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Effects of Low-Carbohydrate Diets Versus Low-Fat Diets on Metabolic Risk Factors: A Meta-Analysis of Randomized Controlled Clinical Trials

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The effects of low-carbohydrate diets (≤45% of energy from carbohydrates) versus low-fat diets (≤30% of energy from fat) on metabolic risk factors were compared in a meta-analysis of randomized controlled trials. Twenty-three trials from multiple countries with a total of 2,788 participants met the predetermined eligibility criteria (from January 1, 1966 to June 20, 2011) and were included in the analyses. Data abstraction was conducted in duplicate by independent investigators. Both low-carbohydrate and low-fat diets lowered weight and improved metabolic risk factors. Compared with participants on low-fat diets, persons on low-carbohydrate diets experienced a slightly but statistically significantly lower reduction in total cholesterol (2.7 mg/dL; 95% confidence interval: 0.8, 4.6), and low density lipoprotein cholesterol (3.7 mg/dL; 95% confidence interval: 1.0, 6.4), but a greater increase in high density lipoprotein cholesterol (3.3 mg/dL; 95% confidence interval: 1.9, 4.7) and a greater decrease in triglycerides (−14.0 mg/dL; 95% confidence interval: −19.4, −8.7). Reductions in body weight, waist circumference and other metabolic risk factors were not significantly different between the 2 diets. These findings suggest that low-carbohydrate diets are at least as effective as low-fat diets at reducing weight and improving metabolic risk factors. Low-carbohydrate diets could be recommended to obese persons with abnormal metabolic risk factors for the purpose of weight loss. Studies demonstrating long-term effects of low-carbohydrate diets on cardiovascular events were warranted.

carbohydrate-restricted diet; fat-restricted diet; meta-analysis; metabolic syndrome; obesity

Abbreviations: CI, confidence interval; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol.

There were an estimated 937 million overweight and 396 million obese people worldwide in 2005 (1). Moreover, it was estimated that 68.0% of American adults were either overweight or obese in 2009 (2). Overweight and obesity are important risk factors for diabetes, cardiovascular disease, cancer, and premature death. The high prevalence of obesity has become a serious public health challenge. The dietary recommendations for weight loss from the American Heart Association and the National Institutes of Health emphasize the importance of low-fat, high-carbohydrate diets (3, 4). However, low-carbohydrate diets have recently become very popular for weight loss (5–7). Because low-carbohydrate diets may include significant amounts of fat and cholesterol, which have been associated with elevated low density lipoprotein (LDL) cholesterol levels, there is concern about their adverse effects on metabolic risk factors.

Some previous studies (6, 8–12), but not others (13–15), showed significant changes in metabolic risk factors associated with low-carbohydrate diets. Many clinical trials of low-carbohydrate diets have small sample sizes and insufficient statistical power to detect small changes in metabolic risk factors that may have public health importance. A previous meta-analysis of clinical trials comparing low-carbohydrate and low-fat diets reported differences in metabolic risk factors between the 2 diets (16). However, that study included

only 5 trials, with a total of 447 participants (16). Since then, several larger trials of longer duration have been published (6, 11, 13, 14, 17). Given this recent additional evidence, a meta-analysis of randomized controlled trials comparing the effects of low-carbohydrate diets with those of low-fat diets on metabolic risk factors is timely and important to public health.

In the present meta-analysis, we aimed to estimate the long-term (6 or more months) effect of low-carbohydrate diets compared with those of low-fat diets on body weight, waist circumference, and metabolic risk factors, including systolic and diastolic blood pressure, total cholesterol, LDL cholesterol, high density lipoprotein (HDL) cholesterol, ratio of total to HDL cholesterol, triglycerides, fasting blood glucose, and serum insulin. In addition, we explored the possible underlying reasons (i.e., study duration, diabetic status, age, gender, and levels of carbohydrate intake in diets) for the observed heterogeneity of effect sizes.

MATERIALS AND METHODS

Data sources and searches

We used the MEDLINE online database (from January 1, 1966 to June 20, 2011), EMBASE, Web of Science, and the Cochrane Database of Systematic Reviews to identify randomized controlled trials that compared the low-carbohydrate diet with the low-fat diet. The following key words or medical subject headings on MEDLINE were used: ("low-carbohydrate diet" or "low sugar diet" or "carbohydrate restriction" or "diet, carbohydrate-restricted") AND ("body mass index" or "BMI" or "waist circumference" or "obesity" or "diabetes" or "blood glucose" or "hypertension" or "HDL" or "LDL" or "triglycerides" or "cholesterol" or "lipids" or "dyslipidemias" or "blood pressure" or "diabetes mellitus" or "heart diseases" or "cardiovascular diseases"). The search was restricted to include studies classified as randomized controlled trials, and no language restriction was applied. In addition, manual searches of the references from selected original research and review articles were conducted.

Study selection

To be included in this meta-analysis, the studies had to be randomized controlled trials conducted in adults that compared a low-carbohydrate diet (≤45% of energy from carbohydrates) with a low-fat diet (≤30% of energy from fat) (18, 19), had an intervention duration of 6 months or more, and reported metabolic risk factors as outcomes. Studies were excluded if treatment allocation was not random, the study included participants less than 18 years of age, there was no difference in carbohydrate or fat intakes between diets, there were differences other than macronutrient and energy intake between the 2 diets, metabolic risk factors were not reported by treatment status, the variance of outcomes could not be calculated, and/or the duration of intervention was less than 6 months (3). When the results of a study were published more than once, only the most recent or most complete article was included in the analysis. Two investigators independently reviewed all potentially relevant publications and made decisions on inclusion. Where these decisions conflicted, additional investigators (co-authors) were involved to discuss discrepancies until mutual agreement was reached.

