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Obesity Comorbidity/Prevention

Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factors

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Summary

A systematic review and meta-analysis were carried out to study the effects of low-carbohydrate diet (LCD) on weight loss and cardiovascular risk factors (search performed on PubMed, Cochrane Central Register of Controlled Trials and Scopus databases). A total of 23 reports, corresponding to 17 clinical investigations, were identified as meeting the pre-specified criteria. Meta-analysis carried out on data obtained in 1,141 obese patients, showed the LCD to be associated with significant decreases in body weight (–7.04 kg [95% CI –7.20/–6.88]), body mass index (–2.09 kg m^{-2} [95% CI –2.15/–2.04]), abdominal circumference (–5.74 cm [95% CI –6.07/–5.41]), systolic blood pressure (–4.81 mm Hg [95% CI –5.33/–4.29]), diastolic blood pressure (–3.10 mm Hg [95% CI –3.45/–2.74]), plasma triglycerides (–29.71 mg dL^{-1} [95% CI –31.99/–27.44]), fasting plasma glucose (–1.05 mg dL^{-1} [95% CI –1.67/–0.44]), glycated haemoglobin (–0.21% [95% CI –0.24/–0.18]), plasma insulin (–2.24 micro IU mL^{-1} [95% CI –2.65/–1.82]) and plasma C-reactive protein, as well as an increase in high-density lipoprotein cholesterol (1.73 mg dL^{-1} [95%CI 1.44/2.01]). Low-density lipoprotein cholesterol and creatinine did not change significantly, whereas limited data exist concerning plasma uric acid.

LCD was shown to have favourable effects on body weight and major cardiovascular risk factors; however the effects on long-term health are unknown.

Keywords: Low carbohydrate diet, meta-analysis, obesity.

obesity reviews (2012)

Introduction

Overweight and obesity are a growing health problem not confined by national borders. According to the World Health Organization, in 2008, 1.5 billion adults (20 years of age and older, as defined by this organization) worldwide were overweight, and more than 1 in 10 adults were obese (1).

Obesity has been shown to be associated with an increased risk of hypertension, dyslipidaemia, metabolic syndrome and type 2 diabetes mellitus, increasing cardiovascular morbidity and mortality (2). Even though this is a well-known and preventable condition, obesity still ranks fifth in the leading risks for global deaths (1). Public opinion has become more and more aware of this problem and of its toll on worldwide health in recent years. This problem is presumed to be due to an excessive energy intake, low energy expenditure or both. A diet high in carbohydrates, particularly refined or high glycaemic index carbohydrates, has also appeared to be associated with obesity, type 2 diabetes and the metabolic syndrome (3–5).

The debate about which type of diet is the most effective for the treatment of obesity has become more intense in

recent years, with some types of diets emphasizing the restriction of carbohydrate, others of protein and others of certain types of fat (6–8).The low-carbohydrate diet (LCD) has risen in popularity in recent years. While it is difficult to estimate the number of people who currently follow LCDs as a way of losing weight, LCDs became more prominent in the early 1970s, likely resulting from a book by R. C. Atkins (9). In this type of diet, the largest proportion of energy in the diet should come from protein and fat instead of carbohydrates.

Independently of the effects on human health, the case for dietary carbohydrates can be summarized on four major aspects: availability, low cost, ease of storage and energy value (10). Dietary carbohydrates, as major products of agriculture, have probably played an important role in the development of sedentary human civilization (11). This important role has led dietary carbohydrates to become an ingrained part of many cultures, even mentioned in some philosophy and religious texts. For instance, Confucius is believed to have given as an example that 'Even when there was plenty of meat, he avoided eating more meat than rice' (12). These cultural aspects may be of importance in what concerns the practical use of present-day diets, such as LCDs, although the scientifically proven health effects of a diet should provide the basis for diet recommendations.

LCDs could predominantly be used to produce a decrease in body weight, whereas a less strict diet could be used to maintain the decreased body weight (as it happens in the case of the Atkins diet, in which the induction phase is quite low in carbohydrates, but then carbohydrates can be added to the diet to maintain body weight).

Most LCDs do not establish a limit for fat or protein consumption on a daily basis. This could theoretically lead to an increase in the blood's triglycerides or cholesterol content and/or weight, which are known to have deleterious cardiovascular effects. It is, therefore, of paramount importance to determine the effects of an LCD on anthropometric measures, cardiovascular risk profile and glycaemic levels. Previous meta-analyses were published on this topic (13,14), as well as a systematic review (15). However, additional reports involving important numbers of patients were subsequently published (16–19), leading to a need to update the topic.

This meta-analysis has the goal of updating the estimation of the effect of LCDs on weight loss and cardiovascular risk factors.

Methods

Search strategy

The study started with a search on Medline (PubMed), Cochrane Central Register of Controlled Trials and Scopus databases, using the query 'diet' + 'trial' + 'low-carbohydrate'. The search took place between January and March 2011 and excluded studies prior to 1980. The aim of our search was to identify randomized clinical trials which analysed the effects of an LCD on body weight and other markers of cardiovascular risk. The option for randomized clinical trials was taken in view of the larger number of patients and the adequate methodological aspects which are characteristic of this type of studies.

The meta-analysis was carried out looking at within LCD group changes as opposed to comparisons between randomized groups, as a special interest existed concerning the viability of the LCD as an option compared with the baseline condition as opposed to a control situation, especially because comparison diets were heterogeneous (some diets were 'high-carb', others 'low-fat', some papers having up to three different comparison diets).

The query resulted in 311 articles on the PubMed database, 221 on Cochrane and 464 on Scopus. Additional articles were selected from the reference lists of the included studies and from review articles previously published.

Inclusion criteria

The study had to be a randomized clinical trial implemented in an adult population (as defined by the minimum age greater than 18 years old) of at least 100 subjects (at the end of the dietary intervention). This number was chosen after a preliminary evaluation of the published reports on this topic showed that a large number of papers exist with less than 100 subjects and with heterogeneous dietary interventions, whereas a significant number of papers with more than 100 subjects existed with less heterogeneity. Larger studies were considered more likely to have power to detect differences in the outcomes of interest, and were also considered to be more likely to generate conclusions that could be generalized to other populations.

The intervention had to be an LCD (as defined by the author of the article). The trial was required to have at least a 3-month follow-up period after the initiation of the diet (as very short term effects were considered to be less important). Weight loss had to be considered a major outcome. Variations in other cardiovascular risk factors (body mass index [BMI], waist circumference, systolic and diastolic blood pressure values, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, fasting insulin, fasting glucose, C-reactive protein (CRP), uric acid and creatinine blood concentrations, as well as glycated haemoglobin percentage) also took part of our analysis.

Studies included in previous meta-analyses on the same topic (13,14) were also considered, in order to increase the ease of comparisons between our present report and previous publications on the same topic.

Exclusion criteria

Articles in which the subjects were selected because they had a specific pathology other than obesity (such as diabetes mellitus, chronic obstructive pulmonary disease, cancer, epilepsy) or altered endocrinological state (such as pregnancy or menopause) were excluded, as were studies written in languages other than English, Spanish, Portuguese or French. Studies focused on diabetic patients, although of great importance, were excluded since patients with diabetes mellitus may differ from the general group of obese patients in several of the parameters under study in the present report, thus possibly adding heterogeneity to the present results.

Quality assessment of studies

Trial eligibility and quality were independently assessed by three investigators. From title and abstract analysis, 30 articles were selected for detailed review. After the analysis of the full-text articles, seven were excluded, as they met at least one of the exclusion criteria (Fig. 1). In three cases, more than one report were found to be derived from the same primary investigation, and in these cases the data were analysed according to the primary investigation, independently of the number of published reports. In the figures corresponding to the meta-analysis, each investigation is identified by the first author of the primary report, even if the data were obtained from a follow-up report.

Data extraction

The data for each study were collected by two investigators, using a standardized form. The authors of some trials were contacted for additional information when necessary.

Statistical analysis

The effects of diet on patients were assessed through the estimation of mean differences for the various continuous variables corresponding to the 14 outcomes considered and for four follow-up period measurements (i.e. less than 6 months, 6 to 11 months, 12 to 23 months, and 24 or more months). However, some outcome variables did not have enough data to allow an analysis across all four follow-up periods. In addition, some variables had only one value available, which nevertheless was considered on the global analysis. Inverse of Variance and I^2 statistics methods were used to estimate fixed effects and statistical heterogeneity, respectively. All data processing and statistical analysis were performed using Review Manager (RevMan) Analyses V 5.1. software (available at http://www.ims.cochrane.org/revman/).

Results

A total number of 23 reports, corresponding to 17 clinical investigations, were identified as meeting the criteria described above (Table 1; Fig. 1) (16–38). Papers classified as relevant but unsuitable for the meta-analysis (20,22,31, 39–47) are shown in Table 2, which includes the reasons for the unsuitability (Fig. 1). The study by Due *et al*. (48), although cited in a previous meta-analysis (14), was actually on the effects of a high-protein diet (with carbohydrate 45.1 to 48.9% of energy intake) and was not included in the present analysis.

Meta-analysis was carried out on data obtained in 1,141 obese patients (Tables 1 and 2). A summary of the findings of the meta-analysis is presented in Table 3.

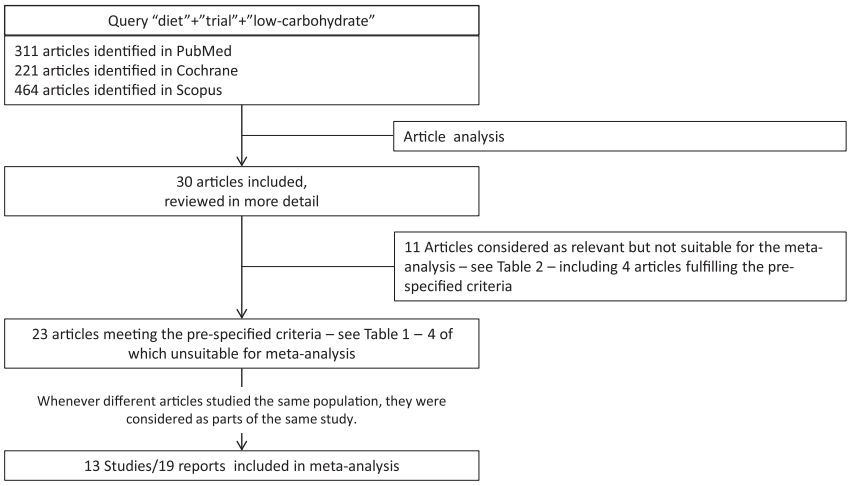


Figure 1 Flow diagram of systematic review.

