Efficacy and Safety of Low-Carbohydrate Diets
A Systematic Review

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Context Low-carbohydrate diets have been popularized without detailed evidence of their efficacy or safety. The literature has no clear consensus as to what amount of carbohydrates per day constitutes a low-carbohydrate diet.

Objective To evaluate changes in weight, serum lipids, fasting serum glucose, and fasting serum insulin levels, and blood pressure among adults using low-carbohydrate diets in the outpatient setting.

Data Sources We performed MEDLINE and bibliographic searches for English-language studies published between January 1, 1966, and February 15, 2003, with key words such as *low carbohydrate*, *ketogenic*, and *diet*.

Study Selection We included articles describing adult, outpatient recipients of low-carbohydrate diets of 4 days or more in duration and 500 kcal/d or more, and which reported both carbohydrate content and total calories consumed. Literature searches identified 2609 potentially relevant articles of low-carbohydrate diets. We included 107 articles describing 94 dietary interventions reporting data for 3268 participants; 663 participants received diets of 60 g/d or less of carbohydrates—of whom only 71 received 20 g/d or less of carbohydrates. Study variables (eg, number of participants, design of dietary evaluation), participant variables (eg, age, sex, baseline weight, fasting serum glucose level), diet variables (eg, carbohydrate content, caloric content, duration) were abstracted from each study.

Data Extraction Two authors independently reviewed articles meeting inclusion criteria and abstracted data onto pretested abstraction forms.

Data Synthesis The included studies were highly heterogeneous with respect to design, carbohydrate content (range, 0-901 g/d), total caloric content (range, 525-4629 kcal/d), diet duration (range, 4-365 days), and participant characteristics (eg, baseline weight range, 57-217 kg). No study evaluated diets of 60 g/d or less of carbohydrates in participants with a mean age older than 53.1 years. Only 5 studies (nonrandomized and no comparison groups) evaluated these diets for more than 90 days. Among obese patients, weight loss was associated with longer diet duration ($P=.002$), restriction of calorie intake ($P=.03$), but not with reduced carbohydrate content ($P=.90$). Low-carbohydrate diets had no significant adverse effect on serum lipid, fasting serum glucose, and fasting serum insulin levels, or blood pressure.

Conclusions There is insufficient evidence to make recommendations for or against the use of low-carbohydrate diets, particularly among participants older than age 50 years, for use longer than 90 days, or for diets of 20 g/d or less of carbohydrates. Among the published studies, participant weight loss while using low-carbohydrate diets was principally associated with decreased caloric intake and increased diet duration but not with reduced carbohydrate content.

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Between 1960 and 2000 the prevalence of obesity among adults aged 20 years to 74 years in the United States increased from 13.4% to 30.9%.[1-3] An estimated 325 000 deaths and between 4.3% and 5.7% of direct health care costs (approximately $39-$52 billion) are attributed to obesity annually.[1,2] Results from the 1998 Behavioral Risk Factor Surveillance Survey indicate that roughly one third of US adults were trying to lose weight at that time, and another third were trying to maintain weight.[4] Recently, low-carbohydrate diets have resurged in popularity as a means of rapid weight loss, yet their long-term efficacy and safety remain poorly understood.

The first low-carbohydrate diet to have enjoyed popular success was that described by William Banting in the 1860s.[5] Banting claimed that he was never hungry and at the age of 66, in a period of a year, lost 46 of his initial 202 pounds. He wrote, "The great charms and comfort of the system are that its effects are palpable within a week of trial and creates a natural stimulus to persevere for a few weeks more."[5]

While it is difficult to estimate the number of people who have followed low-carbohydrate diets, the number and popularity of articles and books from the lay press advocating their use attest to a high level of interest in and demand for these diets by the US public. The most popular text, written by cardiologist and long-time proponent

For editorial comment see p 1853.

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of low-carbohydrate diets Robert Atkins, has been on the *New York Times* bestsellers' list continuously for more than 5 years.[6] Over the past 5 years, 3 books on low-carbohydrate diets collectively sold millions of copies in the United States.[6-8] Advocates of low-carbohydrate diets claim that diets higher in protein and lower in carbohydrates promote the metabolism of adipose tissue in the absence of available dietary carbohydrate and result in rapid weight loss without significant long-term adverse effects.[6]

However, numerous professional organizations, including the American Dietetic Association and the American Heart Association, have cautioned against the use of low-carbohydrate diets.[9-12] There are concerns that low-carbohydrate diets lead to abnormal metabolic functioning that may have serious medical consequences, particularly for participants with cardiovascular disease, type 2 diabetes mellitus, dyslipidemia, or hypertension. Specifically, it has been cautioned that low-carbohydrate diets cause accumulation of ketones and may result in abnormal metabolism of insulin and impaired liver and kidney function; in salt and water depletion that may cause postural hypotension, fatigue, constipation, and nephrolithiasis; in excessive consumption of animal proteins and fats that may promote hyperlipidemia; and in higher dietary protein loads that may impair renal function.[13,14]

The medical literature pertaining to the efficacy and the metabolic effects of low-carbohydrate diets is composed of numerous heterogeneous studies of relatively few participants. The studies vary in terms of dietary interventions provided (eg, percentage of calories from carbohydrate, fat, and protein), type of participants enrolled (eg, participants with diabetes or with hyperlipidemia), and outcomes evaluated (eg, weight loss or change in glycemic control). The purpose of this study was to synthesize the literature on low-carbohydrate diets to evaluate changes in weight, serum lipid, fasting serum glucose, and fasting serum insulin levels, and blood pressure among adults using low-carbohydrate diets in the outpatient setting.

Table 1. Results of Literature Search

Description	No. of Articles
MEDLINE key word searches	
Search 1, *diet**	192 654
Search 2, *low carbohydrate**	567
Search 3, *high fat**	5782
Search 4, *high protein**	3473
Search 5, *ketogenic*	706
Search 6, *isocaloric*	2808
Search 7, *hypocaloric*	706
Search 8, *protein sparing*	2014
Search 9, *carbohydrate restricted*	6362
Combine searches: 1 AND (2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9) LIMIT by (participant types: adults and humans) then discard duplicates	2609
Exclusion criteria	
Articles included only pediatric participants (no adults)	21
Diet duration <4 d	95
Did not report sufficient data to be able to calculate grams per day of carbohydrates per diet	72
Did not report sufficient data to be able to calculate calories per day per diet	97
Participants hospitalized or confined to a research center	146
Diets that provided <500 kcal/d	26
Review article	36
Article not in English	17
Included only pregnant participants	5
Did not report data for any of the outcomes of interest	1994
Total articles excluded from those found in the MEDLINE search†	2509
Articles included from manual searches of bibliographies	7
Total articles included in the analyses	107
Combine duplicated reports on the same study participants	13
Total studies of dietary interventions included	94

*All terms beginning with this root would be included in the search (eg, searching with the root *diet* includes terms such as *diets*, *dieting*, and *dietary*).
†Several articles met more than 1 of the exclusion criteria.

METHODS

Data Sources

Two authors and a professional librarian independently developed search strategies to identify studies that met the eligibility criteria. We performed searches on MEDLINE for English-language studies published between January 1, 1966, and February 15, 2003, that were indexed with key words including *diet*, *low carbohydrate*, *high fat*, *high protein*, and *ketogenic* (TABLE 1). We also reviewed the bibliographies of retrieved articles and conference proceedings to obtain additional citations.