Data extraction and quality assessment

Two investigators independently abstracted the data in duplicate using a standardized data collection form. The following data were collected: article title, primary author's name, year and source of publication, country of origin, study design (parallel, cross-over, or factorial trial), blinding (open, single, or double), dietary composition, loss to follow-up, intention-to-treat analysis, characteristics of the study population (sample size, age, sex, prior disease status, and baseline levels of metabolic risk factors), and the net changes in metabolic risk factors with measures of variance, overall and by prespecified subgroups. Disagreement was resolved by consensus with additional investigators.

Data synthesis and analysis

Mean net change was calculated by subtracting mean change (from baseline to end of trial) in the low-fat-diet group from mean change in the low-carbohydrate-diet group for each metabolic risk factor. Pooled mean net changes and their 95% confidence intervals in metabolic risk factors were calculated using DerSimonian and Laird random-effects models (20). The presence of heterogeneity was assessed with the Q test and the extent of heterogeneity was quantified with the I-squared index. To assess publication bias, we constructed a funnel plot for each outcome. Begg's rank correlation test was used to examine the asymmetry of the funnel plot, and Egger's weighted linear regression test was used to examine the association between the mean effect estimate and its variance. Where these tests or funnel plots indicated possible publication bias, we used the trim-and-fill method to determine whether publication bias could have accounted for the results we observed. Additionally, sensitivity analyses were conducted by excluding each study in turn, by removing studies with a completion rate less than 70%, by removing studies with fewer than 20 participants per group, and by removing studies among postsurgery patients or those with severe diseases, such as cancer, to evaluate their relative influence on the pooled estimates. Finally, subgroup analyses including diabetic versus nondiabetic samples, very-low-carbohydrate (≤60 g carbohydrates per day) versus moderate-carbohydrate (>60 g carbohydrates per day) diets, longer (≥12 months intervention) versus shorter (<12 months) study duration, predominantly male (at least 50% men) versus predominantly female (at least 50% women) samples, and older (mean age ≥50 years) versus younger (mean age <50) samples were conducted to examine differences in all study outcomes between the 2 diets. The Bonferroni and false discovery rate methods were used to correct for multiple comparisons (21). All analyses were conducted using Stata, version 10 (StataCorp LP, College Station, Texas).

RESULTS

The flow of studies in our meta-analysis is depicted in Figure 1. From 785 potentially relevant references, 503 records remained after duplicates between databases were eliminated, and 406 articles were eliminated after reviewing titles and abstracts. A total of 97 full-text articles were reviewed for eligibility. Of those, 23 studies met all of the eligibility criteria and were included in the meta-analysis (5, 6, 8–14, 17, 22–34). These studies included data from 2,788 trial participants (1,392 on low-carbohydrate diets and 1,396 on low-fat diets).

The characteristics of these 23 randomized controlled trials are presented in Table 1. All trials were parallel except for 1 trial that had a factorial design (13). Trial participants were usually not blinded to their assignment because of the nature of the intervention—most interventions provided dietary instruction, leaving food buying and/or preparation to the participants. Study duration ranged from 6 to 24 months, and 16 studies had an intervention duration of 12 months or longer (6, 8, 9, 11–14, 17, 22, 23, 25, 26, 28–31). Most trials were conducted among obese or overweight patients without cardiovascular diseases or diabetes mellitus. However, 4 studies were conducted in patients with diabetes (23, 26, 28, 29), 1 was conducted in patients with prediabetes (31), and 1 was conducted in patients with coronary heart disease (23). The goal dietary nutritional composition varied across the studies, with carbohydrate consumption ranging from 4% to 45% (weighted mean, 23%) of energy intake in the low-carbohydrate group and fat ranging from 10% to 30% (weighted mean, 26%) of energy intake in the low-fat group. Self-reported mean energy intake weighted by trial sample sizes was similar for both diets at approximately 2,000 kcal.

Table 2 shows baseline characteristics of trial participants in the included studies. The mean age ranged from 27 to 60 years. Approximately 40% of participants were male. Baseline levels of body weight and metabolic risk factors were similar between the 2 diets in each study but varied among studies.

Pooled mean net changes and 95% confidence intervals for metabolic risk factors are presented in Web Figure 1 (available at http://aje.oxfordjournals.org/). The weighted mean changes in outcomes were −6.1 versus −5.0 kg for body weight, −6.2 versus −6.0 cm for waist circumference, −4.6 versus −10.1 mg/dL for total cholesterol, −2.1 versus −6.0 mg/dL for LDL cholesterol, 4.5 versus 1.6 mg/dL for HDL cholesterol, −0.7 versus −0.5 for ratio of total to HDL cholesterol, −30.4 versus −17.1 mg/dL for triglycerides, −3.5 versus −3.0 mm Hg for systolic blood pressure, and −10.4 versus −10.1 mg/dL for fasting blood glucose for low-carbohydrate versus low-fat diets, respectively. Pooled mean net changes and 95% confidence intervals representing differences between the diets in body weight (−1.0 kg, 95% confidence interval (CI): −2.2, 0.2) and waist circumference (−0.1 cm, 95% CI: −0.6, 0.4)