Table 1 Overview of studies on low-carbohydrate diets (LCDs) meeting the pre-specified criteria

Source	Number of patients	Mean BMI	Duration of follow-up	Low-carbohydrate diet
Baron *et al.* (20)	135 (66 on LCD)	29.1	12 months	10 carbohydrate units that permitted a daily carbohydrate intake of at most 50 g
Lean *et al.* (21)	110 women (53 on LCD)	32.8	6 months	Carbohydrates corresponding to 35% of energy intake (1,200 kcal d^{-1})
Foster *et al.* (22)	63 (33 on LCD)	33.9	12 months	Atkins diet (carbohydrate intake initially of 20 g d^{-1}, then gradually increased towards 50 g d^{-1}).
Samaha *et al.* (23); Seshadri *et al.* (24); Stern *et al.* (25); Tsai *et al.* (26); Cardillo *et al.* (27)	132 (64 on LCD)	42.9	6–36 months	Carbohydrate intake of 30 g d^{-1} or less
Brehm *et al.* (28)	53 women (26 on LCD)	33.2	6 months	Atkins diet
Yancy *et al.* (29); Westman *et al.* (30)	120 (60 on LCD)	34.6	6 months	Atkins diet
Brinkworth *et al.* (31)	58 (29 on HPD, LCD)	34.6	12 months	40% of energy from carbohydrate
Dansinger *et al.* (32)	160 (40 LCD)	35	12 months	Atkins diet
Krauss *et al.* (33)	178 men (129 on LCD)	29.2*	12 weeks	Three different LCD: 39% CH LSFD, 26% CH LSFD; 26% CH HSFD
Truby *et al.* (34); Morgan *et al.* (35)	293 (57 LCD)	31.9	6 months	Atkins diet
Gardner *et al.* (36)	311 women (77 LCD)	32	12 months	Atkins diet
Shai *et al.* (16)	322 (109 on LCD)	30.8	24 months	Atkins diet based (carbohydrate intake initially of 20 g d^{-1}, then gradually increased towards 120 g d^{-1})
Frisch *et al.* (37)	200 (100 on LCD)	33.5	12 months	Carbohydrate <40% energy
Sacks *et al.* (17)	811 (201 on LCD)	33	24 months	35% carbohydrates
Yancy *et al.* (19)	146 (72 on LCD)	39.9	48 weeks	Carbohydrate intake initially <20 g d^{-1}, then gradually increased.
Foster *et al.* (18)	307 (153 on LCD)	36.1	24 months	Atkins diet based Carbohydrate 20 g d^{-1} 3 months, then gradually increased
Deluis *et al.* (38)	248 (121 on LCD)	36.3*	3 months	Carbohydrates corresponding to 38% of energy intake

*Value for the entire sample (all arms) of participants.
BMI, body mass index; CH, carbohydrates; HPD, high-protein diet; HSFD, high-saturated fat diet; LSFD, low-saturated fat diet; for references see text.

Table 2 Relevant studies on low-carbohydrate diets not included in the meta-analysis, and the corresponding reason

Source	Reason for exclusion from meta-analysis
Baron *et al.* (20)	Lack of dispersion data (standard deviation) for the change from baseline values
Foster *et al.* (22)	Lack of mean value and standard deviation for the change from baseline values (data presented as percent changes)
Brinkworth *et al.* (31)	Lack of mean value and standard deviation for the change from baseline values
Muzio *et al.* (39)	Patients with metabolic syndrome
Wal *et al.* (40)	Short duration of study (4 weeks)
de Luis *et al.* (41,42); Luis *et al.* (43); Deluis *et al.* (38)	Three reports with short duration of study – 2 months (2008, 2009, 2009); lack of mean values and standard deviation for the changes from baseline values.
Grau *et al.* (44)	Short duration of study (10 weeks)
Brinkworth *et al.* (45)	Less than 100 patients completed the study.
Rolland *et al.* (46)	Number of patients randomized <100 (72)
Lim *et al.* (47)	Less than 100 patients completed the study.

Table 3 Overview of the effects of low-carbohydrate diets on body weight and cardiovascular risk factors

	Subgroup								Global	
	<6 months		6–11 months		12–23 months		24 months			
	*n**	Mean† (95% CI)	*n**	Mean† (95% CI)	*n**	Mean† (95% CI)	*n**	Mean† (95% CI)	*n**	Mean† (95% CI)
Diastolic BP (mm Hg)	5	–4,23 (–5.01; –3.45)	8	–3.53 (–4.11; –2.95)	7	–2.51 (–3.17; 1.84)	2	–1.48 (–2.42; –0.54)	22	–3.10 (–3.45; –2.74)
Systolic BP (mm Hg)	5	–6.64 (–7.77; –5.52)	8	–5.19 (–6.06; –4.33)	7	–4.39 (–5.34; –3.44)	2	–1.67 (–3.12; –0.22)	22	–4.81 (–5.33; –4.29)
BMI (kg per m^2)	3	–2.13 (–2.19; –2.08)	4	–2.06 (–2.30; –1.83)	3	–1.46 (–1.74; –1.19)	1	–1.50 (–1.89; –1.11)	11	–2.09 (–2.15; –2.04)
Fasting plasma glucose (mg per dL)	3	–0.67 (–1.84; 0.49)	7	–2.03 (–2.92; –1.13)	4	–3.56 (–5.44; 1.69)	2	3.5 (1.84; 5.16)	16	–1.05 (–1.67; –0.44)
HDL cholesterol (mg per dL)	7	0.72 (0.24; 1.21)	7	0.74 (0.27; 1.20)	6	3.57 (2.91; 4.23)	2	6.50 (5.48; 7.53)	22	1.73 (1.44; 2.01)
LDL cholesterol (mg per dL)	7	2.35 (0.32; 4.38)	7	–0.30 (–1.97; 1.37)	6	–2.71 (–5.02; –0.39)	2	–3.27 (–6.16; –0.38)	22	–0.48 (–1.53; 0.57)
Glycated haemoglobin (%)	0	–	2	–0.20 (–0.24; –0.16)	3	–0.21 (–0.24; –0.17)	1	–0.90 (–1.25; –0.55)	6	–0.21 (–0.24; –0.18)
Abdominal circumference (cm)	3	–4.44 (–5.13; –3.74)	5	–6.80 (–7.35; –6.25)	4	–6.25 (–6.94; –5.57)	2	–4.68 (–5.43; –3.93)	14	–5.74 (–6.07; –5.41)
Plasma creatinine (mg per dL)	0	–	0	–	2	0.02 (–0.01; 0.05)	0	–	2	0.02 (–0.01; 0.05)
Insulin (micro IU mL^{-1})	2	–3.09 (–3.93; –2.25)	4	–2.56 (–3.26; –1.85)	3	–1.81 (–2.75; –0.86)	2	–1.07 (–1.99; –0.15)	11	–2.24 (–2.65; –1.82)
C-reactive protein (mg per L)	1	–0.33 (–0.82; 0.16)	2	–0.71 (–1.34; –0.08)	2	–0.20 (–0.31; –0.08)	1	9 (–4.74; 22.74)	5	–0.22 (–0.33; –0.11)
Trygliceride (mg per dL)	4	–39.82 (–44.37; –35.27)	7	–29.39 (–32.82; –25.96)	6	–21.94 (–26.87; –17)	2	–22.23 (–29.51; –14.96)	19	–29.71 (–31.99:–27.44)
Uric acid (mg per dL)	1	–0.44(–0.48; –0.40)	0	–	1	0.29 (–0.07; 0.64)	0	–	2	–0.43 (–0.47; –0.39)
Weight change (kg)	8	–6.82 (–7.03; –6.61)	9	–8.09 (–8.38; –7.79)	7	–6.33 (–6.87; –5.79)	4	–4.65 (–5.37; –3.93)	28	–7.04 (–7.20; –6.88)

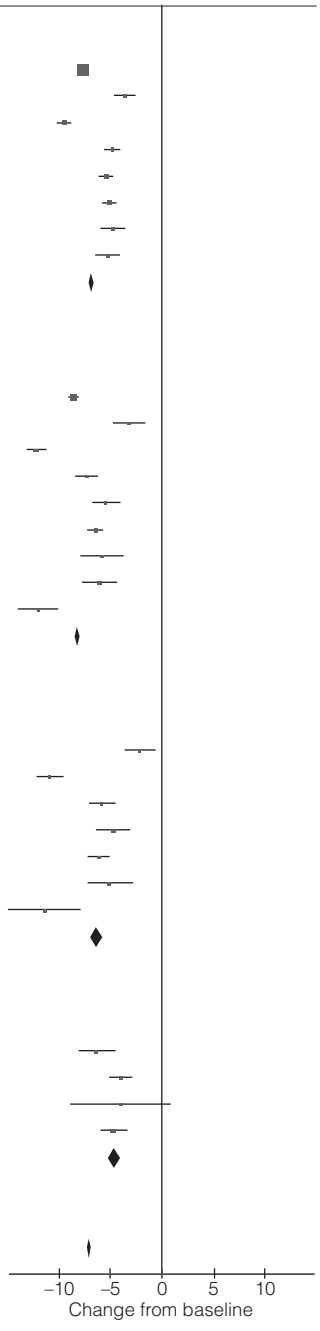
*Total number of articles considered.

†Mean difference.