Study Selection Criteria

English-language studies were considered eligible for this analysis if they evaluated any of the following interventions: low-carbohydrate, ketogenic, higher-protein, or higher-fat diets for adults who were not pregnant. Additionally, the included studies had to report sufficient data to calculate both carbohydrate content (grams per day) and total calories consumed (kilocalories per day). Because we were interested in diets that could be followed by outpatient adults, studies that evaluated diets with the following characteristics were excluded: less than 500 kcal/d, duration of diet less than 4 days, or requirement for participants to be hospitalized or confined to a research or diet center. Articles were excluded if they did not report data for at least 1 of the clinical outcomes of interest.

Abstraction Methods

One author reviewed the 2609 titles and abstracts identified by the combined

MEDLINE search for potentially relevant studies. Two authors independently abstracted study design and participant data onto pretested abstraction forms from each of these publications and reviewed bibliographies for additional potentially relevant studies. Abstraction discrepancies were resolved by repeated review and discussion. If 2 or more studies presented the same data from a single participant population, these data were included only once in the analyses. If a study presented data on 2 types of diets and if 1 of the diets did not meet our inclusion criteria (eg, studies that compared a fast- with a lower-carbohydrate diet), then data were abstracted only for those participants receiving the diet that met the inclusion criteria.

Data Abstracted

Three types of variables were abstracted from each study: dietary intervention, participants studied, and clinical outcomes. The variables for dietary intervention abstracted were carbohydrate, fat, and protein content (grams/day), daily caloric content (kilocalories per day), and the duration of dietary intervention (days). The participant variables abstracted were type of participants enrolled (eg, athletes, healthy volunteers, or participants with obesity, hyperlipidemia, diabetes, or hypertension), age, sex, and race/ethnicity. The outcome variables abstracted were measures of body mass (weight in kilograms, body mass index [BMI] calculated as weight in kilograms divided by the square of height in meters, and percentage of body fat), measures of lipid levels (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and serum triglycerides), measures of glycemic control (fasting serum glucose and insulin levels), and a measure of hypertensive control (systolic blood pressure).

Statistical Analyses

For each study, a weighted mean was calculated for each of the participant and diet characteristics (weighted by the number of participants who completed the study). We calculated an effect size for each outcome variable for each study (ie, standardized mean difference) from the mean change in the variable from the start of the diet to the end of the diet and the variance about this change.[15] If the study did not report these data, a pooled variance was calculated.[15] If an individual study did not report a measure of variance for the start or the end values of each outcome variable, then a weighted mean variance was calculated, and this weighted mean variance was used to calculate the pooled variance.[15] If a study did not report any measure of variance for an outcome, the overall mean pooled variance was used for that study.

Typically, a meta-analysis is the quantitative synthesis of independent studies, each of which was designed to compare the effects of a standard treatment with an experimental treatment. Because the studies are independent, so are the effect sizes. In the case of our analysis, the participant, diet, and outcome variables for each participant studied are correlated; therefore, the corresponding estimated effect sizes for these measures are correlated.[16] Multivariate analysis of variance (weighted by the number of participants who finished each diet) was used to calculate the summary effect of the dietary and participant characteristic variables on the outcome variables.[15] For example, using this method, the effect of carbohydrate content controlled for diet duration and calorie content on weight loss could be determined.

Bivariate analyses were performed to estimate the differences in weight loss, serum lipid, fasting serum glucose, and fasting serum insulin levels, and blood pressure between participants who were grouped into 2 general categories of lower- vs higher-carbohydrate diets. The bivariate analyses required setting a threshold to classify lower- vs higher-carbohydrate diets. Because the literature has no clear consensus as to what amount of carbohydrates per day constitutes a low-carbohydrate diet, the differences between lowest-, lower-, and higher-carbohydrate diets by carbohydrate thresholds of 20 g/d or less, 60 g/d or less, and more than 60 g/d, respectively, were evaluated. Unless otherwise specified, these thresholds will be used to define these categories of low-carbohydrate diets. These thresholds correspond to recommendations found in the popular literature of low-carbohydrate diets.[6-8]

For the bivariate analyses, effect sizes were combined using a fixed effects model, which produces a narrower 95% confidence interval (CI), thereby increasing the likelihood of finding a difference between lower- and higher-carbohydrate diets. Then tests of homogeneity on summary effect sizes using the Q statistic were calculated. We attempted to minimize multiple comparisons. Because 4 outcome groups of interest (changes in body mass, serum lipid levels, glycemic indicators, and blood pressure) were included, a Bonferroni adjustment was used and the null hypothesis was rejected only if the level of significance was less than .0125 (.05/4 = .0125). Analyses were performed using SAS version 6.12 (SAS Institute, Cary, NC), SPSS version 9.0 (SPSS Inc, Chicago, Ill) and Microsoft Excel 2000 (Microsoft Corp, Redmond, Wash).

RESULTS

Identified Studies

Our MEDLINE search identified 2609 titles of potentially relevant articles. We obtained 7 additional references from manual searches of the bibliographies of retrieved articles (Table 1). A total of 107 articles met the inclusion criteria. After combining multiple reports on the same study participants, we included 94 dietary interventions (Table 1 and TABLE 2).

Study Characteristics

The designs of the included studies were highly heterogeneous (Table 2). Several studies included a washout phase at the beginning of the study interval, during which participants typically received a standard or maintenance diet that was intended to simulate their usual diet in calories and macronutrient composition. For those studies including a washout phase, we considered the participants' weight at the end of the washout phase as their baseline weight.

Forty-three studies used randomized research designs: 24 studies were randomized controlled trials[17-46] in which participants were randomized to receive 1 of 2 or more diets and 19 studies were randomized crossover trials[47-65] in which participants were randomized to receive one diet first and then to receive a second diet. Of those studies that did not use randomized research designs, 17 studies[66-84] compared participants receiving a lower-carbohydrate diet with a comparison group receiving an alternative diet. In some studies, participants were allowed to decide which diet they would prefer to maximize adherence to the prescribed diet. Nine studies[85-94] had a sequential design in which