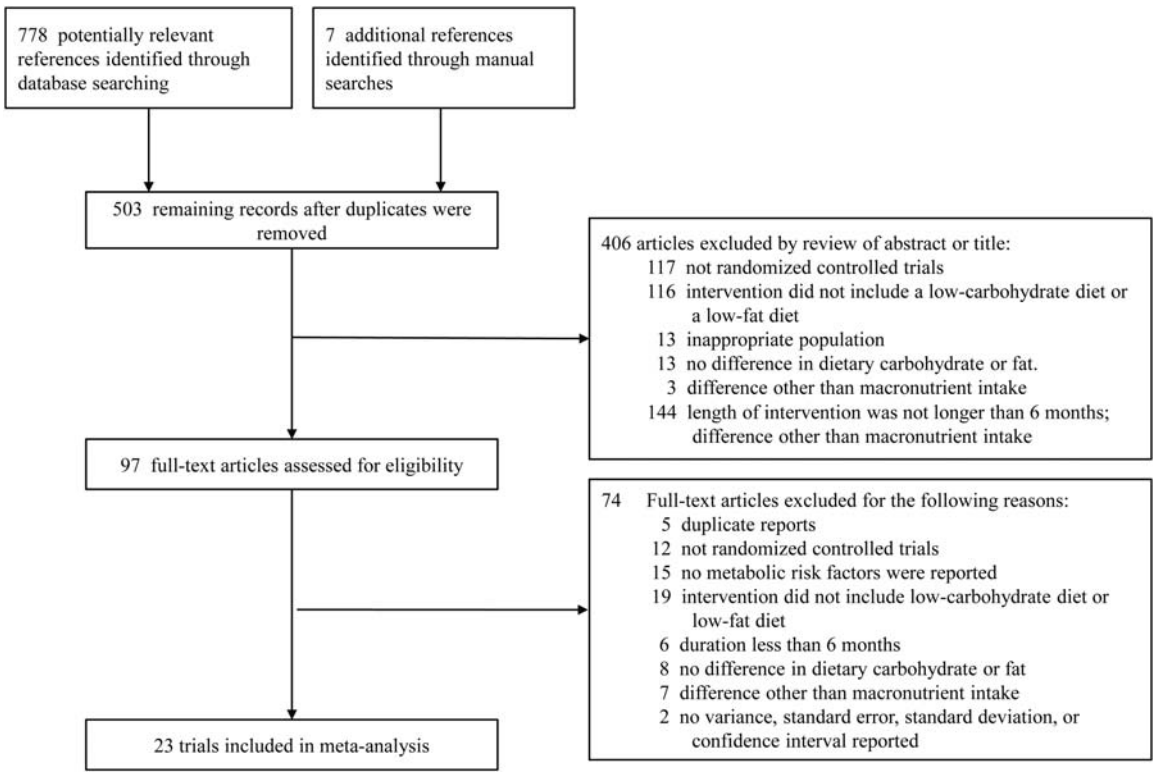

Figure 1. Flow diagram of systematic review (from January 1, 1966 to June 20, 2011).

reductions were not statistically significant. Compared with participants on low-fat diets, those on low-carbohydrate diets experienced slightly but statistically significantly less reduction in total cholesterol (pooled mean net change, 2.7 mg/dL, 95% CI: 0.8, 4.6) and LDL cholesterol (pooled mean net change, 3.7 mg/dL, 95% CI: 1.0, 6.4) but a greater increase in HDL cholesterol (pooled mean net change, 3.3 mg/dL, 95% CI: 1.9, 4.7) and a greater decrease in triglycerides (pooled mean net change, −14.0 mg/dL, 95% CI: −19.4, −8.7). These differences remained statistically significant after correction for multiple comparisons. Pooled mean net changes in systolic blood pressure (−1.0 mm Hg, 95% CI: −3.5, 1.5), ratio of total to HDL cholesterol (−0.1, 95% CI: −0.3, 0.1), and fasting blood glucose (−0.3 mg/dL, 95% CI: −1.9, 1.3) were not significantly different between the 2 diets. The pooled mean net changes in diastolic blood pressures and serum insulin were also not significant (data not shown).

There was no significant heterogeneity in the net changes in total cholesterol ($I^2 = 0.2\%$, $P = 0.45$), triglycerides ($I^2 = 55.6\%$, $P = 0.07$), waist circumference ($I^2 = 12.5\%$, $P = 0.33$), fasting blood glucose ($I^2 = 41.2\%$, $P = 0.06$), or serum insulin ($I^2 = 7.8\%$, $P = 0.29$) among these trials. However, statistically significant heterogeneity was detected for body weight ($I^2 = 85.7\%$, $P < 0.001$), systolic blood pressure ($I^2 = 91.7\%$, $P < 0.001$), diastolic blood pressure ($I^2 = 40.8\%$, $P = 0.04$), LDL cholesterol ($I^2 = 50.0\%$, $P = 0.01$), HDL cholesterol ($I^2 = 78.6\%$, $P < 0.001$), and ratio of total to HDL cholesterol ($I^2 = 75.0\%$, $P = 0.003$) among trials.

We examined the potential for publication bias by plotting sample sizes against mean net changes in each metabolic risk factor (Web Figure 2). Possible publication bias was detected for triglycerides ($P = 0.02$) using Begg's rank correlation and for body weight ($P = 0.03$), total cholesterol ($P = 0.03$), LDL cholesterol ($P = 0.001$), HDL cholesterol ($P < 0.001$), ratio of total to HDL cholesterol ($P = 0.03$), and insulin ($P = 0.03$) using Egger's linear regression tests. We used the trim-and-fill method to estimate the potential effect of publication bias on our results. When corrected for the effects of possible publication bias, pooled net change estimates for total cholesterol, LDL cholesterol, and HDL cholesterol became nonsignificant, but the pooled mean net change in body weight was significant at −3.2 kg (95% CI: −4.5 to −2.0), favoring low-carbohydrate diets.