95% CI, 95% confidence interval; BMI, body mass index; BP, blood pressure;.HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 4 Forest plot for weight change associated to low-carbohydrate diets (kg)

Study or subgroup	Mean difference	SE	Weight (%)	Mean difference IV, fixed, 95% CI
14.1.1 Weight 6M				
Brehm *et al.* (28)	–7.6	0.15	29.1	–7.60 (–7.89, –7.31)
Dansinger *et al.* (32)	–3.6	0.52	2.4	–3.60 (–4.62, –2.58)
Foster *et al.* (18)	–9.49	0.31	6.8	–9.49 (–10.10, –8.88)
Krauss (33) – diet a	–4.8	0.4	4.1	–4.80 (–5.58, –4.02)
Krauss (33) – diet b	–5.4	0.3	7.3	–5.40 (–5.99, –4.81)
Krauss (33) – diet c	–5	0.4	4.1	–5.00 (–5.78, –4.22)
Lean *et al.* (21)	–4.7	0.6	1.8	–4.70 (–5.88, –3.52)
Truby *et al.* (34)	–5.2	0.58	1.9	–5.20 (–6.34, –4.06)
Subtotal (95% CI)			57.6	–6.82 (–7.03, –6.61)
Heterogeneity: $Chi^2 = 228.46$, d.f. = 7 ($P < 0.00001$); $I^2 = 97\%$				
Test for overall effect: $Z = 63.95$ ($P < 0.00001$)				
14.1.2 Weight 6–11M				
Brehm *et al.* (28)	–8.5	0.21	14.9	–8.50 (–8.91, –8.09)
Dansinger *et al.* (32)	–3.2	0.77	1.1	–3.20 (–4.71, –1.69)
Foster *et al.* (18)	–12.18	0.47	3.0	–12.18 (–13.10, –11.26)
Frisch *et al.* (37)	–7.2	0.54	2.2	–7.20 (–8.26, –6.14)
Lean *et al.* (21)	–5.4	0.7	1.3	–5.40 (–6.77, –4.03)
Sacks *et al.* (17)	–6.42	0.39	4.3	–6.42 (–7.18, –5.66)
Samaha *et al.* (23)	–5.8	1.08	0.6	–5.80 (–7.92, –3.68)
Truby *et al.* (34)	–6	0.85	0.9	–6.00 (–7.67, –4.33)
Yancy *et al.* (29)	–12	0.92	0.8	–12.00 (–13.80, –10.20)
Subtotal (95% CI)			29.1	–8.09 (–8.38, –7.79)
Heterogeneity: $Chi^2 = 184.29$, d.f. = 8 ($P < 0.00001$); $I^2 = 96\%$				
Test for overall effect: $Z = 53.85$ ($P < 0.00001$)				
14.1.3 Weight 12–23M				
Dansinger *et al.* (32)	–2.1	0.76	1.1	–2.10 (–3.59, –0.61)
Foster *et al.* (18)	–10.87	0.63	1.7	–10.87 (–12.10, –9.64)
Frisch *et al.* (37)	–5.8	0.61	1.8	–5.80 (–7.00, –4.60)
Gardner *et al.* (36)	–4.7	0.82	1.0	–4.70 (–6.31, –3.09)
Sacks *et al.* (17)	–6.08	0.54	2.2	–6.08 (–7.14, –5.02)
Samaha *et al.* (23)	–5.1	1.1	0.5	–5.10 (–7.26, –2.94)
Yancy *et al.* (19)	–11.37	1.77	0.2	–11.37 (–14.84, –7.90)
Subtotal (95% CI)			8.5	–6.33 (–6.87, –5.79)
Heterogeneity: $Chi^2 = 97.19$, d.f. = 6 ($P < 0.00001$); $I^2 = 94\%$				
Test for overall effect: $Z = 22.82$ ($P < 0.00001$)				
14.1.4 Weight 24M				
Foster *et al.* (18)	–6.34	0.88	0.8	–6.34 (–8.06, –4.62)
Sacks *et al.* (17)	–3.98	0.55	2.2	–3.98 (–5.06, –2.90)
Samaha *et al.* (23)	–4.04	2.44	0.1	–4.04 (–8.82, 0.74)
Shai *et al.* (16)	–4.7	0.62	1.7	–4.70 (–5.92, –3.48)
Subtotal (95% CI)			4.8	–4.65 (–5.37, –3.93)
Heterogeneity: $Chi^2 = 5.24$, d.f. = 3 ($P < 0.15$); $I^2 = 43\%$				
Test for overall effect: $Z = 12.62$ ($P < 0.00001$)				
Total (95% CI)			100.0	–7.04 (–7.20, –6.88)
Heterogeneity: $Chi^2 = 616.56$, d.f. = 27 ($P < 0.00001$); $I^2 = 96\%$				
Test for overall effect: $Z = 87.00$ ($P < 0.00001$)				
Test for subgroup differences: $Chi^2 = 101.38$, d.f. = 3 ($P < 0.00001$), $I^2 = 97.0\%$				



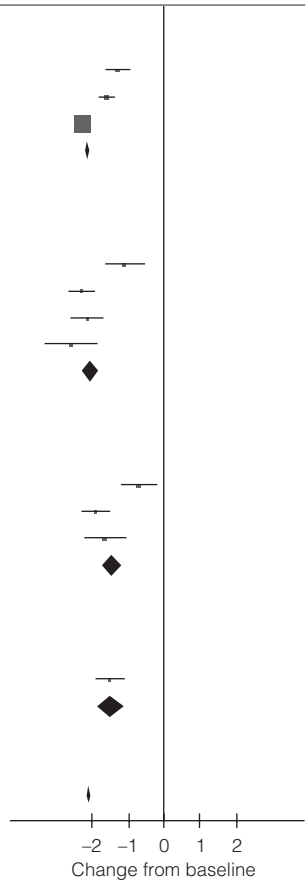
Studies are grouped according to length (see text for details).
CI, confidence interval; M, months.

Body weight

A significant decrease in body weight was seen in subjects following an LCD, as compared to the corresponding baseline values (Table 4), with a global change of –7.04 kg (95% CI –7.20/–6.88). As shown in Table 3, significant decreases in body weight were seen in studies with a duration under 6 months, as well as in

Table 5 Forest plot for body mass index (BMI) change associated to low-carbohydrate diets (kg per m^2)

Study or subgroup	Mean difference	SE	Weight (%)	Mean difference IV, fixed, 95% CI
2.4.1 BMI 6M				
Dansinger *et al.* (32)	–1.3	0.17	2.5	–1.30 (–1.63, –0.97)
Gardner *et al.* (36)	–2.69	0.11	6.0	–1.60 (–1.82, –1.38)
Lean *et al.* (21)	–2.2	0.03	80.9	–2.20 (–2.26, –2.14)
Subtotal (95% CI)			89.4	–2.13 (–2.19, –2.08)
Heterogeneity: $Chi^2 = 52.47$, d.f. = 2 ($P < 0.00001$); $I^2 = 96\%$				
Test for overall effect: $Z = 74.80$ ($P < 0.00001$)				
2.4.2 BMI 6–11M				
Dansinger *et al.* (32)	–1.1	0.27	1.0	–1.10 (–1.63, –0.57)
Frisch *et al.* (37)	–2.3	0.18	2.2	–2.30 (–2.65, –1.95)
Gardner *et al.* (36)	–2.16	0.24	1.3	–2.16 (–2.63, –1.69)
Lean *et al.* (21)	–2.6	0.36	0.6	–2.60 (–3.31, –1.89)
Subtotal (95% CI)			5.1	–2.06 (–2.30, –1.83)
Heterogeneity: $Chi^2 = 16.84$, d.f. = 3 ($P = 0.0008$); $I^2 = 82\%$				
Test for overall effect: $Z = 17.21$ ($P < 0.00001$)				
2.4.3 BMI 12–23M				
Dansinger *et al.* (32)	–0.7	0.25	1.2	–0.70 (–1.19, –0.21)
Frisch *et al.* (37)	–1.9	0.21	1.7	–1.90 (–2.31, –1.19)
Gardner *et al.* (36)	–1.65	0.29	0.9	–1.65 (–2.22, –1.08)
Subtotal (95% CI)			3.7	–1.46 (–1.74, –1.19)
Heterogeneity: $Chi^2 = 14.06$, d.f. = 6 ($P = 0.0009$); $I^2 = 86\%$				
Test for overall effect: $Z = 10.39$ ($P < 0.00001$)				
2.4.4 BMI 24M				
Shai *et al.* (16)	–1.5	0.2	1.8	–1.50 (–1.89, –1.11)
Subtotal (95% CI)			1.8	–1.50 (–1.89, –1.11)
Heterogeneity: Not applicable				
Test for overall effect: $Z = 7.50$ ($P < 0.00001$)				
Total (95% CI)			100.0%	–2.09 (–2.15, –2.04)
Heterogeneity: $Chi^2 = 114.49$, d.f. = 10 ($P < 0.00001$); $I^2 = 91\%$				
Test for overall effect: $Z = 77.62$ ($P < 0.00001$)				
Test for subgroup differences: $Chi^2 = 31.11$, d.f. = 3 ($P < 0.00001$), $I^2 = 90.4\%$				



Studies are grouped according to length (see text for details).
CI, confidence interval; M, months.

studies with durations of 6–11 months, 12–23 months and 24 months.

BMI

A significant decrease in BMI was seen in subjects following an LCD, as compared to baseline, in all subgroups of studies, divided by duration of follow-up (Tables 3,5) with a global change of –2.09 kg m^{-2} (95% CI –2.15/–2.04).

Abdominal circumference

A significant decrease in abdominal circumference was seen in subjects following an LCD, as compared to baseline values, in all subgroups of studies, divided by time length of studies (Tables 3,6). The overall change in abdominal circumference was –5.74 cm (95% CI –6.07/–5.41).

Systolic and diastolic blood pressure

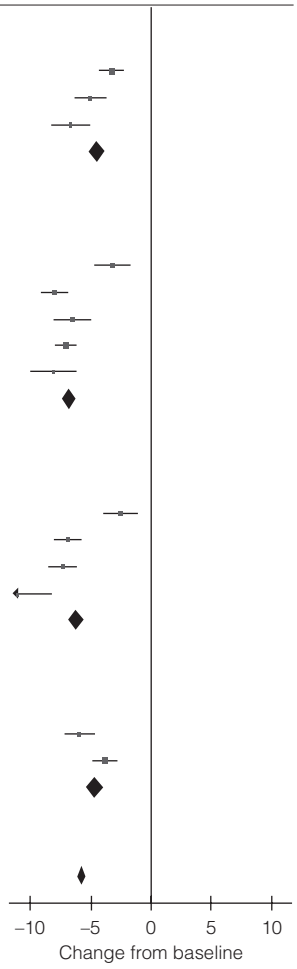
As can be seen in Tables 7 and 8 as well as in Table 3, both systolic and diastolic blood pressure values were shown to decrease under LCD. A global change of –4.81 mm Hg (95% CI –5.33/–4.29) and –3.10 mm Hg (95% CI –3.45/–2.74) was seen (systolic/diastolic, respectively).

HDL-C

HDL-C levels were increased after LCD, when compared to baseline values (Table 9 and Table 3) with a global increase of 1.73 mg dL^{-1} (95% CI 1.44/2.01). The increase in HDL-C was 0.72 mg dL^{-1} (95% CI 0.24/1.21), 0.74 mg dL^{-1} (95% CI 0.27/1.20), 3.57 mg dL^{-1} (95% CI 2.91/4.23) and 6.50 mg dL^{-1} (95% CI 5.48/7.53), when the data were separated into the different durations of the studies (under 6 months; 6–11 months; 12–23 months; 24 months).