Table 2. Characteristics of Low-Carbohydrate Studies by Study Design*

Source	Total No. of Participants†	Age, Mean (Range), y	Sex, % Male	Duration of Diet, d	No. of Arms in Study†	Dietary Composition, Range: Carbohydrates, g	Proteins, g	Fats, g	Total Calories, kcal
Randomized Controlled Trials									
Vessby et al[17]	162	49 (30-65)	53	90	2	236-247	80-81	88-89	2140-2150
Hockaday et al[18]	93	52 (22-65)	56	365	2	150-203	75	43-67	1500
Shah et al[19]	89	36 (25-45)	0	180	2	225-242	63-66	49-63	1684-1740
Lean et al[20]	82	51 (18-68)	0	180	2	110-186	62-89	27-47	1197-1198
Baron et al[21]‡	63	40	15	90	1	50	NA	NA	1200
Kratz et al[22]	58	26 (18-43)	0-100	28	6	272-304	79-92	100-110	2318-2574
Saltzman et al[23,24]	43	45	43-50	42	2	229-234	79-82	67-69	1827-1872
Schlundt et al[25]	49	44	13	140	2	179-210	61-64	28-30	1265-1426
Foster et al[26]‡	47	41	0	84	2	30-100	70-90	13-20	660-800
Skov et al[27-29] and Haulrik et al[30]	46	40 (18-56)	23	180	2	248-386	79-131	70-83	2139-2605
Heilbronn et al[31]	45	NA (56-58)	46-57	56	2	212-218	78-80	27-29	1436-1442
Helge[32]	41	27	100	49	3	184-566	127-149	79-245	3370-3561
Scott et al[33]	36	38 (29-49)	0	56	2	104-152	51-53	22-46	1003-1005
Brussaard et al[34]	35	NA (19-30)	66	94.5	2	315-375	93-98	57-85	2460-2470
Wolever and Mehling[35]	34	56 (30-65)	18-23	112	3	223-232	75-82	47-74	1695-1879
Brown et al[36]	32	26 (16-62)	94	84	2	359-631	114-124	50-196	3378-3670
Luscombe et al[37]	26	NA (62-64)	33-55	56	2	167-219	64-112	46-49	1583-1585
Fagerberg et al[38]	23	50 (44-56)	100	28	2	81-204	69-70	26-72	1370-1400
Kogon et al[39]	23	40 (23-55)	0	28	2	29-116	69	23-62	950
Racette et al[40]	23	39 (21-47)	0	84	4	76-182	32-74	69-74	1147-1231
Hammer et al[41]§	14	33	0	112	1	114	50	16	800
Mathieson et al[42] and Walberg et al[43]	12	NA (23-36)	0	28	2	44-94	33	3-25	530
Foster et al[44] and Wadden et al[45]‡	9	41	0	336	1	146	60	41	1194
Coyle et al[46]	7	25	100	14	2	718-901	113-117	9-105	4358-4444
Randomized Crossover Trials									
Parker et al[47]	54	61	35	56	2	167-211	63-111	45-49	1543-1587
Miller et al[48]	43	54	43	56	1	289	95	63	2100
Peterson and Jovanovic-Peterson[49]	25	36 (21-50)	0	42	1	150	NA	NA	1500
Muller et al[50]	25	31	0	20-22	3	243-330	77-85	45-89	2069-2115
vanStratum et al[51]	22	53	0	14	2	174-287	90	53-102	1970-1987
Luscombe et al[52]	21	57	67	28	2	202-272	106-110	77-42.4	1910-1924
Rosen et al[53]	20	29 (20-38)	5	14	2	0-50	77-105	33-55	800-917
Jenkins et al[54]	20	56 (35-71)	75	30	2	323-415	111-189	78-80	2764-2835
Weinsier et al[55]‡	18	59 (43-69)	61	112	2	190-264	69-74	56-90	1847-1849
Simpson et al[56]	14	54	83	42	2	209-375	98	63-137	2458-2462
Straznicky et al[57]	14	26	100	14	2	250-301	106-109	60-136	2187-2636
Pomerleau et al[58]	12	58	67	21	2	299-302	52-125	56-80	2103-2175
Lousley et al[59]	11	64 (51-75)	NA	42	2	115-202	67-70	23-60	1240
Wolfe and Piche[60]	10	28 (20-57)	20	28	2	258-304	64-116	84-85	2155-2178
Wolfe and Giovannetti[61]	10	50 (24-67)	40	28	2	263-344	52-108	52-53	1909-2011
Whitehead et al[62]	8	49 (31-57)	25	7	3	80-133	38-90	36-59	1004
Carey et al[63]	7	24	100	6	2	183-787	183-185	82-346	4584-4629
Holmback et al[64]	7	32 (26-43)	100	6	2	299-485	112	66-149	2988
Spaulding et al[65]	6	NA (25-43)	NA	14	4	0-200	0-55	0-71	800-1066

(continued)

Table 2. Characteristics of Low-Carbohydrate Studies by Study Design* (cont)

Source	Total No. of Participants†	Age, Mean (Range), y	Sex, % Male	Duration of Diet, d	No. of Arms in Study†	Dietary Composition, Range: Carbohydrates, g	Proteins, g	Fats, g	Total Calories, kcal
Trials With Control or Comparison Group									
Bialkowska et al[66]	101	NA	0	42	2	75-113	55-71	43-73	1066-1237
Fleming[67]	100	43 (23-67)	47	365	4	36-315	51-100	15-97	1350-2100
Golay et al[68]	68	45	22	84	2	70-132	85-86	34-57	1142-1179
Luntz and Reuter[69]	61	54 (27-87)	34	180	2	100	NA	NA	1000
Mezzano et al[70]	42	22	100	90	2	207-269	86	59-87	1952
Alford et al[71]	35	39 (31-56)	0	70	3	75-225	45-90	13-60	1200
Heilbronn et al[72]	35	58	23	84	3	198-280	65-73	17-57	1541-1613
Donnelly et al[73]	35	NA	0	90	3	79	50	1	525
Thompson et al[74]‡	27	29	100	14	2	183-668	116-126	77-296	3856-3871
Volek et al[75] and Sharman et al[76]	20	36.7	100	42	2	46-283	80-176	56-157	1950-2335
Ireland et al[77]	18	30	38	14	2	87-124	96-250	28-111	1617-1887
Gumbiner et al[78] and Low et al[79]	17	53	47	42	2	39-312	84-87	21-127	1635-1785
Vaswani[80]	17	31	0	84	2	10-70	NA	NA	800
Young et al[81]	8	23 (21-28)	100	63	3	30-104	115	103-135.5	1800
Simonyi et al[82]	7	28-47	0-100	6-10	7	15-25	NA	NA	1537-2010
Greenhaff et al[83]	6	28	100	4	3	20-486	100-174	36-207	2622-2673
Greenhaff et al[84]	5	31	100	4	2	22-617	75-179	29-242	2988-3011
Sequential Study Design									
Hulley et al[85]	41	NA (24-59)	100	180	2	160-277	97-102	114-117	2100-2523
Pieke et al[86]	19	39.2 (28-58)	100	14-28	2	242-312	101-105	71-102	2313-2390
Bonanome et al[87]	19	55 (40-61)	53	60	3	182-242	57-61	42-72	1518-1616
Serog et al[88] and Apfelbaum et al[89]	18	NA (18-22)	NA	NA	2	70-525	105	31-233	2800
Hallak et al[90]	16	NA (18-30)	100	14	2	160-327	59-64	17-104	1696-1834
O'Dea et al[91]	10	61 (50-69)	100	14	4	91-292	95-246	19-129	1586-2115
Cattran et al[92]	8	34 (24-57)	63	21	3	92-242	70-84	40-117	1638-1760
Ekstedt et al[93]	7	NA (21-37)	100	8	4	323-542	109-162	54-220	2300-3800
Fery et al[94]‡	6	NA (22-46)	NA	4	1	25	101	169	2026
Pre-Post Studies									
Nobels et al[95]	113	37	NA	180	1	38	84	29	750
Rabast et al[96]	104	37	33	106	1	40	60	100	1340
Kirby et al[97]	59	NA (18-70)	20	126	1	30	NA	NA	1000
Bettens et al[98]	57	41	21	60	1	40	NA	NA	1200
Calle-Pascual et al[99]	54	43	15	140	1	113	73	54	1260
Comi et al[100]	46	52 (40-60)	57	30	1	211	63	40	1400
Harvey et al[101]	42	52	38	180	1	180	45	40	1260
Westman et al[102]	41	44	24	168	1	23	115	98	1447
Spiller et al[103]	26	56 (29-81)	NA	63	1	241	103	90	2194
Mogul et al[104]‡	26	47, 54	0	365	2	159	122	38	1500
Krotkiewski et al[105]	25	40	0	28	1	65	55	7	544
Larosa et al[106]	24	NA (20-58)	58	56	1	6	107	108	1461
Engelhart et al[107]	19	NA (34-71)	15	84	1	193	112	45	1625
De Lorenzo et al[108]	19	32	0	60	1	214	78	43	1554
Serog et al[22] and Apfelbaum et al[93]	14	NA (18-22)	10	14	1	36	70	16	560
Marsoobian et al[109]	13	NA (18-28)	0	14	1	30	NA	NA	600
Cangiano et al[110]	10	43	0	42	1	245	85	87	2066
Volek et al[111,112]	10	26	100	56	1	39	147	151	2110
Buffenstein et al[113]	9	NA (20-36)	0	28	1	102	41	15	743
Cordera et al[114]	8	37	100	60	1	165	98	50	1500
Evans et al[115]	8	NA (21-40)	0	42	1	86	75	94	1490
Benoit et al[116-117] and Grande et al[118]	7	29 (22-45)	100	10	1	10	35	91	1000
Staudacher et al[119]‡	7	24	100	6	1	197	171	351	4628
Kwan et al[120]	6	21 (20-23)	0	7	1	49	103	164	2066
Elliot et al[121]	2	23 (22-23)	50	24	1	7	180	225	2773