In sensitivity analyses, the exclusion of any one study from the analysis did not significantly alter the net changes in metabolic risk factors. In addition, after removing studies with fewer than 20 participants per group or studies among patients with breast cancer, polycystic ovarian syndrome, or coronary heart disease or who had undergone gastric bypass surgery, body weight reduction was significantly greater on low-carbohydrate diets, with pooled mean net changes in body weight of −1.3 kg (95% CI: −2.5 to −0.1, $n = 19$ studies) and −1.4 kg (95% CI: −2.6 to −0.2, $n = 18$ studies), respectively (Table 3).

Subgroup analyses by gender, diabetic status, level of carbohydrate restriction, and study duration did not identify statistically significant differences in the majority of metabolic risk factor reductions between low-carbohydrate and low-fat diets (Web Tables 1–5). However, there was a significantly greater reduction in body weight among participants who were on low-carbohydrate diets for more than 1 year (−0.9 kg, 95% CI: −1.6, −0.3) and those with a high level of carbohydrate restriction (−2.0 kg, 95% CI: −3.4 to −0.6) when compared with persons on low-fat diets. In addition, in the younger age group, low-carbohydrate diets resulted in significantly greater reductions in systolic blood pressure (−2.7 mm Hg, 95% CI: −4.5 to −0.9), diastolic blood pressure (−1.5 mm Hg, −2.7 to −0.2), and serum insulin (−0.9 μIU/mL, −1.8 to −0.1) as compared with results in the older age groups. However, these findings were not statistically significant after adjustment for multiple testing.

DISCUSSION

In the present meta-analysis of randomized controlled trials comparing low-carbohydrate diets with low-fat diets, we found that both diets were equally effective at reducing body weight and waist circumference. Both diets reduced participants' blood pressures, total to HDL cholesterol ratios, and total cholesterol, LDL cholesterol, triglycerides, blood glucose, and serum insulin levels and raised HDL cholesterol; however, participants on low-carbohydrate diets had greater increases in HDL cholesterol and greater decreases in triglycerides but experienced less reduction in total and LDL cholesterol compared with persons on low-fat diets. These findings have important clinical and public health implications. Over the past several decades, low-fat diets have been recommended to the public for weight loss primarily because of their beneficial effects on metabolic risk factors (4). Our study suggests that low-carbohydrate diets might provide an alternative approach for weight reduction without worsening metabolic risk factors.

Our results for blood pressure and lipids are consistent with those of a meta-analysis of randomized trials of low-carbohydrate dietary interventions conducted by Nordmann et al. in 2006 (16). That study found that low-carbohydrate diets produced significantly greater weight loss after 6 months than did low-fat diets, although the differences were not statistically significant at 1 year. In contrast, the present analysis showed that both diets were equally effective in reducing weight. The meta-analysis conducted by Nordmann et al. included only 5 trials with data on 447 participants, whereas the present study included 23 trials with data on 2,788 participants (16). Moreover, our study used a broader definition of low-carbohydrate diets (a maximum 45% of energy intake from carbohydrates) than did the previous study (≤60 g/day) and examined a much wider variety of metabolic outcomes.

There is a substantial body of evidence indicating that low-carbohydrate diets are effective for weight loss. With the exception of a study of severely obese patients, body weight and waist circumference were reduced among all of the low-carbohydrate dietary intervention studies, with mean reductions ranging from 1.5 to 14.3 kg and from 2.2 to 9.3 cm, respectively. Our findings suggest that low-carbohydrate diets are at least as effective as low-fat diets for weight loss, regardless of gender, age, length of intervention, diabetes status, and level of carbohydrate restriction.

Table 1. Characteristics of 23 Randomized Controlled Clinical Trials From Multiple Countries Comparing Low-Carbohydrate Diets With Low-Fat Diets, 1966–2011