Table 6 Forest plot for abdominal circumference change associated to low-carbohydrate diets (cm)

Study or subgroup	Mean difference	SE	Weight (%)	Mean difference IV, fixed, 95% CI
8.1.1 AP6M				
Dansinger *et al.* (32)	–3.3	0.49	11.7	–3.30 (–4.62, –2.34)
Lean *et al.* (21)	–5	0.66	6.5	–5.00 (–6.29, –3.71)
Truby *et al.* (34)	–6.7	0.81	4.3	–6.70 (–8.29, –5.11)
Subtotal (95% CI)			22.4	–4.44 (–5.13, –3.74)
Heterogeneity: $Chi^2 = 13.92$, d.f. = 2 ($P < 0.0010$); $I^2 = 86\%$				
Test for overall effect: $Z = 12.54$ ($P < 0.00001$)				
8.1.2 AP6–11M				
Dansinger *et al.* (32)	–3.2	0.77	4.7	–3.20 (–4.71, –1.67)
Frisch *et al.* (37)	–8	0.55	9.3	–8.00 (–9.08, –6.92)
Lean *et al.* (21)	–6.5	0.82	4.2	–6.50 (–8.11, –4.89)
Sacks *et al.* (17)	–7.03	0.44	14.5	–7.03 (–7.89, –6.17)
Truby *et al.* (34)	–8.1	0.98	2.9	–8.10 (–10.02, –6.18)
Subtotal (95% CI)			35.6	–6.80 (–7.35, –6.25)
Heterogeneity: $Chi^2 = 28.79$, d.f. = 4 ($P < 0.00001$); $I^2 = 86\%$				
Test for overall effect: $Z = 24.22$ ($P < 0.00001$)				
8.1.3 AP12–23M				
Dansinger *et al.* (32)	–2.5	0.71	5.6	–2.50 (–3.89, –1.11)
Frisch *et al.* (37)	–6.9	0.61	7.6	–6.90 (–8.10, –5.70)
Sacks *et al.* (17)	–7.37	0.58	8.4	–7.37 (–8.51, –6.23)
Yancy *et al.* (19)	–11.07	1.42	1.4	–11.07 (–13.85, –8.29)
Subtotal (95% CI)			22.9	–6.25 (–6.94, –5.57)
Heterogeneity: $Chi^2 = 44.28$, d.f. = 3 ($P = 0.00001$); $I^2 = 93\%$				
Test for overall effect: $Z = 17.84$ ($P < 0.00001$)				
8.1.4 AP24M				
Sacks *et al.* (17)	–5.95	0.6	7.8	–5.95 (–7.13, –4.77)
Shai *et al.* (16)	–3.8	0.5	11.2	–3.80 (–4.78, –2.82)
Subtotal (95% CI)			19.0	–4.68 (–5.43, –3.93)
Heterogeneity: $Chi^2 = 7.58$, d.f. = 1 ($P = 0.006$); $I^2 = 87\%$				
Test for overall effect: $Z = 12.19$ ($P < 0.00001$)				
Total (95% CI)			100.0%	–5.74 (–6.07, –5.41)
Heterogeneity: $Chi^2 = 132.08$, d.f. = 13 ($P < 0.00001$); $I^2 = 90\%$				
Test for overall effect: $Z = 34.25$ ($P < 0.00001$)				
Test for subgroup differences: $Chi^2 = 37.52$, d.f. = 3 ($P < 0.00001$), $I^2 = 92.0\%$				



Studies are grouped according to length (see text for details).
CI, confidence interval; M, months.

LDL-C

Concerning plasma LDL-C, and as shown in Table 10 and Table 3, no significant global change was seen in association to LCD. However, a significant decrease in LDL-C with LCD was noted in the data corresponding to studies with duration of 12–23 months and longer than 24 months (Table 10). Decreases of –2.71 mg dL^{-1} (95% CI –5.02/–0.39) and –3.27 mg dL^{-1} (95% CI –6.16/–0.38), respectively, were seen.

Triglycerides

As shown in Table 11 and in Table 3, a significant decrease in plasma triglycerides was seen with LCD. A global decrease of 29.71 mg dL^{-1} was noted (95% CI –31.99/–27.44).

Fasting plasma glucose

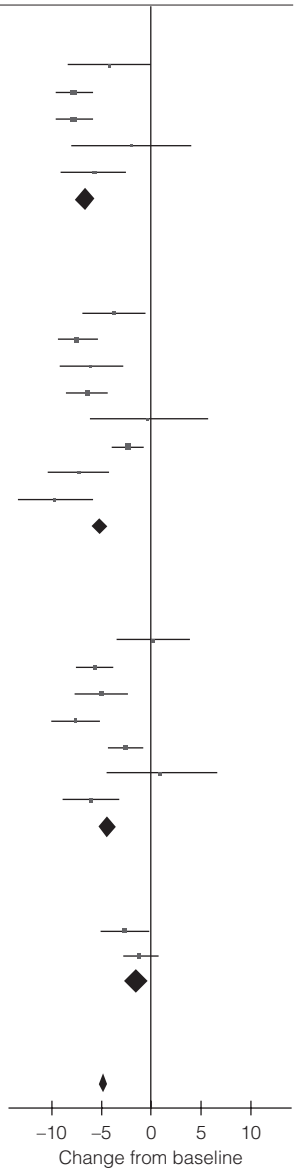
As shown in Table 12 and in Table 3, a slight but significant decrease in fasting plasma glucose was seen in patients following an LCD. A global decrease of 1.05 mg dL^{-1} was noted (95% CI –1.67/–0.44). As described in the article inclusion criteria, none of the papers dealt exclusively with diabetic patients.

Glycated haemoglobin percentage

A slight but significant decrease in glycated haemoglobin was seen in subjects under LCD, as compared to baseline values (Table 13), of –0.21% (95% CI –0.24/–0.18).

Table 7 Forest plot for systolic blood pressure change associated to low-carbohydrate diets (mm Hg)

Study or subgroup	Mean difference	SE	Weight (%)	Mean difference IV, fixed, 95% CI
7.1.1 Systolic BP 6M				
Dansinger *et al.* (32)	–4.2	2.06	1.7	–4.20 (–8.24, –0.16)
Foster *et al.* (18)	–7.74	0.94	7.9	–7.74 (–9.58, –5.90)
Gardner *et al.* (36)	–6.8	0.91	8.5	–6.80 (–8.58, –5.02)
Lean *et al.* (21)	–1.9	3.01	0.8	–1.90 (–7.80, –4.00)
Truby *et al.* (34)	–5.7	1.68	2.5	–5.70 (–8.99, –2.41)
Subtotal (95% CI)			21.3	–6.64 (–7.77, –5.52)
Heterogeneity: $Chi^2 = 5.60$, d.f. = 4 ($P = 0.23$); $I^2 = 29\%$				
Test for overall effect: $Z = 11.58$ ($P < 0.00001$)				
7.1.2 Systolic BP 6–11M				
Dansinger *et al.* (32)	–3.7	1.58	2.8	–3.70 (–6.80, –0.60)
Foster *et al.* (18)	–7.36	0.97	7.5	–7.36 (–9.26, –5.46)
Frisch *et al.* (37)	–6	1.6	2.7	–6.00 (–9.14, –2.86)
Gardner *et al.* (36)	–6.4	1.08	6.0	–6.40 (–8.52, –4.28)
Lean *et al.* (21)	–0.3	2.96	0.8	–0.30 (–6.10, –5.50)
Sacks *et al.* (17)	–2.27	0.8	11.0	–2.27 (–3.84, –0.70)
Truby *et al.* (34)	–7.2	1.54	3.0	–7.20 (–10.22, –4.18)
Yancy *et al.* (29)	–9.6	1.89	2.0	–9.60 (–13.30, –5.90)
Subtotal (95% CI)			35.7	–5.19 (–6.06, –4.33)
Heterogeneity: $Chi^2 = 30.61$, d.f. = 7 ($P < 0.0001$); $I^2 = 77\%$				
Test for overall effect: $Z = 11.72$ ($P < 0.00001$)				
7.1.3 Systolic BP 12–23M				
Dansinger *et al.* (32)	0.2	1.9	1.9	0.20 (–3.52, –3.92)
Foster *et al.* (18)	–5.64	1.01	6.9	–5.64 (–7.62, –3.66)
Frisch *et al.* (37)	–5	1.4	3.6	–5.00 (–7.74, –2.26)
Gardner *et al.* (36)	–7.6	1.25	4.5	–7.60 (–10.05, –5.15)
Sacks *et al.* (17)	–2.54	0.88	9.1	–2.54 (–4.26, –0.82)
Samaha *et al.* (23)	1	2.86	0.9	1.00 (–4.61, –6.61)
Yancy *et al.* (19)	–5.94	1.46	3.3	–5.94 (–8.80, –3.08)
Subtotal (95% CI)			30.1	–4.39 (–5.34, –3.44)
Heterogeneity: $Chi^2 = 23.25$, d.f. = 6 ($P = 0.0007$); $I^2 = 74\%$				
Test for overall effect: $Z = 9.09$ ($P < 0.00001$)				
7.1.4 Systolic BP 24M				
Foster *et al.* (18)	–2.68	1.22	4.7	–2.68 (–5.07, –0.29)
Sacks *et al.* (17)	–1.09	0.93	8.1	–1.09 (–2.91, –0.73)
Subtotal (95% CI)			12.8	–1.67 (–3.12, –0.22)
Heterogeneity: $Chi^2 = 1.07$, d.f. = 1 ($P = 0.30$); $I^2 = 7\%$				
Test for overall effect: $Z = 2.26$ ($P = 0.02$)				
Total (95% CI)			100.0%	–4.80 (–5.53, –4.29)
Heterogeneity: $Chi^2 = 90.22$, d.f. = 21 ($P < 0.00001$); $I^2 = 77\%$				
Test for overall effect: $Z = 18.15$ ($P < 0.00001$)				
Test for subgroup differences: $Chi^2 = 29.69$, df = 3 ($P < 0.00001$), $I^2 = 89.9\%$				



Studies are grouped according to length (see text for details).
BP, blood pressure; CI, confidence interval; M, months.

Fasting plasma insulin

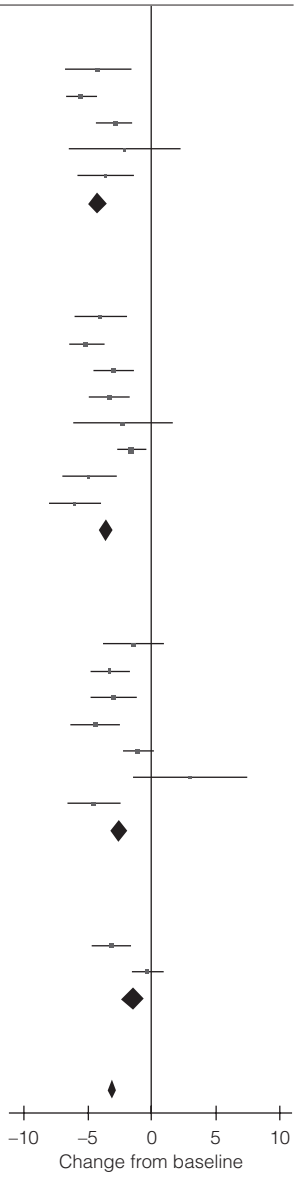
As shown in Table 14 and Table 3, a significant decrease in insulin plasma levels, compared to the corresponding baseline values, was seen in subjects following an LCD, with an overall change of –2.24 micro IU mL^{-1} (95% CI –2.65/–1.82).

