the rate of refeeding or using meal replacements during maintenance (57). Two studies of exercise to facilitate weight maintenance after a VLCD yielded mixed results (58,59).

Together, these findings suggest that efforts to maintain mean weight losses of 15% to 25% of initial weight are unlikely to be successful in a majority of patients, given current behavioral therapy and behavioral and pharmacologic therapies (i.e., sibutramine and orlistat). Factors responsible for weight regain after treatment with VLCD may include behavioral fatigue (60) in adhering to rigorous diet and exercise regimens in the presence of a toxic environment, as well as compensatory changes in peripheral and central hormones that regulate appetite and energy expenditure (61–63). At present, bariatric surgery appears to be the only reliable method of sustaining weight losses of 20% or more of initial weight (64).

Cycles of weight loss and regain do not seem to have the adverse health and metabolic consequences once feared (65). Thus, patients potentially could be encouraged to lose as much weight as possible through aggressive dieting, even if weight regain were likely (as indicated by the present meta-analysis). This approach, however, overlooks the substantial costs of medically supervised VLCDs in the United States. Even if the costs of meal replacements during a VLCD (i.e., about \$10 a day) were canceled out by the usual costs of food, a 12-week program would still run approximately \$1000 because of the extensive medical supervision required during rapid weight loss (14). These costs make VLCDs impractical for persons of low socioeconomic status, including minority members, in whom the rates of obesity are disproportionately high (66,67). As described previously, the European experience differs because the lack of mandatory medical supervision decreases the cost of using a VLCD. The cost of medical monitoring after the 3rd week on a VLCD probably varies from country to country within the European Union and may not result in significant out-of-pocket expenses for patients in some nations.

In the United States, one solution to the high costs and rapid weight regain associated with VLCDs is the use of liquid meal replacements as part of a 1000 to 1500 kcal/d diet that includes conventional foods. This latter regimen is designed to induce a mean loss of ~10% to 12% of initial weight (68,69). The higher calorie level reduces the need for intensive medical monitoring and, thus, should decrease

costs. Although the use of a 1000 to 1500 kcal/d partial meal replacement plan will not induce initial losses as great as those produced by all-liquid VLCDs, these greater losses presently cannot be maintained.

As used on an outpatient basis, partial meal replacement plans facilitate greater weight loss than the prescription of equivalent-calorie diets comprised solely of conventional foods. Heymsfield et al. (70) performed a meta-analysis of six randomized trials (71–76) that compared traditional LCDs (comprised of conventional foods) with isocaloric diets in which two meals and two snacks per day were replaced with a liquid diet and/or meal bars. They found significantly greater weight loss (of ~2.5 kg) at 3 months and at 1 year among participants who used the partial meal replacement plans (70). Since the publication of the meta-analysis, one additional randomized trial found greater weight loss with a meal replacement plan than with a conventional diet (77). A second randomized study found equal weight losses among the two groups (78).

How do meal replacements induce greater weight loss? Obese individuals typically underestimate their calorie intake by 40% to 50% when consuming a diet of conventional foods (79) because of difficulty in estimating portion sizes, macronutrient composition, and calorie content and in remembering all foods consumed. Meal replacements seem to decrease these difficulties and simplify food choices (7). Portion-controlled servings of conventional foods similarly facilitate weight loss, as shown by Jeffery et al. (80) and other investigators (81,82).

Further research is needed to determine the optimal macronutrient composition of meal replacements for treating obese persons with different weight-related conditions including type 2 diabetes, hypertension, and hyperlipidemia. Preliminary findings, for example, suggest that high-protein, low-carbohydrate diets may substantially improve glycemic control in obese patients with type 2 diabetes (83) and may be more effective, in this regard, than traditional, low-fat reducing diets (84). The first of two studies conducted by Wing et al. (44) similarly observed superior glycemic control among patients treated with a high-protein VLCD than with a more traditional, low-fat LCD, despite comparable weight losses. However, widespread adoption of the low-carbohydrate approach for diabetic patients should await further long-term safety data concerning lipids, cardiovascular and renal disease, and bone mineral density.

Persons prescribed a 1000 to 1500 kcal/d partial meal replacement plan as part of a comprehensive behavioral approach are likely to lose 10% to 12% of initial weight in the first 12 to 16 weeks (68,69). A minority of individuals may continue to lose substantially larger amounts of weight, an occurrence that need not be discouraged. The National Weight Control Registry has shown that some obese individuals can lose and maintain reductions of 25% to 30% of

initial weight (achieved by a variety of different approaches) (85). However, except in highly selected cases, we do not recommend the use of expensive VLCDs to induce losses of 15% to 25% of initial weight, when the present findings indicate that few patients will be able to maintain these losses, even under the best of circumstances. In contrast, numerous studies have shown that obese individuals can maintain (for 1 year or more) mean losses of 10% to 12% of initial weight when provided behavioral weight maintenance therapy (45,86–88) or pharmacotherapy (89,90). Weight losses of this size clearly are associated with significant improvements in health and well being (6), including a reduction in the risk of developing type 2 diabetes (91,92).

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