First Author, Year (Reference No.)	Country	Design	Blinding	Inclusion Criteria	Intervention or Targeted Dietary Composition		Mean Intervention Duration, months	Completion %	
					LCD	LFD		LCD	LFD
Brehm, 2003 (5)	United States	Parallel	Open	Female sex; BMI[a] 30–35; no DM or CVD; normal BP; NP	<20 g carbohydrates/day for 1–2 weeks, then increasing to 40–60 g/day only if self-testing of urinary ketones continued to indicate ketosis	30% fat, 55% carbohydrate, 15% protein	6	85	74
Brinkworth, 2009 (22)	Australia	Parallel	Open	Abdominal obesity and ≥1 METS components; no DM or CVD; NP	4% carbohydrate, 35% protein, 61% fat (20% saturated fat), <20 g carbohydrates/day during weeks 1–8 and then <40 g/day thereafter	30% fat (8% or 10 g/day saturated fat), 46% carbohydrate, 24% protein	12	58	59
Dansinger, 2005 (8)	United States	Parallel	Open	Obesity and ≥1 METS; BMI 27–42; no CKD; NP	<20 g carbohydrates/day, increasing to 50 g/day	Vegetarian diet, 10% fat	12	52	50
Davis, 2009 (23)	United States	Parallel	Open	DM; overweight; no CKD; coronary heart disease	20–25 g carbohydrates/day in weeks 1–2 depending on baseline weight, then increasing by 5 g carbohydrates/week	25% fat	12	86	88
Due, 2008 (24)	Denmark	Parallel	Open	BMI 28–36; NP	45% carbohydrate, 40% fat (20% MUFA), 15% protein	60% carbohydrate, 25% fat (20% MUFA), 15% protein	6	56	73
Ebbeling, 2007 (25)	United States	Parallel	Open	BMI ≥30; no DM	40% carbohydrate, 35% fat, 25% protein; low-glycemic-load foods and limited intake of high-glycemic-load foods	20% fat, 55% carbohydrates, 25% protein; low-fat grains, vegetables, fruits, and legumes and limited intake of added fats sweets and high-fat snacks	18	78	62
Elhayany, 2009 (26)	Israel	Parallel	Open	DM; BMI 27–34	35% carbohydrate, 45% fat (23% MUFA), 20% protein; 4–6 meals/day, only low-glycemic-index carbohydrates	30% fat (10% MUFA), 20% protein, 50% carbohydrate; 4–6 meals/day, mixed glycemic index carbohydrates	12	72	71
Foster, 2003 (9)	United States	Parallel	Open	No DM; obesity	20 g carbohydrates/day, gradually increasing until a stable and desired weight is achieved	25% fat, 60% carbohydrate, 15% protein; limited energy intake of 1200–1500 kcal/day for women and 1500–1800 kcal/day for men	12	61	57
Foster, 2010 (17)	United States	Parallel	Open	BMI 30–40; no DM; normal BP	20 g carbohydrates/day (low-glycemic index-vegetables) during weeks 1–12, increasing by 5 g/week through consumption of a limited amount of fruits, more vegetables, and eventually small quantities of whole grains and dairy products, until a stable and desired weight was achieved	30% fat, 55% carbohydrate, 15% protein; energy intake limited to 1200–1500 kcal/day for women and 1500–1800 kcal/day for men	24	58	68
Frisch, 2009 (27)	Germany	Parallel	Open	BMI >27; no CVD or type 1 DM	40% carbohydrate, 35% fat, 25% protein	30% fat, 55% carbohydrates, 15% protein	6	95	89
Gardner, 2007 (6)	United States	Parallel	Single	Female sex; BMI 27–40; normal BP; no DM CVD; NP	≤20 g carbohydrates/day for the first 2–3 months and ≤50 g carbohydrates/day for the subsequent phase	10% fat	12	88	78

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Country	Design	Blinding	Inclusion Criteria	Intervention or Targeted Dietary Composition		Mean Intervention Duration, months	Completion %	
					LCD	LFD		LCD	LFD
Hockaday, 1978 (28)	United Kingdom	Parallel	Open	DM; no myocardial infarction or stroke	40% carbohydrates, 40% fat, 20% protein	25% fat, 54% carbohydrates, 21% protein	12		
Iqbal, 2010 (29)	United States	Parallel	Open	DM; obesity; no CKD	30 g/day carbohydrates	30% fat with a deficit of 500 kcal/day	24	40	54
Klemsdal, 2010 (14)	Norway	Parallel	Open	No DM or CVD; ≥1 METS components and BMI 28–40 for men and 28–35 for women	30%–35% carbohydrates, 35%–40% fat, 25%–30% protein	30% fat, 55–60% carbohydrate, 15% protein,	12	78	84
Lim, 2009 (30)	Australia	Parallel	Open	BMI 28–40; ≥1 CVD risk factors; No CVD or DM	4% carbohydrate, 60% fat (20% saturated fat), 35% protein	10% fat (3% saturated fat), 70% carbohydrate, 20% protein	15	63	64
McAuley, 2006 (31)	New Zealand	Parallel	Open	Female sex; prediabetes; NP	≤20 g carbohydrates/day during weeks 1–2, increasing to 50 g/day by 8 weeks and continuing thereafter	30% fat, 55% carbohydrate, 15% protein	12	77	75
Moran, 2006 (32)	United Kingdom	Parallel	Open	Female sex; overweight with polycystic ovary syndrome; no DM; NP	120 g carbohydrates/day	50 g fat/day	6	78	57
Sacks, 2009 (13)	United States	Factorial	Double	No DM or CVD; BMI >25	35% carbohydrate, 40% fat, 25% protein	30% fat, 55% carbohydrate, 25% protein	24	83	78
Shai, 2008 (11)	Israel	Parallel	Open	DM or CVD or BMI >27; NP	20 g carbohydrates/day for the 2-month induction phase and with a gradual increase to ≤120 g/day to maintain the weight loss	30% fat (10% saturated fat) with 1500 kcal/day for women and 1800 kcal/day for men, and 300 mg cholesterol/day	24	78	90
Stern, 2004 (12)	United States	Parallel	Open	BMI ≥35; no CKD	<30 g carbohydrates/day	<30% fat with a deficit of 500 kcal/day	12	69	63
Swenson, 2007 (33)	United States	Parallel	Single	Gastric bypass surgery; obesity	South Beach diet	16% fat, 72%–74% carbohydrate, 10–12% protein	6		
Thomson, 2010 (34)	United States	Parallel	Open	Female sex; stage 1–2 breast cancer; BMI 25–35; No DM, CKD, or CVD	35% carbohydrates, 35%–40% fat, 25%–30% protein	25% fat, 55%–60% carbohydrates, 15%–20% protein	6	91	68
Yancy, 2004 (10)	United States	Parallel	Open	BMI 30–60; dyslipidemia; NP	<20 g carbohydrates/day during weeks 1–10, increasing by 5 g/week until body weight was maintained	<30% fat (<10% saturated fat)	6	76	57

Abbreviation: BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular diseases; DM, diabetes mellitus; LCD, low-carbohydrate diets; LFD, low-fat diets; METS, metabolic syndrome; MUFA, monounsaturated fatty acid; NP, no pregnancy.

[a] Weight (kg)/height $(m)^2$.