CRP

Changes from baseline in CRP plasma levels in association with LCD are shown in Table 3 and Table 15. A consistent pattern was not observed, with a relatively small number of studies yielding different results. An overall significant decrease was nevertheless observed.

Table 8 Forest plot for diastolic blood pressure change associated to low-carbohydrate diets (mm Hg)

Study or subgroup	Mean difference	SE	Weight (%)	Mean difference IV, fixed, 95% CI
1.1.1 Diastolic BP 6M				
Dansinger *et al.* (32)	–4.2	1.31	1.9	–4.20 (–6.77, –1.63)
Foster *et al.* (18)	–5.53	0.6	9.0	–5.53 (–6.71, –4.35)
Gardner *et al.* (36)	–2.9	0.71	6.4	–2.90 (–4.29, –1.51)
Lean *et al.* (21)	–2.1	2.19	0.7	–2.10 (–6.39, –2.19)
Truby *et al.* (34)	–3.6	1.11	2.6	–3.60 (–5.78, –1.42)
Subtotal (95% CI)			20.6	–4.23 (–5.01, –3.45)
Heterogeneity: $Chi^2 = 9.47$, d.f. = 4 ($P = 0.05$); $I^2 = 58\%$				
Test for overall effect: $Z = 10.67$ ($P < 0.00001$)				
1.1.2 Diastolic BP 6–11M				
Dansinger *et al.* (32)	–4	1.03	3.1	–4.00 (–6.02, –1.98)
Foster *et al.* (18)	–5.15	0.68	7.0	–5.15 (–6.48, –3.82)
Frisch *et al.* (37)	–3	0.8	5.1	–3.00 (–4.57, –1.43)
Gardner *et al.* (36)	–3.3	0.79	5.2	–3.30 (–4.85, –1.75)
Lean *et al.* (21)	–2.3	1.94	0.9	–2.30 (–6.10, –1.50)
Sacks *et al.* (17)	–1.59	0.57	10.0	–1.59 (–2.71, –0.47)
Truby *et al.* (34)	–4.9	1.07	2.8	–4.90 (–7.00, –2.80)
Yancy *et al.* (29)	–6	1.02	3.1	–6.00 (–8.00, –4.00)
Subtotal (95% CI)			37.1	–3.53 (–4.11, –2.95)
Heterogeneity: $Chi^2 = 25.90$, d.f. = 7 ($P = 0.0005$); $I^2 = 73\%$				
Test for overall effect: $Z = 11.95$ ($P < 0.00001$)				
1.1.3 Diastolic BP 12–23M				
Dansinger *et al.* (32)	–1.4	1.19	2.3	–1.40 (–3.73, 0.93)
Foster *et al.* (18)	–3.25	0.76	5.6	–3.25 (–4.47, –1.76)
Frisch *et al.* (37)	–3	0.9	4.0	–3.00 (–4.76, –1.24)
Gardner *et al.* (36)	–4.4	0.96	3.5	–4.40 (–6.28, –2.52)
Sacks *et al.* (17)	–1.08	0.6	9.0	–1.08 (–2.26, –0.10)
Samaha *et al.* (23)	3	2.26	0.6	3.00 (–1.43, –7.43)
Yancy *et al.* (19)	–4.53	1.04	3.0	–4.53 (–6.57, –2.49)
Subtotal (95% CI)			28.1	–2.51 (–3.17, –1.84)
Heterogeneity: $Chi^2 = 21.39$, d.f. = 6 ($P = 0.002$); $I^2 = 72\%$				
Test for overall effect: $Z = 7.37$ ($P < 0.00001$)				
1.1.4 Diastolic BP 24M				
Foster *et al.* (18)	–3.19	0.75	5.8	–3.19 (–4.66, –1.72)
Sacks *et al.* (17)	–0.31	0.62	8.4	–0.31 (–1.53, 0.91)
Subtotal (95% CI)			14.2	–1.48 (–2.42, –0.54)
Heterogeneity: $Chi^2 = 8.76$, d.f. = 1 ($P = 0.003$); $I^2 = 89\%$				
Test for overall effect: $Z = 3.10$ ($P = 0.02$)				
Total (95% CI)			100.0%	–3.10 (–3.45, –2.74)
Heterogeneity: $Chi^2 = 90.33$, d.f. = 21 ($P < 0.00001$); $I^2 = 77\%$				
Test for overall effect: $Z = 17.20$ ($P < 0.00001$)				
Test for subgroup differences: $Chi^2 = 24.82$, d.f. = 3 ($P < 0.0001$), $I^2 = 87.9\%$				



Studies are grouped according to length (see text for details).
BP, blood pressure; CI, confidence interval; M, months.

Plasma creatinine

Plasma creatinine did not change significantly in association with LCD (Table 3).

Uric acid

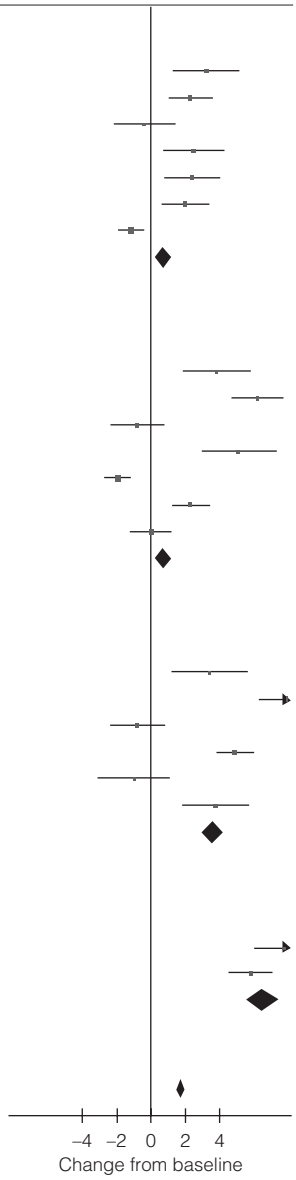
The effect of LCD on plasma uric acid was only described in two reports, with conflicting results (Table 3).

Discussion

In the present report, a systematic review and meta-analysis were carried out, aimed at studying the effects of LCD on body weight and major cardiovascular risk factors. The effects of LCD were under study by comparing the observed data after LCD to baseline values of the same cohorts of patients; the effects of LCD in comparison to other diets were not examined. This strategy was chosen to

Table 9 Forest plot for HDL-cholesterol change associated to low-carbohydrate diets (mg per dL)

Study or subgroup	Mean difference	SE	Weight (%)	Mean difference IV, fixed, 95% CI
4.1.1 HDL 6M				
Dansinger *et al.* (32)	3.2	0.98	2.2	3.20 (1.28, 5.12)
Foster *et al.* (18)	2.3	0.64	5.2	2.30 (1.05, 3.55)
Gardner *et al.* (36)	–0.4	0.88	2.8	–0.40 (–2.12, 1.32)
Krauss (33) – diet a	2.5	0.9	2.7	2.50 (0.74, 4.26)
Krauss (33) – diet b	2.4	0.8	3.4	2.40 (0.83, 3.97)
Krauss (33) – diet c	2	0.7	4.4	2.00 (0.62, 3.37)
Lean *et al.* (21)	–1.16	0.39	14.1	–1.16 (–1.92, –0.40)
Subtotal (95% CI)			34.8	0.72 (0.24, 1.21)
Heterogeneity: $Chi^2 = 49.02$, d.f. = 6 ($P < 0.00001$); $I^2 = 88\%$				
Test for overall effect: $Z = 2.91$ ($P = 0.004$)				
4.1.2 HDL 6–11M				
Dansinger *et al.* (32)	3.8	1.01	2.1	3.80 (1.82, 5.78)
Foster *et al.* (18)	6.21	0.75	3.8	6.21 (4.74, 7.68)
Frisch *et al.* (37)	–0.77	0.77	3.6	–0.77 (–2.28, 0.74)
Gardner *et al.* (36)	5.1	1.09	1.8	5.10 (2.96, 7.24)
Lean *et al.* (21)	–1.93	0.39	14.1	–1.93 (–2.69, –1.17)
Sacks *et al.* (17)	2.36	0.54	7.4	2.36 (1.30, 3.42)
Samaha *et al.* (23)	0	0.63	5.4	0.00 (–1.23, 1.23)
Subtotal (95% CI)			38.3	0.74 (0.27, 1.20)
Heterogeneity: $Chi^2 = 139.47$, d.f. = 6 ($P < 0.00001$); $I^2 = 96\%$				
Test for overall effect: $Z = 3.12$ ($P = 0.002$)				
4.1.3 HDL 12–23M				
Dansinger *et al.* (32)	3.4	1.12	1.7	3.40 (1.20, 5.60)
Foster *et al.* (18)	7.96	0.83	3.1	7.96 (6.33, 9.59)
Frisch *et al.* (37)	–0.77	0.81	3.3	–0.77 (–2.36, 0.82)
Gardner *et al.* (36)	4.9	0.56	6.9	4.90 (3.80, 6.00)
Samaha *et al.* (23)	–1	1.06	1.9	–1.00 (–3.08, 1.08)
Yancy *et al.* (19)	3.77	0.98	2.2	3.77 (1.85, 5.69)
Subtotal (95% CI)			19.1	3.57 (2.91, 4.23)
Heterogeneity: $Chi^2 = 80.98$, d.f. = 5 ($P < 0.00001$); $I^2 = 94\%$				
Test for overall effect: $Z = 10.65$ ($P < 0.00001$)				
4.1.4 HDL 24M				
Foster *et al.* (18)	7.75	0.88	2.8	7.75 (6.03, 9.47)
Sacks *et al.* (17)	5.82	0.65	5.1	5.82 (4.55, 7.09)
Subtotal (95% CI)			7.9	6.50 (5.48, 7.53)
Heterogeneity: $Chi^2 = 3.11$, d.f. = 1 ($P = 0.08$); $I^2 = 68\%$				
Test for overall effect: $Z = 12.43$ ($P < 0.00001$)				
Total (95% CI)			100.0	1.73 (1.44, 2.01)
Heterogeneity: $Chi^2 = 419.84$, d.f. = 21 ($P < 0.00001$); $I^2 = 95\%$				
Test for overall effect: $Z = 11.79$ ($P < 0.00001$)				
Test for subgroup differences: $Chi^2 = 147.26$, d.f. = 3 ($P < 0.00001$), $I^2 = 98.0\%$				