Abbreviation: NA, not available.
*Study and design: Randomized controlled trials were those in which participants were randomized to receive 1 of 2 or more diets; randomized crossover trials were those in which participants were randomized to receive one diet first and then to receive a second diet. Sequential study designs were those in which all participants received 2 or more diets in the same order; pre-post studies were those in which a single group received a single diet.
†Total number of participants completing the diets. Number of arms equals number of diets evaluated.
‡Only data for participants receiving dietary interventions meeting the exclusion critria were included.

Table 3. Diet Characteristics

	Carbohydrates in Diet, g/d						
	Lower, ≤60			Higher, >60			
	No. of Diets	Mean (SD)	Median (Range)	No. of Diets	Mean (SD)	Median (Range)	*P* Value
Carbohydrate content, g/d	38	29 (15)	30 (0-60)	157	236 (141)	211 (65-901)	<.001
Protein content, g/d	26	96 (45)	95 (33-180)	150	89 (36)	83 (0-250)	.30
Fat content, g/d	26	104 (65)	99 (16-242)	150	69 (58)	57 (0-351)	.01
Caloric content, kcal/d	38	1446 (653)	1454 (530-2988)	157	1913 (880)	1740 (525-4629)	.002
Diet duration, d	37	50 (70)	24 (4-365)	152	73 (83)	42 (4-365)	.10

all participants received 2 or more diets in the same order. Twenty-five studies[95-121] were pre-post evaluations in which a single group received a single diet. For those participants in studies with randomized crossover and sequential diet designs, we did not use the data from the second diet interval in our analyses because participants did not typically return to their baseline weight between diets.

Diet Characteristics

The included studies reported on 38 lower-carbohydrate diets,* (≤ 60 g/d of carbohydrates); 13† of these 38 were lowest-carbohydrate diets (≤20g/d of carbohydrates). Lower-carbohydrate diets had lower caloric contents (mean, 1446 kcal/d) than higher-carbohydrate (>60 g/d of carbohydrates) diets (mean, 1913 kcal/d, $P = .002$). Studies of lower-carbohydrate diets tended to have a shorter duration than studies of higher-carbohydrate diets (mean, 50 days and mean, 73 days, respectively; $P = .10$) (TABLE 3). Studies of the lowest-carbohydrate diets had shorter duration (mean [range], 19 [4-84] days) than the lower- and higher-carbohydrate diets ($P = .02$). Only 5 studies evaluated lower-carbohydrate diets for more than 90 days, and these studies were nonrandomized and noncontrolled designs (Table 2).[67,95-97,102]

All of the studies in our systematic review included participants in the outpatient setting. The studies used a variety of methods to verify that the participants adhered to the prescribed diet. These methods included food diaries, measured ketonuria or serum β-hydroxybutyrate levels, comparison of the expected sodium intake with observed urinary sodium levels, and multiple or no verification methods.

Because most weight loss programs include both diet and exercise, we were interested in comparing lower-carbohydrate diets with and without exercise. However, the included studies varied significantly with respect to the amount of description of the exercise component. For example, many studies simply stated that exercise was encouraged but did not present information about the type, frequency, or duration of exercise by participants. Therefore, given the lack of sufficiently detailed data, we excluded exercise information from our analyses.

Participant Characteristics

The included studies present data on 3268 participants who completed the diets: 663 participants received lower-carbohydrate diets, of whom only 71 received lowest-carbohydrate diets (TABLE 4). No significant difference was found in the age or sex of recipients of lower- vs higher-carbohydrate diets. The mean (SD) age of recipients of lower-carbohydrate diets was 37.6 (8.5) years and no study of lower-carbohydrate diets had a mean age older than 53.1 years. The participants' weight before diet, BMI, percentage of body fat, serum lipid, fasting serum glucose, and fasting serum insulin levels, and systolic blood pressure did not differ significantly between the lower- and higher-carbohydrate groups (Table 4). The definitions of what constituted a healthy volunteer, obese participant, or participant with diabetes varied among studies. The classifications of racial/ethnic groups also varied among studies that reported data on race/ethnicity; thus, these classifications were not included in our analyses.

Effect of Diet and Participant Characteristics on Efficacy and Safety Variables

Results of the bivariate analyses compare the differences in each of the outcome variables between recipients of lower- vs higher-carbohydrate diets (TABLE 5). The interpretation of these analyses is complicated by the significant heterogeneity of the included studies. For example, because the included diets were not isocaloric, the lower-carbohydrate diets vary significantly with respect to the percentage of calorie intake from carbohydrates. We have attempted to compare diets with similar caloric contents, durations, and study designs to account for this heterogeneity.

Change in Weight, BMI, and Percentage of Body Fat. At the end of both lower- and higher-carbohydrate diets, participants' weight, BMI, and percentage of body fat decreased (Table 5). In general, for both lower- and higher-carbohydrate diets, we found the greatest weight loss occurred among those participants receiving diets with the lowest caloric content and for those participants with the highest baseline weights (Table 5).

*References 21, 26, 39, 42, 43, 53, 65, 67, 75, 76, 78-80, 82-84, 88, 89, 94-98, 102, 106, 109, 111, 112, 116-118, 121.
†References 53, 65, 80, 82, 83, 106, 116-118, 121.

The 72 young participants of the 14 diets* of very short duration (<15 days) receiving lower-calorie diets (mean [SD] age, 26.8 [8.5] years; mean [SD], 23 [13] g/d of carbohydrates; mean [SD], 1597 [715] kcal/d for participants with a mean [SD] weight before diet of 78.4 [5.2] kg) demonstrated significant mean [SD] weight loss (13.6 [0.1] kg); however, no data were available about whether they maintained this weight loss beyond the study period.