Table 2. Baseline Characteristics of Study Participants in 23 Randomized Controlled Trials From Multiple Countries Comparing Low-Carbohydrate Diets With Low-Fat Diets[a], 1966–2011

First Author, Year (Reference No.)	Diet	No.	Age, years (mean (SD))	Men, %	Weight, kg (mean (SD))	Metabolic Risk Factors, mean (SD)								
						WC, cm	TC, mg/dL	LDL, mg/dL	HDL, mg/dL	TG, mg/dL	SBP, mmHg	DBP, mmHg	Glucose, mg/dL	Insulin, μIU/mL
Brehm, 2003 (5)	LFD	20	43 (9)	0	92 (6)		185 (29)	114 (30)	49 (11)	109 (45)	115 (12)	75 (9)	91 (10)	24 (11)
	LCD	22	44 (7)	0	91 (8)		206 (30)	125 (24)	52 (13)	149 (60)	116 (14)	79 (12)	99 (12)	17 (8)
Brinkworth, 2009 (22)	LFD	36	50 (7)	41	96 (15)	107 (3)	212 (4)	131 (4)	53 (2)	159 (12)	135 (12)	77 (11)	101 (2)	10 (4)
	LCD	33	51 (8)	32	95 (16)	106 (3)	209 (8)	124 (4)	56 (2)	148 (12)	132 (13)	72 (10)	103 (2)	8 (3)
Dansinger, 2005 (8)	LFD	40	49 (12)	43	103 (15)	111 (13)	214 (34)	136 (37)	45 (2)	174 (130)	133 (17)	76 (9)	121 (55)	30 (18)
	LCD	40	47 (12)	53	100 (14)	109 (11)	214 (31)	136 (31)	48 (16)	152 (98)	129 (17)	77 (9)	127 (62)	22 (16)
Davis, 2009 (23)	LFD	50	53 (7)	26	101 (19)		166 (33)	93 (28)	46 (11)	124 (59)	130 (17)	77 (10)		
	LCD	55	54 (6)	18	94 (18)		170 (32)	97 (27)	50 (9)	124 (74)	125 (18)	73 (9)		
Due, 2008 (24)	LFD	43	29 (5)	41	97 (14)	103 (9)	175 (39)	107 (32)	48 (13)	102 (59)			87 (6)	6 (2)
	LCD	39	27 (5)	43	95 (13)	104 (9)	171 (31)	106 (31)	47 (12)	90 (42)			90 (9)	6 (3)
Ebbeling, 2007 (25)	LFD	37	27 (4)	22	103 (15)			126 (34)	54 (13)	126 (81)	108 (11)	62 (9)	88 (10)	10 (7)
	LCD	36	28 (4)	19	104 (17)			102 (35)	57 (20)	112 (96)	105 (12)	63 (8)	86 (8)	11 (6)
Elhayany, 2009 (26)	LFD	63	57 (6)	56	86 (11)	111 (9)	212 (31)	124 (31)	43 (8)	266 (62)			182 (32)	12 (7)
	LCD	61	56 (7)	51	87 (14)	113 (10)	209 (35)	120 (31)	43 (8)	283 (71)			189 (36)	14 (6)
Foster, 2003 (9)	LFD	30	44 (7)	26	98 (16)		192 (33)	120 (30)	49 (13)	123 (83)	123 (14)	75 (9)		
	LCD	33	44 (9)	36	99 (20)		189 (30)	130 (30)	47 (11)	131 (114)	121 (11)	78 (11)		
Foster, 2010 (17)	LFD	154	45 (10)	32	104 (14)			124 (9)	45 (12)	124 (74)	125 (16)	76 (10)		
	LCD	153	46 (9)	33	103 (16)			120 (9)	46 (14)	113 (55)	124 (14)	74 (9)		
Frisch, 2009 (27)	LFD	100	47 (10)	24	99 (17)	108 (13)	214 (43)	138 (35)	56 (14)	123 (58)	128 (14)	86 (8)	101 (15)	
	LCD	100	47 (11)	38	100 (16)	110 (11)	212 (36)	137 (31)	58 (14)	116 (50)	126 (13)	86 (8)	102 (20)	
Gardner, 2007 (6)	LFD	76	42 (6)	0	86 (10)			111 (27)	50 (11)	118 (62)	116 (10)	75 (8)	93 (13)	10 (5)
	LCD	77	42 (5)	0	86 (13)			109 (29)	53 (14)	125 (78)	118 (11)	75 (8)	92 (9)	10 (7)
Hockaday, 1978 (28)	LFD	39	50 (24–65)[b]	51	82 (56–114)[b]		239 (48)			141 (66)			225 (81)	11 (7)
	LCD	54	53 (22–65)[b]	59	76 (51–99)[b]		251 (60)			150 (78)			195 (77)	11 (7)
Iqbal, 2010 (29)	LFD	72	60 (10)	95	116 (17)		181 (42)	108 (37)	41 (13)	167 (96)	140 (20)	80 (12)	145 (51)	
	LCD	53	60 (9)	84	118 (21)		180 (46)	110 (39)	41 (13)	155 (108)	139 (20)	79 (10)	158 (62)	
Klemsdal, 2010 (14)	LFD	102	50 (8)	38	100 (15)	110 (10)	232 (40)	148 (39)	50 (14)	169 (100)	129 (16)	92 (10)	101 (12)	18 (11)
	LCD	100	50 (5)	46	100 (16)	111 (11)	224 (38)	145 (36)	49 (14)	171 (107)	130 (13)	91 (9)	101 (17)	16 (8)
Lim, 2009 (30)	LFD	28	49 (11)	20	89 (3)		220 (46)	104 (73)	54 (15)	142 (53)	129 (12)	76 (10)	96 (11)	8 (4)
	LCD	27	48 (8)	20	88 (2)		228 (39)	120 (66)	50 (12)	159 (89)	130 (15)	77 (13)	97 (11)	11 (6)
McAuley, 2006 (31)	LFD	24	45 (8)	0	98 (16)	109 (13)	232 (35)	151 (31)	45 (9)	166 (50)	126 (12)	81 (11)	90 (11)	
	LCD	24	45 (7)	0	97 (10)	110 (10)	224 (43)	147 (35)	44 (11)	166 (73)	131 (14)	84 (10)	92 (11)	
Moran, 2006 (32)	LFD	16	33 (5)	0	96 (22)								94 (7)	11 (5)
	LCD	18	32 (6)	0	96 (18)								94 (7)	15 (9)