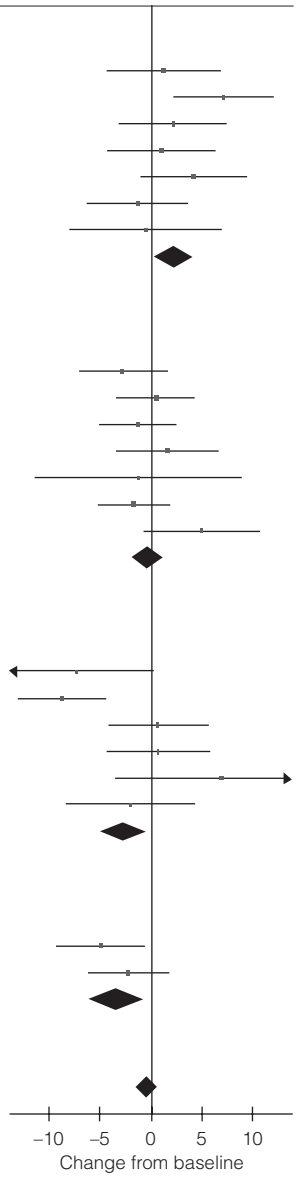
Studies are grouped according to length (see text for details).
CI, confidence interval; HDL, high-density lipoprotein; M, months.

elucidate the beneficial or detrimental effects an LCD might have in comparison to a person's baseline diet, as opposed to examining the superiority of one test diet vs. another test diet. Compared with baseline, an LCD was shown to be associated with significant decreases in body weight, BMI, abdominal circumference, systolic blood pressure, diastolic blood pressure, plasma triglycerides, fasting plasma glucose, glycated haemoglobin, plasma insulin and plasma CRP, as well as with an increase in HDL-cholesterol. LDL-cholesterol and creatinine did not change significantly, whereas limited and conflicting data were available regarding effects on plasma uric acid.

A possible 'duration effect' could exist in several of the parameters under study – more favourable results over time under LCD in parameters such as HDL-C and LDL-C (Tables 9,10), but less favourable (albeit still favourable) results over time regarding parameters such as body weight and blood pressure (Tables 4,7,8). Different studies,

Table 10 Forest plot for LDL-cholesterol change associated to low-carbohydrate diets (mg per dL)

Study or subgroup	Mean difference	SE	Weight (%)	Mean difference IV, fixed, 95% CI
6.1.1 LDL 6M				
Dansinger *et al.* (32)	1.3	2.85	3.5	1.30 (–4.29, 6.89)
Foster *et al.* (18)	7.2	2.46	4.7	7.20 (2.38, 12.02)
Gardner *et al.* (36)	2.3	2.68	4.0	2.30 (–2.95, 7.55)
Krauss (33) – diet a	1.1	2.7	3.9	1.10 (–4.19, 6.39)
Krauss (33) – diet b	4.3	2.7	3.9	4.30 (–0.99, 9.59)
Krauss (33) – diet c	–1.2	2.5	4.6	–1.20 (–6.10, 3.70)
Lean *et al.* (21)	–0.39	3.74	2.0	–0.39 (–7.72, 6.94)
Subtotal (95% CI)			26.8	2.35 (0.32, 4.38)
Heterogeneity: $Chi^2 = 7.31$, d.f. = 6 ($P = 0.029$); $I^2 = 18\%$				
Test for overall effect: $Z = 2.27$ ($P = 0.002$)				
6.1.2 LDL 6–11M				
Dansinger *et al.* (32)	–2.7	2.21	5.9	–2.70 (–7.03, 1.63)
Foster *et al.* (18)	0.54	1.93	7.7	0.54 (–3.24, 4.32)
Frisch *et al.* (37)	–1.16	1.93	7.7	–1.16 (–4.94, 2.62)
Gardner *et al.* (36)	1.7	2.54	4.4	1.70 (–3.28, 6.68)
Lean *et al.* (21)	–1.16	5.13	1.1	–1.16 (–11.21, 8.89)
Sacks *et al.* (17)	–1.58	1.76	9.3	–1.58 (–5.03, 1.87)
Samaha *et al.* (23)	5	2.88	3.5	5.00 (–0.64, 10.64)
Subtotal (95% CI)			39.5	–0.30 (–1.97, 1.37)
Heterogeneity: $Chi^2 = 6.13$, d.f. = 6 ($P = 0.41$); $I^2 = 2\%$				
Test for overall effect: $Z = 0.35$ ($P = 0.73$)				
6.1.3 LDL 12–23M				
Dansinger *et al.* (32)	–7.1	3.79	2.0	–7.10 (–14.53, 0.33)
Foster *et al.* (18)	–8.57	2.21	5.9	–8.57 (–12.90, –4.24)
Frisch *et al.* (37)	0.77	2.51	4.5	0.77 (–4.15, 5.69)
Gardner *et al.* (36)	0.8	2.58	4.3	0.80 (–4.26, 5.86)
Samaha *et al.* (23)	7	5.28	1.0	7.00 (–3.35, 17.35)
Yancy *et al.* (19)	–1.91	3.18	2.8	–1.91 (–8.14, 4.32)
Subtotal (95% CI)			20.6	–2.71 (–5.02, –0.39)
Heterogeneity: $Chi^2 = 15.59$, d.f. = 5 ($P = 0.008$); $I^2 = 68\%$				
Test for overall effect: $Z = 2.29$ ($P = 0.02$)				
6.1.4 LDL 24M				
Foster *et al.* (18)	–4.78	0.24	5.7	–4.78 (–9.17, –0.39)
Sacks *et al.* (17)	–2.12	1.96	7.5	–2.12 (–5.96, 1.72)
Subtotal (95% CI)			13.2	–3.27 (–6.16, –0.38)
Heterogeneity: $Chi^2 = 0.80$, d.f. = 1 ($P = 0.37$); $I^2 = 0\%$				
Test for overall effect: $Z = 2.22$ ($P = 0.03$)				
Total (95% CI)			100.0	–0.48 (–1.53, 0.57)
Heterogeneity: $Chi^2 = 44.49$, d.f. = 21 ($P = 0.002$); $I^2 = 53\%$				
Test for overall effect: $Z = 0.89$ ($P = 0.37$)				
Test for subgroup differences: $Chi^2 = 14.66$, d.f. = 3 ($P = 0.002$), $I^2 = 79.5\%$				



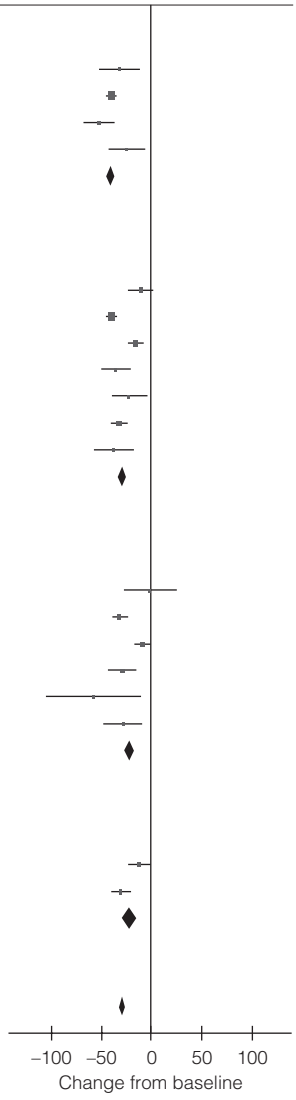
Studies are grouped according to length (see text for details).
CI, confidence interval; LDL, low-density lipoprotein; M, months.

however, reported data obtained with different durations of follow-up, and relatively few studies had durations up to 24 months, so statistical testing for a duration effect was not performed. Additionally, levels of recommended carbohydrate intake varied, as did the mean degree of obesity at baseline, among the different studies considered (Table 1). Both of these factors might be related to the magnitude of improvement observed in certain parameters in these studies, but the small number of studies and varying durations precluded examination of these effects across studies.

In 1935, McCay *et al.* showed that calorie restriction was associated with an increase in lifespan in male rats (49). Indirect evidence for a similar effect in humans was obtained by several researchers who reported that bariatric surgery led to decreases both in body weight and in mortality (compared with non-randomized controls) in obese patients (50–53). The decrease in body weight and BMI observed in association with LCD is therefore important, especially because LCD does not involve surgery. The effects of LCD on body weight were seen up to 36 months

Table 11 Forest plot for plasma triglyceride change associated to low-carbohydrate diets (mg per dL)

Study or subgroup	Mean difference	SE	Weight (%)	Mean difference IV, fixed, 95% CI
12.1.1 Triglic 6M				
Dansinger *et al.* (32)	–32.2	10.44	1.2	–32.20 (–52.66, –11.74)
Foster *et al.* (18)	–40.08	2.61	19.8	–40.08 (–45.20, –34.96)
Gardner *et al.* (36)	–52.3	7.61	2.3	–52.30 (–67.22, –37.38)
Lean *et al.* (21)	–24.78	9.03	1.7	–24.78 (–42.48, –7.08)
Subtotal (95% CI)			25.0	–39.82 (–44.37, –35.27)
Heterogeneity: $Chi^2 = 6.01$, d.f. = 3 ($P = 0.11$); $I^2 = 50\%$				
Test for overall effect: $Z = 17.15$ ($P < 0.00001$)				
12.1.2 Triglic 6–11M				
Dansinger *et al.* (32)	–10.6	6.32	3.4	–10.60 (–22.99, 1.79)
Foster *et al.* (18)	–40.06	2.88	16.3	–40.06 (–45.70, –34.42)
Frisch *et al.* (37)	–15.93	3.54	10.8	–15.93 (–22.87, –8.99)
Gardner *et al.* (36)	–35.6	7.34	2.5	–35.60 (–49.99, –21.21)
Lean *et al.* (21)	–22.12	8.58	1.8	–22.12 (–38.94, –5.30)
Sacks *et al.* (17)	–32.05	4.14	7.9	–32.05 (–40.16, –23.94)
Samaha *et al.* (23)	–38	10	1.3	–38.00 (–57.60, –18.40)
Subtotal (95% CI)			43.9	–29.39 (–32.82, –25.96)
Heterogeneity: $Chi^2 = 39.61$, d.f. = 6 ($P < 0.00001$); $I^2 = 85\%$				
Test for overall effect: $Z = 16.78$ ($P < 0.00001$)				
12.1.3 Triglic 12–23M				
Dansinger *et al.* (32)	–1.2	13.28	0.8	–1.20 (–27.23, 24.83)
Foster *et al.* (18)	–31.52	4.08	8.1	–31.52 (–39.52, –23.52)
Frisch *et al.* (37)	–8.85	4.16	7.8	–8.85 (–17.00, –0.70)
Gardner *et al.* (36)	–29.3	6.72	3.0	–29.30 (–42.47, –16.13)
Samaha *et al.* (23)	–58	23.82	0.2	–58.00 (–104.69, –11.31)
Yancy *et al.* (19)	–28.83	9.82	1.4	–28.83 (–48.08, –9.58)
Subtotal (95% CI)			21.3	–21.94 (–26.87, –17.00)
Heterogeneity: $Chi^2 = 21.84$, d.f. = 5 ($P = 0.0006$); $I^2 = 77\%$				
Test for overall effect: $Z = 8.71$ ($P < 0.00001$)				
12.1.4 Triglic 24M				
Foster *et al.* (18)	–12.19	5.46	4.5	–12.19 (–22.89, –1.49)
Sacks *et al.* (17)	–30.86	5.06	5.3	–30.86 (–40.78, –20.94)
Subtotal (95% CI)			9.8	–22.23 (–29.51, –14.96)
Heterogeneity: $Chi^2 = 6.29$, d.f. = 1 ($P = 0.01$); $I^2 = 84\%$				
Test for overall effect: $Z = 5.99$ ($P < 0.00001$)				
Total (95% CI)			100.0	–29.71 (–31.99, –27.44)
Heterogeneity: $Chi^2 = 106.32$, d.f. = 18 ($P < 0.00001$); $I^2 = 83\%$				
Test for overall effect: $Z = 25.59$ ($P < 0.00001$)				
Test for subgroup differences: $Chi^2 = 32.57$, d.f. = 3 ($P < 0.00001$), $I^2 = 90.8\%$				