Of the 34† of 38 lower-carbohydrate diets for which weight change after diet was calculated, these lower-carbohydrate diets were found to produce greater weight loss than higher-carbohydrate diets (absolute summary mean [SD] change, 16.9 [0.2] kg; 95% CI, 16.6-17.3 kg vs 1.9 [0.2] kg; 95% CI, 1.6-2.2 kg) (Table 5). Because the 95% CIs for the lower- and higher-carbohydrate diets do not overlap, it suggests that a difference may exist in weight change between the 2 types of diets. However, the highly heterogeneous nature of the 34 diets is reflected in the significant Q statistic associated with the summary mean changes in weight calculated when all studies were included in the analysis.

*References 53, 82, 84, 88, 89, 109, 116-118, 120.

†References 21, 26, 39, 42, 43, 53, 67, 75, 76, 78-80, 82, 84, 88, 89, 95-98, 102, 106, 109, 111, 112, 116-118, 121.

Table 4. Participant Characteristics Before and After Diet

	Carbohydrates in Diet, g/d								
	Lower, ≤60				Higher, >60				
	No. of Diets	No. of Participants	Mean (SD)*	Median (Range)	No. of Diets	No. of Participants	Mean (SD)*	Median (Range)	*P* Value
Age, y	38	692	37.6 (8.5)	35 (20-53.1)	147	2605	44.3 (12.6)	39.6 (20-64.2)	.90
Sex, % male	34	561	30 (43)	29 (0-100)	131	2483	42.0 (40.0)	46 (0-100)	.60
Weight, kg									
Before diet	23	568	91.7 (15.8)	87 (57.2-115.6)	118	2247	86.2 (19.7)	81.4 (61-217)	.90
After diet	18	435	79.3 (10.1)	77.5 (55.5-94.5)	113	1844	82.8 (18.9)	77.6 (60.1-210)	.30
BMI, kg/m^2									
Before diet	3	145	36.3 (5.2)	36.3 (36.0-37.5)	36	925	30.6 (4.1)	29.2 (21.8-39.7)	.05
After diet	1	113	29.7 (4.1)	29.7 (29.7-29.7)	28	739	28.0 (3.5)	26.3 (21.7-35.0)	.50
Percentage of body fat, %									
Before diet	5	76	38.1 (6.2)	31.4 (20.5-44)	33	655	37.2 (4.5)	39.0 (12.8-47.3)	.70
After diet	5	66	33.9 (5.0)	22.3 (16.9-41)	27	536	33.2 (4.9)	33.2 (12.2-39.8)	.60
Cholesterol, mg/dL									
Total									
Before diet	13	227	191.1 (21.2)	186 (148.2-214)	79	1519	246.4 (42.5)	201 (124-267.8)	.03
After diet	12	205	188.3 (29.4)	186 (119.6-348)	75	1322	201.8 (36.1)	197 (136.6-252.5)	.60
LDL									
Before diet	7	181	118.6 (20.7)	119.9 (103.6-136)	43	934	137.4 (30.9)	129 (86.5-212.7)	.20
After diet	7	168	123.1 (20.7)	116.6 (96.7-151)	42	852	130.2 (20.2)	127.9 (47-189.5)	.60
HDL									
Before diet	10	197	51.3 (12.7)	49.1 (27.1-87)	48	1080	48.7 (13.4)	47.3 (30.9-72.8)	.60
After diet	9	175	53.3 (8.1)	53.0 (37.1-87)	48	984	48.4 (9.9)	46.4 (27.1-77.3)	.20
Triglycerides, mg/dL									
Before diet	13	227	136.5 (60.8)	115 (68.7-283.4)	74	1674	138.3 (53.4)	129.6 (47.8-377.1)	.50
After diet	13	214	98.1 (38.7)	93.0 (57.9-130.2)	70	1245	126.2 (46.8)	123 (50-247.1)	.01
Fasting serum glucose, mg/dL									
Before diet	11	252	101.3 (11.1)	95.0 (73.8-226.8)	60	1040	130.5 (37.1)	97.2 (72.5-225)	.90
After diet	11	249	91.4 (19.3)	87.0 (68-144)	59	871	112.4 (24.6)	99 (67.5-205.2)	.10
Fasting serum insulin, μIU/mL									
Before diet	6	55	10.2 (4.7)	10.2 (3.4-16.4)	44	839	10.3 (8.5)	10.3 (1.0-36.0)	.90
After diet	6	55	6.6 (2.6)	6.3 (2.2-10.2)	46	778	9.4 (4.3)	7.9 (0.98-38.0)	.50
Systolic blood pressure, mm Hg									
Before diet	3	132	138.9 (16.2)	126.0 (112-141.9)	23	507	134.6 (16.7)	133 (111-148)	.50
After diet	3	132	125.1 (12.6)	119.0 (107.7-126.8)	20	403	127.4 (12.3)	129.6 (105-136)	.20

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
SI conversion factors: To convert mg/dL to mmol/L for total cholesterol, LDL, and HDL, multiply by 0.0259. To convert mg/dL to mmol/L for triglycerides, multiply by 0.0113. To convert mg/dL to mmol/L for fasting serum glucose, multiply by 0.0555. To convert μIU/mL to pmol/L for fasting serum insulin, multiply by 6.945.
*Means are weighted by the number of participants (eg, mean BMI before diet is weighted by the number of participants starting the diet and the mean BMI after diet is weighted by the number of participants completing the diet). Because the studies used to calculate the data before and after diet often differ, the change in outcomes should not be interpreted as the difference between the means before and after the diet (data reflecting the summary mean changes in outcomes are presented in Table 5).

Given this heterogeneity, little can be concluded about the summary mean change in weight loss when all studies are combined. When only the randomized controlled trials and the randomized crossover trials in the analysis are included, the result of the Q statistic suggests that the studies are homogeneous. From this selected group of relatively similar randomized studies of 7 lower-carbohydrate diets[21,26,39,42,43,53] and 75 higher-carbohydrate diets we found