Table continues

Table 2. Continued

First Author, Year (Reference No.)	Diet	No.	Age, years (mean (SD))	Men, %	Weight, kg (mean (SD))	Metabolic Risk Factors, mean (SD)								
						WC, cm	TC, mg/dL	LDL, mg/dL	HDL, mg/dL	TG, mg/dL	SBP, mmHg	DBP, mmHg	Glucose, mg/dL	Insulin, μIU/mL
Sacks, 2009 (13)	LFD	202	50 (10)	33	92 (13)	102 (12)	203 (36)	126 (32)	49 (13)	144 (79)	120 (13)	75 (9)	92 (17)	12 (8)
	LCD	201	51 (9)	36	94 (16)	104 (13)	204 (35)	126 (31)	51 (16)	141 (85)	120 (15)	76 (10)	92 (13)	12 (8)
Shai, 2008 (11)	LFD	104	51 (7)	86	91 (12)	105 (9)		117 (36)	39 (10)	157 (62)	130 (13)	79 (9)	87 (26)	13 (7)
	LCD	109	52 (7)	91	92 (14)	106 (9)		117 (35)	38 (9)	182 (117)	131 (15)	79 (9)	93 (29)	14 (10)
Stern, 2004 (12)	LFD	64	54 (9)	85	129 (20)			121 (28)	41 (9)	162 (78)	139 (16)	82 (9)		
	LCD	62	53 (9)	80	132 (23)			112 (32)	41 (10)	201 (204)	133 (16)	77 (11)		
Swenson, 2007 (33)	LFD	13	40 (8)	15	167 (71)	140 (25)								
	LCD	19	42 (10)	5	198 (85)	145 (16)								
Thomson, 2010 (34)	LFD	19	56 (9)	0	83 (11)	98 (10)	201 (40)	119 (34)	54 (18)	138 (54)	136 (21)	78 (10)	100 (12)	16 (9)
	LCD	21	56 (9)	0	85 (14)	102 (11)	195 (26)	112 (23)	60 (15)	115 (45)	127 (14)	81 (11)	98 (15)	17 (17)
Yancy, 2004 (10)	LFD	60	46 (9)	22	97 (19)		240 (35)	147 (31)	54 (15)	191 (106)	133 (16)	82 (8)		
	LCD	59	44 (10)	25	98 (15)		245 (35)	159 (27)	55 (15)	158 (106)	134 (16)	82 (9)		
Total	LFD	1396	48	39	98	108	208	125	48	149	127	79	109	13
	LCD	1392	48	40	99	108	209	124	49	149	126	78	111	13

Abbreviations: DBP, diastolic blood pressure; HDL, high density lipoprotein cholesterol; LCD, low-carbohydrate diet; LDL, low density lipoprotein cholesterol; LFD, low-fat diet; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

[a] Baseline data were from all participants in the study.

[b] Expressed as mean (range).

Table 3. Main Results and Results From Sensitivity Analyses, 1966–2011

Variable	All Trials			Trials With ≥70% Completion Rate			Trials ≥With 20 Participants per Group			Trials With Healthy Participants[a]		
	No. of Trials	Net Change	95% CI	No. of Trials	Net Change	95% CI	No. of Trials	Net Change	95% CI	No. of Trials	Net Change	95% CI
Weight, kg	22	−1.0	−2.2, 0.2	12	−1.3	−2.8, 0.2	19	−1.3	−2.5, −0.1	18	−1.4	−2.6, −0.2
WC, cm	10	−0.1	−0.6, 0.4	8	−0.3	−1.0, 0.5	8	−0.2	−0.7, 0.3	8	−0.2	−0.7, 0.3
TC, mg/dL	15	2.7	0.8, 4.6	9	3.5	0.1, 6.9	14	3.3	1.0, 5.5	13	2.7	0.6, 4.9
LDL, mg/dL	19	3.7	1.0, 6.4	11	2.8	0.3, 5.3	18	3.7	1.0, 6.4	17	3.6	0.7, 6.4
HDL, mg/dL	19	3.3	1.9, 4.7	11	3.0	1.9, 4.1	18	3.4	1.9, 4.8	17	3.3	1.9, 4.8
TC:HDL ratio	5	−0.1	−0.3, 0.1	1	−0.5	−0.8, −0.1	5	−0.1	−0.3, 0.1	5	−0.1	−0.3, 0.1
TG, mg/dL	20	−14.0	−19.4, −8.7	12	−11.2	−16.9, −5.5	19	−13.4	−18.7, −8.1	18	−13.6	−19.2, −8.0
SBP, mmHg	18	−1.0	−3.5, 1.5	10	−0.1	−2.5, 2.3	17	−1.4	−3.9, 1.2	17	−1.6	−4.2, 1.0
DBP, mmHg	18	−0.7	−1.6, 0.2	10	−1.1	−2.4, 0.2	17	−0.8	−1.7, 0.2	17	−0.8	−1.7, 0.2
Glucose, mg/dL	14	−0.3	−1.9, 1.3	10	−0.6	−2.7, 1.4	13	−0.4	−2.1, 1.4	13	−0.4	−2.1, 1.4
Insulin, IU/mL	12	−0.1	−0.8, 0.6	8	−0.1	−1.0, 0.8	10	−0.1	−0.9, 0.7	10	−0.3	−0.9, 0.7

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

[a] Trials with participants who had breast cancer, polycystic ovary syndrome, or coronary heart disease or who had undergone gastric bypass surgery were excluded.