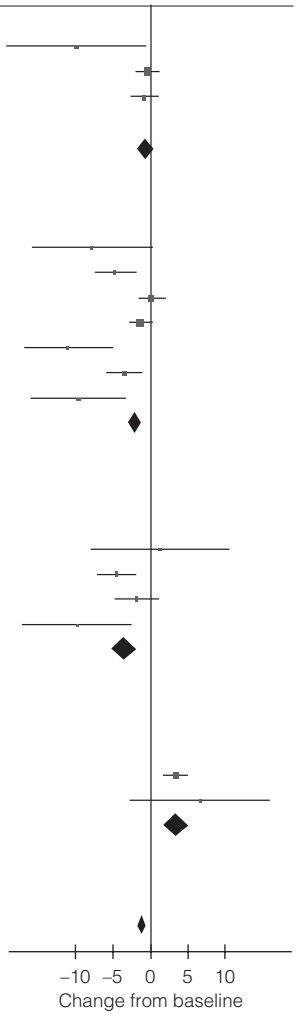
Studies are grouped according to length (see text for details).
CI, confidence interval; M, months.

after the start of the diet (the same happening with plasma glucose, insulin and CRP) (27). An overall decrease of 7.04 kg was seen with LCD, a value inferior to the decrease in weight associated with bariatric surgery (for instance, Buchwald *et al*. reported a value of 39.71 kg (54)), but higher than the 5% weight loss that is commonly suggested as beneficial to health. The decrease in waist circumference (5.74 cm overall) is also an interesting finding, as waist circumference is an established risk factor for cardiovascular disease (55), and it has been stated that waist circumference explains obesity-related health risk more accurately than BMI (56).

Arterial hypertension is yet another established risk factor for cardiovascular disease, and blood pressure lowering has been shown to be associated to major reductions in stroke, in coronary events and in the incidence of heart failure (57). The decrease in both systolic (4.81 mm Hg) and diastolic (3.10 mm Hg) blood pressure in association with LCD are therefore extremely interesting. These data are in good agreement with data from bariatric surgery (54) – in the SOS study, a decrease of 9 mm Hg in systolic and 6 mm Hg in diastolic blood pressure was seen 6 months after surgery; however, a relapse was seen in the following 5 years (58).

Table 12 Forest plot for fasting plasma glucose change associated to low-carbohydrate diets (mg per dL)

Study or subgroup	Mean difference	SE	Weight (%)	Mean difference IV, fixed, 95% CI
3.1.1 Glucose 6M				
Dansinger *et al.* (32)	–9.8	4.74	0.4	–9.80 (–19.09, –0.51)
Gardner *et al.* (36)	–0.4	0.77	16.6	–0.40 (–1.91, –1.11)
Truby *et al.* (34)	–0.72	0.95	10.9	–0.72 (–2.58, –1.14)
Subtotal (95% CI)			28.0	–0.67 (–1.84, –0.49)
Heterogeneity: $Chi^2 = 3.84$, d.f. = 2 ($P = 0.15$); $I^2 = 48\%$				
Test for overall effect: $Z = 1.13$ ($P = 0.26$)				
3.1.2 Glucose 6–11M				
Dansinger *et al.* (32)	–7.8	4.11	0.6	–7.80 (–15.86, –0.26)
Frisch *et al.* (37)	–4.68	1.37	5.3	–4.68 (–7.37, –1.99)
Gardner *et al.* (36)	0.2	0.87	13.0	0.20 (–1.51, –1.91)
Sacks *et al.* (17)	–1.27	0.71	19.6	–1.27 (–2.66, 0.12)
Samaha *et al.* (23)	–11	3	1.1	–11.00 (–16.88, –5.12)
Truby *et al.* (34)	–3.42	1.19	7.0	–3.42 (–5.75, –1.09)
Yancy *et al.* (29)	–9.6	3.27	0.9	–9.60 (–16.01, –3.19)
Subtotal (95% CI)			47.4	–2.03 (–2.92, –1.13)
Heterogeneity: $Chi^2 = 29.09$, d.f. = 6 ($P < 0.0001$); $I^2 = 79\%$				
Test for overall effect: $Z = 4.44$ ($P < 0.00001$)				
3.1.3 Glucose 12–23M				
Dansinger *et al.* (32)	1.4	4.74	0.4	1.40 (–7.89, –10.69)
Frisch *et al.* (37)	–4.5	1.35	5.4	–4.50 (–7.15, –1.85)
Gardner *et al.* (36)	–1.8	1.53	4.2	–1.80 (–4.80, 1.20)
Yancy *et al.* (19)	–9.74	3.67	0.7	–9.74 (–16.93, –2.55)
Subtotal (95% CI)			10.8	–3.56 (–5.44, –1.69)
Heterogeneity: $Chi^2 = 5.74$, d.f. = 3 ($P = 0.13$); $I^2 = 48\%$				
Test for overall effect: $Z = 3.73$ ($P = 0.0002$)				
3.1.4 Glucose 24M				
Sacks *et al.* (17)	3.4	0.86	13.3	3.40 (1.71, 5.09)
Samaha *et al.* (23)	6.68	4.78	0.4	6.68 (–2.69, 16.05)
Subtotal (95% CI)			13.8	3.50 (1.84, 5.16)
Heterogeneity: $Chi^2 = 0.46$, d.f. = 1 ($P = 0.50$); $I^2 = 0\%$				
Test for overall effect: $Z = 4.14$ ($P < 0.0001$)				
Total (95% CI)			100.0%	–1.05 (–1.67, –0.44)
Heterogeneity: $Chi^2 = 79.96$, d.f. = 15 ($P < 0.00001$); $I^2 = 81\%$				
Test for overall effect: $Z = 3.35$ ($P = 0.0008$)				
Test for subgroup differences: $Chi^2 = 40.83$, d.f. = 3 ($P < 0.00001$), $I^2 = 92.7\%$				



Studies are grouped according to length (see text for details).
CI, confidence interval; M, months.

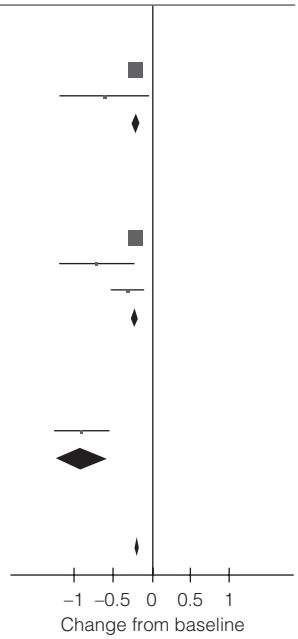
As for plasma lipids, LCD was associated with a decrease in triglycerides (of 29.71 mg dL^{-1}) and an increase in HDL-cholesterol (of 1.73 mg dL^{-1}), with no change in LDL-C.

Triglyceride levels are associated with coronary heart disease risk (59), as well as with the risk of ischaemic stroke (60). Higher HDL-C values are well known to be associated to a decreased incidence of coronary artery disease (61). The finding of decreased triglyceride values and increased HDL-C values, in association with LCD, is therefore most interesting, and the pattern observed is somewhat different to the results obtained with bariatric surgery, which typically results in decreases in LDL-C and triglycerides but no overall change in HDL-C (HDL-C only increased with gastric banding and gastroplasty) (54). The results are also interesting because LCDs often have a higher saturated fat composition, which has been shown to increase LDL-cholesterol (62). The lack of increase in LDL-cholesterol may reflect the weight loss during the diet or that the LCD is also higher in unsaturated fatty acids, which lower LDL-C.