Table 5. Summary Mean Change in Outcomes*

	Carbohydrates in Diet, g/d							
	Lower, ≤60				Higher, >60			
	No. of Diets†	No. of Participants	Summary Mean Change‡ (SD)	95% CI	No. of Diets	No. of Participants	Summary Mean Change‡ (SD)	95% CI
Weight change, kg								
All studies, all participants	34	668	−16.9 (0.2)§	−16.6, −17.3	130	2092	−1.9 (0.2)§	−1.6, −2.2
RCT and R-Cross only	7	132	−3.6 (1.2)	−1.2, −6.0	75	1122	−2.1 (0.3)	−1.6, −2.7
Caloric content of the diet, kcal/d								
<1500	18	614	−17.5 (0.2)§	−17.1, −17.8	45	870	−3.1 (0.4)§	−2.4, −3.8
≥1500	16	53	−5.7 (0.2)§	−5.4, −6.0	84	1222	−1.5 (0.2)§	−1.2, −1.9
Diet duration, d								
<15	14	72	−13.6 (0.1)§	−13.5, −13.8	25	198	−1.5 (0.2)§	−1.1, −1.8
16-60	9	142	−5.3 (0.6)§	−4.2, −6.4	52	827	−3.5 (0.4)§	−2.9, −4.3
>60	10	447	−2.4 (2.1)	+1.8, −6.5	45	968	−1.1 (0.6)	−.01, −2.3
Participant age, y								
<40	22	426	−17.7 (0.2)§	−17.4, −18.1	59	642	−1.4 (0.2)§	−1.0, −1.8
≥40	12	242	−5.0 (0.6)§	−3.8, −6.2	62	1231	−2.9 (0.3)§	−2.4, −3.5
Baseline weight, kg								
<70	3	22	−19.6 (0.2)§	−19.2, −20.0	19	230	−3.2 (0.6)§	−1.9, −4.4
70-100	13	365	−0.8 (1.6)	+2.4, −4.0	77	1357	−2.4 (0.4)	−1.3, −0.4
>100	7	138	−6.6 (0.7)§	−5.2, −8.0	18	301	−8.1 (0.8)§	−6.5, −9.7
BMI, kg/m²								
All studies, all participants	1	113	−1.4 (4.6)	+7.6, −10.3	27	739	−0.4 (0.4)	+0.3, −1.1
Body fat, %								
All studies, all participants	5	66	−1.0 (5.6)	+4.0, −6.0	27	536	−1.0 (0.6)	+0.1, −2.1
Cholesterol, mg/dL								
Total								
All studies, all participants	13	214	−1.2 (7.3)	+13.2, −15.5	87	1633	−8.1 (1.4)	−5.5, −10.8
RCT and R-Cross only	3	77	−1.9 (9.7)§	+17.1, −20.8	43	903	−1.4 (3.3)	+5.0, −7.9
LDL								
All studies, all participants	7	168	−0.3 (9.7)	+19.3, −18.7	42	852	−0.7 (3.1)	+5.3, −6.8
RCT and R-Cross only	1	63	+0.4 (30.7)	+60.5, −59.7	22	563	−1.0 (3.7)	+6.3, −8.3
HDL								
All studies, all participants	9	175	−0.2 (2.1)	+4.0, −4.3	46	964	−0.8 (0.6)	+0.4, −2.0
RCT and R-Cross only	3	77	−0.8 (4.2)	+7.5, −9.1	22	553	−0.9 (0.7)	+0.4, −2.3
Triglycerides, mg/dL								
All studies, all participants	13	214	+4.1 (4.5)	+13.0, −4.6	78	1531	−0.6 (3.3)	+7.1, −6.0
RCT and R-Cross only	3	77	+0.3 (19.0)	+37.6, −37.0	43	903	−1.3 (4.4)	+9.9, −7.4
Fasting serum glucose, mg/dL								
All studies, all participants	11	249	−1.3 (2.8)	+4.3, −6.8	59	871	−0.4 (1.2)	+1.9, −2.7
RCT and R-Cross only	2	69	−0.3 (27.4)	+53.4, −54.0	17	455	−0.3 (1.3)	+2.4, −3.0
Fasting serum insulin, pmol/L								
All studies, all participants	5	45	−0.8 (9.9)	+18.5, −20.1	44	764	−0.4 (1.6)	+2.9, −3.7
RCT and R-Cross only	0	. . .	. . .	. . .	26	467	−0.01 (2.3)	+4.4, −4.5
Systolic blood pressure, mm Hg								
All studies, all participants	4	173	0.7 (5.2)	+10.8, −9.5	25	481	0.6 (2.5)	+5.6, −4.3

Abbreviations: BMI, body mass index; CI, confidence limits; ellipses, insufficient data to calculate outcome; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RCT, randomized controlled trial; R-Cross, randomized crossover trial.
*See Table 4 for the conversion of conventional units to SI units.
†The reason that the number of diets and number of participants for whom we were able to calculate a difference in each of the outcomes is greater than the number of diets and number of participants for whom we presented in the data before and after diet (Table 4) is that some studies reported only the change in the outcome but not before or after diet data.
‡Summary mean change in each outcome variable was calculated from a standardized mean difference. A negative change in any of the outcome variables denotes a reduction in that variable after the diet interval. For example, the absolute summary mean change in weight loss calculated from all studies of lower-carbohydrate diets was 16.9 kg.
§The Q statistic for that summary mean change calculation was significant (ie, studies were not homogeneous).

that the absolute summary mean [SD] change decrease in weight for lower-carbohydrate diets was 3.6 (1.2) kg (95% CI, 1.2-6.0 kg) and for higher-carbohydrate diets was 2.1 (0.3) kg (95% CI, 1.6-2.7 kg). This overlap in 95% CIs suggests no difference in weight loss between the lower- and higher-carbohydrate diets.

To evaluate the weight loss demonstrated in the studies with the lowest-carbohydrate content, we calculated the summary mean [SD] change in weight loss found in the 13 diets* of these diets with 71 participants. In this group of studies, we found a summary mean (SD) change in weight of −1.2 (−2.3) kg (95% CI, −5.7 kg to 3.3 kg). The result of the Q statistic suggests homogeneity; however, we note that these studies vary with respect to study design, including studies that are not randomized and that do not include a comparison group. Thus, based on the data, it can be concluded that lowest-carbohydrate diets did not result in significantly greater weight loss than lower-carbohydrate diets.

When we consider the 22 diets† with the greatest mean weight loss (ie, mean weight loss of ≥10 kg), we found that they varied widely with respect to carbohydrate content (mean [range], 97 [10-271] g/d of carbohydrate) (data not shown). However, these diets restricted caloric intake (mean [range], 1077 [525-1800] kcal/d), were longer in duration (mean [range], 142 [42-365] days), and included participants who were significantly overweight at the start of the diets (mean [range], 101 [84-183] kg) (data not shown). These results suggest that these 3 variables may be more important predictors of weight loss than carbohydrate content.

Change in Serum Lipid Levels. For all studies and participants of lower-carbohydrate diets, no change was found in any of the serum lipid levels (ie, the 95% CIs for the summary mean [SD] change in total, LDL, and HDL cholesterol, and triglycerides levels all included 0) (Table 5). However, heterogeneity and paucity of studies complicate the interpretation of the outcomes of serum lipid levels. In contrast, among the more homogeneous group of studies of higher-carbohydrate diets, we found a significant decline in total cholesterol levels (summary mean [SD] change, −8.1 [1.4] mg/dL; 95% CI, −5.5 to −10.8 or −0.21 [0.04] mmol/L; 95% CI, −0.14 to −0.28 mmol/L) but not in the other serum lipid levels (95% CIs include 0).

From the 3 studies[80,106,121] of lowest-carbohydrate diets that reported data for total cholesterol levels for 36 participants, we found no change in serum lipid levels (summary mean [SD] change for total cholesterol, +0.1 [28.0] mg/dL; 95% CI, −54.8 to +55.1 mg/dL or 0.0026 [0.73] mmol/L; 95% CI, −1.4 to 1.4 mmol/L) (data not shown). None of the studies specifically evaluated the effect of lower-carbohydrate diets on serum lipid levels among participants with hyperlipidemia, and only 1 study[79] reported outcomes for serum lipid levels for participants with diabetes.

Change in Fasting Serum Glucose and Insulin Levels. No change was observed in either fasting serum glucose or insulin levels among recipients of either lower- or higher-carbohydrate diets—even among those participants with the greatest weight loss or those participants receiving the lowest-carbohydrate diets (Table 5). Only 1 small study[78] (9 participants) specifically evaluated the effect of lower-carbohydrate diets on fasting serum glucose or insulin levels among obese participants with diabetes (both 95% CIs include 0) (data not shown).