Both diets also improved lipid profiles. Low-carbohydrate diets resulted in reductions in total cholesterol (−4.6 mg/dL), LDL cholesterol (−2.1 mg/dL), the ratio of total to HDL cholesterol (−0.7), and triglycerides (−30.4 mg/dL) and an increase in HDL cholesterol (4.5 mg/dL) from baseline to at least 6 months of follow-up. Although compared with low-fat diets, low-carbohydrate diets resulted in less reductions in total and LDL cholesterol but greater reductions in triglycerides and increases in HDL cholesterol, the reduction in ratio of total to HDL cholesterol, which has been identified as a predictor of coronary heart disease (35), was not significantly different between the 2 diets. It is tempting to suggest that the differential effect of the 2 diets on lipid fractions may translate to a differential effect on cardiovascular risk; however, to clearly demonstrate such a difference, randomized trials with clinical event outcomes may be necessary.

Dietary intake may affect multiple body systems. Although to our knowledge, there have been no clinical trials examining the association between low-carbohydrate diets and clinical outcomes such as depression, some studies have suggested that low-carbohydrate diets may result in mood changes. However, weight loss has also been associated with improved mood, whereas obesity has often been associated with depression (36, 37). Similarly, low-carbohydrate diets, which are high in protein, may increase calcium excretion in urine; however, this increase has not been associated with low bone density in prospective cohort studies (38–41) and may be offset by increased calcium absorption in the intestines (42). Low-carbohydrate diets are often high in fat, and high-fat diets have been associated with increased risks of certain types of cancer in some observational studies (43, 44). Thus, moderating the amount and types of fat substituted for carbohydrates is prudent not only to improve cardiovascular and metabolic risk factors but also to avoid increasing risk for other chronic diseases. Given the difficulty in disentangling dietary components, weight status, and other confounding factors that can vary over time in observational studies, these remaining questions may require large clinical trials of many years' duration.

Protein and fat sources may mediate the association between low-carbohydrate diets and long-term cardiovascular and metabolic risk factors, cancer, and mortality (45). A prospective cohort study of 82,802 US nurses reported that a low-carbohydrate dietary pattern that incorporated high intakes of vegetable protein and unsaturated fat was associated with a lower risk of coronary heart disease over 19 years of follow-up (46). The investigators also found this pattern was associated with a lower risk of cardiovascular and all-cause mortality among both men and women (47). In contrast, a low-carbohydrate diet emphasizing animal sources of fat and protein was associated with a higher risk of type 2 diabetes mellitus and all-cause mortality (47). Unfortunately, few studies in the present meta-analysis reported data on sources of dietary protein and fat. In the future, randomized controlled clinical trials that examine and compare metabolic and cardiovascular effects of different low-carbohydrate dietary patterns are warranted.

The present study has several limitations. First, losses to follow-up were substantial, especially in some trials (8, 22, 29). Almost half of the studies included in our meta-analysis had completion rates less than 70%. However, the sensitivity analysis suggested a nonsignificant influence of studies with a low completion rate on the overall study results. Second, moderate to high heterogeneity existed for some metabolic risk factors. Thus, we used random-effect models, which allow for between-study heterogeneity. Third, publication bias may be responsible for the significant differences in reductions of total and LDL cholesterol and increases in HDL cholesterol between diets. Statistical testing indicated significant publication bias for lipid outcomes, and when using the trim-and-fill method, which accounted for potential publication bias, pooled mean net changes in total, LDL, and HDL cholesterol were no longer statistically significant. However,

the results of the trim-and-fill analysis should be interpreted cautiously because publication bias against low-carbohydrate diets may be different from what is typically encountered in research in which publication bias leaves out predominantly the negative studies.

There are also several strengths in the present study. We conducted this meta-analysis following a stringent protocol. Two investigators independently reviewed articles and abstracted the data using a standard abstraction form. The studies that we used were all randomized controlled trials, which are subject to fewer biases than observational studies and are the gold standard for evaluating the effects of an intervention. This meta-analysis had a sample size of 2,788, which provided the power to detect statistically significant mean differences, assess publication bias, and conduct sensitivity and subgroup analyses. Moreover, we used both false discovery rate and Bonferroni correction to adjusted *P* values (21). The results with regard to lipids remained significant when they were corrected using either method. Finally, we only included trials that were at least 6 months in duration to evaluate long-term changes in metabolic risk factors.

Because metabolic risk factors are important determinants of cardiovascular disease morbidity and mortality, recommending a diet in clinical practice that can improve these factors is vital to curbing the epidemics of obesity and cardiovascular diseases in the general population. Low-carbohydrate diets had beneficial effects on weight loss and metabolic risk factors, and these effects were comparable to those seen on low-fat diets. Although the present study did not examine long-term clinical effects on cardiovascular diseases, these findings suggest that low-carbohydrate diets can be recommended to obese persons with metabolic risk factors for the purpose of weight loss. Dietary recommendations for weight loss should be revisited to consider additional evidence of the benefits of low-carbohydrate diets.

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