Change in Systolic Blood Pressure. We found no change in systolic blood pressure after diet in participants receiving either lower- or higher-carbohydrate diets. Four studies[39,42,95,102] of 173 recipients of lower-carbohydrate diets demonstrated a summary mean (SD) change in decrease in blood pressure of 0.7 (5.2) mm Hg (95% CI, +10.8 to −9.5 mm Hg) (Table 5).

Outcome Variables for Low-Carbohydrate Diets

To determine the effect of diet and participant characteristics on the outcomes of interest, a weighted analysis of variance was performed (**TABLE 6**). The weighted analysis of variance was used because the outcome variables are correlated; the diets vary with respect to total caloric content, duration, and carbohydrate content; and to avoid the use of a threshold to define what constitutes a lower-carbohydrate diet. Because only a few studies evaluated all of the dietary, participant, and outcome variables of interest, we were limited in our ability to include all studies or all variables in this analysis. The results of the analysis of variance using all diet data from all studies reporting weight loss, baseline weight, age, sex, and diet variables demonstrate that weight loss was significantly associated with longer diet duration ($P = .008$) and baseline weight ($P < .001$). For obese participants, restriction of calorie intake also was associated with weight loss, albeit not statistically significant after applying the Bonferroni adjustment ($P = .03$) (Table 6). Reduced carbohydrate content was not significantly associated with weight loss.

For all diets and all participants, reductions in LDL cholesterol levels were associated with high baseline weight ($P = .005$), weight loss ($P = .005$), younger age ($P = .004$), restriction of calorie intake ($P = .002$), and longer diet duration ($P = .002$)(Table 6). Overall dietary and participant characteristics were not significantly associated with changes in total cholesterol, HDL cholesterol, or triglyceride levels. Reductions in fasting serum glucose and insulin levels were consistently associated with longer diet duration ($P = .01$ and $P = .002$, respectively). Restriction of carbohydrate intake was not significantly associated with changes in serum lipid levels, change in fasting serum glucose levels, or systolic blood pressure.

COMMENT

Our quantitative synthesis of the 107 studies of 94 diets from the English-language literature on the efficacy and

*References 53, 65, 80, 82, 83, 106, 116-118.
†References 23, 24, 26, 40, 44, 45, 67, 73, 78, 79, 95-97.

Table 6. Results of Weighted Analysis of Variance to Determine the Effects of Diets and Participants on Outcome Variables for Lower-Carbohydrate Diets*

			P Values§							
Outcome	No. of Diets†	R^2‡	Baseline Weight, kg	% Male	Mean Age, y	Carbohydrates, g/d	Caloric Content, kcal/d	Diet Duration, d	Weight Loss, kg‖	Reduction of Fasting Glucose, mg/dL¶
Weight loss, kg										
All diets, all participants	35	0.69	<.001	.04	.02	.90	.50	.008	. . .	. . .
RCT and R-Cross studies only	15	0.94	<.001	.90	.30	.10	.50	.06	. . .	. . .
Healthy volunteers	12	0.57	. . .	. . .	. . .	.40	.90	.08	. . .	. . .
Obese participants	33	0.33	. . .	. . .	. . .	.90	.03	.002	. . .	. . .
Diabetic participants	12	0.60	. . .	. . .	. . .	.40	.02	.30	. . .	. . .
Reduction in total cholesterol, mg/dL										
All diets, all participants	25	0.31	. . .	.20	.30	.20	.50	.30	.90	. . .
RCT and R-Cross studies only	9	0.88	. . .	.80	.80	.20	.30	.70	.40	. . .
Healthy volunteers	9	0.59	. . .	. . .	. . .	.10	.30	.80	.80	. . .
Obese participants	12	0.21	. . .	. . .	. . .	.70	.90	.90	.50	. . .
Diabetic participants	29	0.12	. . .	. . .	. . .	.90	.09	.90	. . .	. . .
Reduction in LDL cholesterol, mg/dL										
All diets, all participants	10	1.00	.005	.02	.004	.10	.002	.002	.005	. . .
RCT and R-Cross studies only	13	0.83	.01	.10	.06	.20	.50	.07	. . .	. . .
Healthy volunteers	11	0.21	. . .	. . .	. . .	.20	.50	.80	. . .	. . .
Obese participants	8	0.97	.30	.20	.90	.30	.20	.90	. . .	. . .
Diabetic participants	15	0.55	.07	.30	.30	.90	.10	.60	. . .	. . .
Increase in HDL cholesterol, mg/dL										
All diets, all participants	9	0.94	. . .	.90	.50	.60	.70	.20	.30	. . .
RCT and R-Cross studies only	19	0.19	. . .	.20	.70	.60	.70	.60	. . .	. . .
Healthy volunteers	12	0.26	. . .	. . .	. . .	.90	.20	.70	. . .	. . .
Obese participants	13	0.73	. . .	. . .	. . .	.20	.01	.003	. . .	. . .
Diabetic participants	20	0.02	. . .	. . .	. . .	.60	.90	.90	. . .	. . .
Reduction in triglycerides, mg/dL										
All diets, all participants	8	0.99	. . .	. . .	. . .	.04	.05	.20	.09	.40
RCT and R-Cross studies only	9	0.41	. . .	. . .	. . .	.90	.80	.30	.60	. . .
Healthy volunteers	22	0.19	. . .	. . .	. . .	.10	.70	.90	. . .	. . .
Obese participants	12	0.51	. . .	. . .	. . .	.10	.20	.70	.30	. . .
Diabetic participants	20	0.11	. . .	. . .	. . .	.50	.90	.40	. . .	.30
Reduction in fasting serum glucose, mg/dL										
All diets, all participants	10	0.79	. . .	. . .	. . .	.90	.10	.01	.06	. . .
RCT and R-Cross studies only	31	0.56	. . .	. . .	. . .	.30	.10	<.001	. . .	. . .
Healthy volunteers	17	0.36	. . .	. . .	. . .	.10	.20	.20	. . .	. . .
Obese participants	20	0.09	. . .	. . .	. . .	.50	.80	.30	. . .	. . .
Diabetic participants	27	0.61	. . .	. . .	. . .	.90	.003	.001	. . .	. . .
Change in fasting serum insulin, µIU/L										
All diets, all participants	49	0.24	. . .	. . .	. . .	.10	.90	.002	. . .	. . .
RCT and R-Cross studies only	28	0.46	. . .	. . .	. . .	.10	.40	<.001	. . .	. . .
Healthy volunteers	12	0.55	. . .	. . .	. . .	.03	.20	.70	. . .	. . .
Obese participants	16	0.35	. . .	. . .	. . .	.80	.20	.20	. . .	. . .
Diabetic participants	18	0.51	. . .	. . .	. . .	.10	.50	.003	. . .	. . .
Change in systolic blood pressure, mm Hg										
All diets, all participants	10	0.56	. . .	. . .	. . .	.30	.20	.20	.40	. . .
RCT and R-Cross studies only	9	0.53	. . .	. . .	. . .	.80	.90	.20	.50	. . .
Healthy volunteers	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Obese participants	16	0.21	. . .	. . .	. . .	.90	.50	.40	. . .	. . .
Diabetic participants	8	0.34	. . .	. . .	. . .	.80	.80	.50	. . .	. . .

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; RCT, randomized controlled trial; R-Cross, randomized crossover trial. Ellipses indicate insufficient data to calculate.

*See Table 4 for the conversion of conventional units to SI units.

†Number of diets refers to the number of dietary interventions that could be included in each analysis. To be included in the analysis of variance, a study had to report data for each of the predictor and outcome variables of interest. For example, studies of 10 dietary interventions provided data on change in fasting serum glucose levels and included information about the carbohydrate content of the diet, the caloric content of the diet duration, and participants' weight loss. However, the RCTs and R-Cross studies did not provide sufficient data about weight loss as a predictor of reduction in fasting serum glucose levels.

‡Using the weighted analysis of variance (weighted by the number of participants who finished each diet), the R^2 was calculated to estimate the amount of variance in the outcome variables accounted for by the predictor variables.

§*P* value associated with the effect of these predictor variables on the outcome variables

‖Weight loss was included as a predictor variable for the weighted analyses of variance for change in serum lipid, fasting serum glucose, and fasting serum insulin levels, and systolic blood pressure as allowed by the availability of data.

¶Reduction of fasting serum glucose levels was included as a predictor variable for the weighted analyses of variance for change in serum triglyceride levels as allowed by the availability of data.

safety of low-carbohydrate diets suggests that there is insufficient evidence to make recommendations for or against the use of these diets. Despite the large number of Americans who have apparently adopted this approach to weight loss and/or weight maintenance, we know little of its effects or consequences. In particular, these diets have not been adequately evaluated for use longer than 90 days, for individuals aged 53 years or older, or for use by participants with hyperlipidemia, hypertension, or diabetes. The lowest-carbohydrate diets (eg, ≤20 g/d of carbohydrates, the recommended threshold for some of the most popular diets) have been studied in only 71 participants for whom no data on serum lipid, fasting serum glucose, and fasting serum insulin levels or blood pressure was reported.

We found insufficient evidence to conclude that lower-carbohydrate content is independently associated with greater weight loss compared with higher-carbohydrate content. We did find, however, that diets that restricted calorie intake and were longer in duration were associated with weight loss. Given the limited evidence in this review, when lower-carbohydrate diets result in weight loss, it also is likely due to the restriction of calorie intake and longer duration rather than carbohydrate intake. Lower-carbohydrate diets were not associated with adverse effects on serum lipid levels, fasting serum glucose levels, or blood pressure. However, because few studies reported on these outcomes, this systematic review lacked statistical power to detect small changes in these measures.

The heterogeneity of all the studies included in this review precludes drawing conclusions from the synthesis of the total group of studies. The statistically significant weight loss demonstrated when we compared all studies of lower- and higher-carbohydrate diets using the threshold of 60 g/d of carbohydrates was not confirmed by any other analyses (eg, evaluating the recipients of diets containing ≤20 g/d of carbohydrates or the participants with the greatest weight loss). We attribute this finding to the inclusion of studies of lower-carbohydrate diets with relatively short durations for obese participants in whom significant weight loss was achieved while using diets of 60 g/d or less of carbohydrates, primarily through restriction of calorie intake. It may be that these obese participants were better able to tolerate the restriction of calorie intake while using lower-carbohydrate diets than while using higher-carbohydrate diets. This observation suggests the need for additional studies of isocaloric diets with different carbohydrate contents in which participants are specifically assessed for symptoms of hunger and on the tolerability of the diet.

Our analyses were limited by a small number of studies that evaluated more than 1 of the outcomes of interest or that provided sufficiently detailed information about their participants or dietary intervention. Specifically, our systematic review highlights 5 significant gaps in the published literature of low-carbohydrate diets. First, the lack of adequate long-term follow-up data significantly limits our understanding of the efficacy and safety of low-carbohydrate diets. In particular, the long-term effects of low-carbohydrate diets on serum lipid, fasting serum glucose, and fasting serum insulin levels and blood pressure may differ between hypocaloric diets intended for weight loss and isocaloric diets intended for weight maintenance. Second, we were not able to evaluate the effects of these diets on different racial/ethnic groups. The absence of data regarding the efficacy and safety of lower-carbohydrate diets by race/ethnicity critically limits our ability to make participant-specific recommendations about these diets. Third, because exercise can have a significant effect on weight loss, we had hoped to include a measure of energy expenditure as a covariate in our analyses. We were unable to report data on exercise because many studies either did not report any information about participants' exercise patterns or simply stated that participants were encouraged to maintain baseline levels of exercise. Fourth, some of the included diets provided counseling or other supportive measures to encourage participants to adhere to the dietary intervention. The heterogeneity of the information reported about how adherence was measured limited our ability to include them in our analyses. Finally, many of the included studies reported only the number of participants who completed the dietary intervention. Among those studies that reported both the total number enrolled and the total number who completed the intervention, very few performed an intention-to-treat analysis. This limitation of both the lower- and higher-carbohydrate diets has the potential to bias the results in the direction of overstating the effects of the dietary intervention.

Our search strategies may have introduced biases into our results. First, we only included English-language studies. We found 17 foreign-language articles that we could not exclude on the basis of the English title or abstract. Extrapolating from our finding that 94 evaluated dietary interventions of 60 g/d or less of carbohydrates, it is likely that about a third of these would have evaluated lower-carbohydrate diets. However, we believe that the data from these estimated 5 or 6 foreign-language articles that may have met our inclusion criteria would not have changed the result of our analyses, as to do so all of these studies would need to have included significantly larger number of participants than the included studies, found very different results than those described, or evaluated diets for more than 90 days. Given the important cultural and ethnic differences in dietary habits, including foreign-language studies may have increased the heterogeneity of the participants evaluated. Second, our search was limited to MEDLINE and the bibliographies of retrieved publications. Although the major nutrition science publications are included in the MEDLINE database, we may have missed some relevant articles. Given the multiple clinical outcomes evaluated, we did not perform a formal analysis of publication bias.

The results of our systematic review suggest that if participants without diabetes tolerate a lower-carbohydrate diet better than a higher-carbohydrate alternative, this diet may be an effective means of achieving short-term weight loss without significant adverse effects on serum lipid levels, glycemic control, or blood pressure. However, there is insufficient evidence to recommend or condemn the use of these diets among participants with diabetes or for long-term use. Because of the complex relationships between serum lipid levels, plasma insulin levels, cortisol and glucogon levels during dieting,[88] and because of the claim by some proponents of low-carbohydrate diets that these diets work best when producing ketosis,[6] future evaluations of lower-carbohydrate diets should enroll participants with and without diabetes and with and without abnormal lipid levels to more fully describe the effects of lower-carbohydrate (sometimes called "ketogenic") diets on lipid and glycemic indices and ketogenesis.

Despite the abundance of lay literature on the topic of low-carbohydrate diets, to date our study is the first published synthesis of the evidence from the English-language literature. Our results demonstrated the marked discordance between the knowledge needed to guide dietary choices and the information that is available in the medical literature. Investigations that will examine the long-term effects and consequences of low-carbohydrate diets among both older and younger participants with and without diabetes, hyperlipidemia, and hyperkalemia are in urgent need.

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