Diabetes mellitus increases the risk for myocardial infarction (63). Elevated glycated haemoglobin has also been shown to be associated with a higher risk of coronary heart disease (64). Plasma glucose was shown to decrease slightly in association with LCD; a decrease in glycated haemoglobin was also seen. While the decreases are not large, they may be important nevertheless, given that the studies

Table 13 Forest plot for plasma glycated haemoglobin change associated to low-carbohydrate diets (%)

Study or subgroup	Mean difference	SE	Weight (%)	Mean difference IV, fixed, 95% CI
5.1.1 Haemoglobin Alc 6–11M				
Frisch *et al.* (37)	–0.2	0.02	48.6	–0.20 (–0.24, –0.16)
Samaha *et al.* (23)	–0.6	0.29	0.2	–0.60 (–1.17, –0.03)
Subtotal (95% CI)			48.8	–0.20 (–0.24, –0.16)
Heterogeneity: $Chi^2 = 1.89$, d.f. = 1 ($P = 0.17$); $I^2 = 47\%$				
Test for overall effect: $Z = 10.12$ ($P < 0.00001$)				
5.1.2 Haemoglobin Alc 12–23M				
Frisch *et al.* (37)	–0.2	0.02	48.6	–0.20 (–0.24, –0.16)
Samaha *et al.* (23)	–0.7	0.24	0.3	–0.70 (–1.17, –0.23)
Yancy *et al.* (19)	–0.3	0.11	1.6	–0.30 (–0.52, –0.08)
Subtotal (95% CI)			50.6	–0.21 (–0.24, –0.17)
Heterogeneity: $Chi^2 = 5.06$, d.f. = 2 ($P = 0.08$); $I^2 = 60\%$				
Test for overall effect: $Z = 10.53$ ($P < 0.00001$)				
5.1.3 Haemoglobin Alc 24M				
Shai *et al.* (16)	–0.9	0.18	0.6	0.90 (–1.25, –0.55)
Subtotal (95% CI)			0.6	0.90 (–1.25, –0.55)
Heterogeneity: Not applicable				
Test for overall effect: $Z = 5.00$ ($P < 0.0001$)				
Total (95% CI)			100.0	–0.21 (–0.24, –0.18)
Heterogeneity: $Chi^2 = 21.83$, d.f. = 5 ($P = 0.0006$); $I^2 = 77\%$				
Test for overall effect: $Z = 14.95$ ($P < 0.00001$)				
Test for subgroup differences: $Chi^2 = 14.88$, d.f. = 2 ($P < 0.0006$), $I^2 = 86.6\%$				



Studies are grouped according to length (see text for details).
CI, confidence interval; M, months.

reviewed were in patients with or without diabetes. The decrease in plasma insulin is also interesting, as it has been speculated that 'increases in levels of insulin, not glucose, may be etiologic in cardio-vascular disease risk' (65). In the present report, LCD has been shown to be associated with favourable changes in insulin/glucose metabolism. Bariatric surgery was shown to lead to complete resolution of diabetes in 78.1% of patients, with improvement or resolution of diabetes in 86.6% of cases (66), and was also shown to result in better glucose control than medical therapy (67,68).

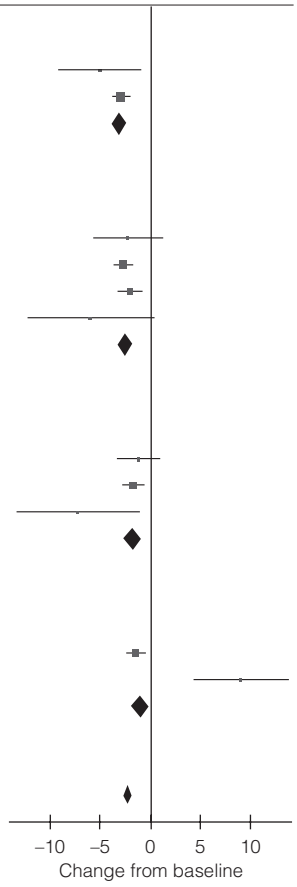
The overall picture obtained in the present investigation is favourable to LCD, and most changes associated to LCD follow, although in a lesser magnitude, the changes seen with bariatric surgery – pointing in the direction of the existence of favourable changes in cardiovascular risk factors associated with weight loss – in this sense, it is probable that beneficial effects might be obtained through weight loss on any form of currently used diets. LCD seems to be able to increase HDL-C – a goal frequently difficult to achieve. LCD was in fact associated to favourable changes in the parameters constituting the metabolic syndrome, according to the NCEP 2001 definition (69): waist circumference, triglycerides, HDL-C, blood pressure and glucose. According to Nordmann *et al.*, LCD was associated with more favourable changes in triglycerides and HDL-C, but to less favourable changes in total and LDL-C, when compared to low-fat diets (13). However, whereas pharmacological increases in HDL-C have led to disappointing results in some clinical trials (70,71), lowering of LDL-C with statins (HMG CoA reductase inhibitors) is associated with a favourable impact on clinical endpoints (72). The clinical importance of such changes in the serum lipid profile resulting from dietary intervention is less clear.

The long-term effects of LCD, as well as the effects of LCD on clinical endpoints such as the incidence of myocardial infarction, stroke and total mortality, are unknown, and concern has been raised on 'reliance on the traditional cardiovascular risk factors as a gauge of safety' (73). Research should be carried out concerning major cardiovascular endpoints and long-term effects of LCD, perhaps including the follow-up of cohorts previously studied, as was the case of studies carried out in other contexts (74).

In conclusion, 23 reports, corresponding to 17 clinical investigations, were identified as meeting the pre-specified criteria. Meta-analysis showed LCD to be clearly associated with significant decreases in body weight, BMI, abdominal circumference, systolic blood pressure, diastolic blood pressure, plasma triglycerides, fasting plasma glucose, glycated haemoglobin, plasma insulin and plasma CRP, as well as with an increase in HDL-C. LDL-C and

Table 14 Forest plot for plasma insulin change associated with low-carbohydrate diets (micro IU mL^{-1})

Study or subgroup	Mean difference	SE	Weight (%)	Mean difference IV, fixed, 95% CI
10.1.1 Insulin 6M				
Dansinger *et al.* (32)	–5.1	2.06	1.1	–5.10 (–9.14, –1.06)
Gardner *et al.* (36)	–3	0.44	23.5	–3.00 (–3.86, –2.14)
Subtotal (95% CI)			24.6	–3.09 (–3.93, –2.25)
Heterogeneity: Chi^2 = 0.99, d.f. = 1 (P = 0.32); I^2 = 0%				
Test for overall effect: Z = 7.18 (P < 0.00001)				
10.1.2 Insulin 6–11M				
Dansinger *et al.* (32)	–2.3	1.74	1.5	–2.30 (–5.71, 1.11)
Gardner *et al.* (36)	–2.8	0.47	20.6	–2.80 (–3.72, –1.88)
Sacks *et al.* (17)	–2.07	0.6	12.7	–2.07 (–3.25, –0.89)
Samaha *et al.* (23)	–6	3.2	0.4	–6.00 (–12.27, 0.27)
Subtotal (95% CI)			35.2	–2.56 (–3.26, –1.85)
Heterogeneity: Chi^2 = 2.11, d.f. = 3 (P = 0.55); I^2 = 0%				
Test for overall effect: Z = 7.11 (P < 0.00001)				
10.1.3 Insulin 12–23M				
Dansinger *et al.* (32)	–1.2	1.06	4.1	–1.20 (–3.28, –0.88)
Gardner *et al.* (36)	–1.8	0.55	15.1	–1.80 (–2.28, –0.72)
Yancy *et al.* (19)	–7.32	3.15	0.5	–7.32 (–13.49, –1.15)
Subtotal (95% CI)			19.6	–1.81 (–2.75, –0.86)
Heterogeneity: Chi^2 = 3.39, d.f. = 2 (P = 0.18); I^2 = 41%				
Test for overall effect: Z = 3.74 (P = 0.0002)				
10.1.4 Insulin 24M				
Sacks *et al.* (17)	–1.48	0.48	19.8	–1.48 (–2.42, –0.54)
Samaha *et al.* (23)	–8.99	2.23	0.8	8.99 (4.33, 13.65)
Subtotal (95% CI)			20.6	–1.07 (–1.99, –0.15)
Heterogeneity: Chi^2 = 18.60, d.f. = 1 (P < 0.0001); I^2 = 95%				
Test for overall effect: Z = 2.28 (P = 0.02)				
Total (95% CI)			100.0	–2.24 (–2.65, –1.82)
Heterogeneity: Chi^2 = 36.77, d.f. = 10 (P = 0.0001); I^2 = 73%				
Test for overall effect: Z = 10.47 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 11.68, d.f. = 3 (P = 0.009), I^2 = 74.3%				



Studies are grouped according to length (see text for details).
CI, confidence interval; M, months.

creatinine did not change significantly, whereas limited data were conflicted regarding plasma uric acid. The long-term effects of LCD, as well as the effects of LCD on clinical endpoints such as the incidence of myocardial infarction, stroke and total mortality, are essentially unknown and should be the object of future research.

Conflict of interest statement

No conflict of interest was declared.

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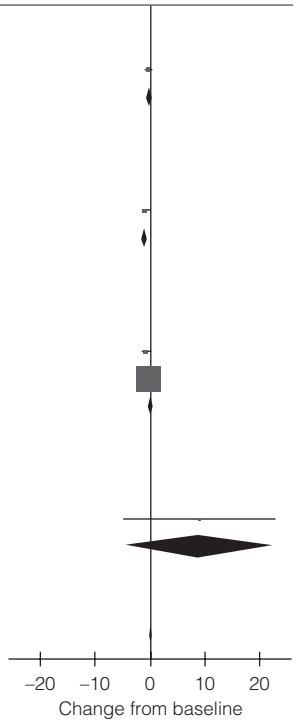
Table 15 Forest plot for plasma C-reactive protein change associated to low-carbohydrate diets (mg per L)

Study or subgroup	Mean difference	SE	Weight (%)	Mean difference IV, fixed, 95% CI
11.1.1 C-reactive protein 6M				
Dansinger *et al.* (32)	–0.33	0.25	5.1	–0.33 (–0.82, –0.16)
Subtotal (95% CI)			5.1	–0.33 (–0.82, –0.16)
Heterogeneity: Not applicable				
Test for overall effect: $Z = 1.32$ ($P = 0.19$)				
11.1.2 C-reactive protein 6–12M				
Dansinger *et al.* (32)	–0.71	0.32	3.1	–0.71 (–1.34, –0.08)
Subtotal (95% CI)			3.1	–0.71 (–1.34, –0.08)
Heterogeneity: Not applicable				
Test for overall effect: $Z = 2.22$ ($P = 0.03$)				
11.1.3 C-reactive protein 12–23M				
Dansinger *et al.* (32)	–0.7	0.33	2.9	–0.70 (–1.35, –0.05)
Yancy *et al.* (29)	–0.18	0.06	88.8	–0.18 (–0.30, –0.06)
Subtotal (95% CI)			91.8	–0.20 (–0.31, –0.08)
Heterogeneity: $Chi^2 = 2.40$, d.f. = 1 ($P = 0.12$); $I^2 = 58\%$				
Test for overall effect: $Z = 3.33$ ($P = 0.0009$)				
11.1.4 C-reactive protein 24M				
Samaha *et al.* (23)	9	7.01	0.0	9.00 (–4.74, 22.74)
Subtotal (95% CI)			0.0	9.00 (–4.74, –22.74)
Heterogeneity: Not applicable				
Test for overall effect: $Z = 1.28$ ($P = 0.20$)				
Total (95% CI)			100.0	–0.22 (–0.33, –0.11)
Heterogeneity: $Chi^2 = 6.83$, d.f. = 4 ($P = 0.15$); $I^2 = 41\%$				
Test for overall effect: $Z = 3.87$ ($P = 0.0001$)				
Test for subgroup differences: $Chi^2 = 4.42$, d.f. = 3 ($P = 0.22$), $I^2 = 32.2\%$				



Studies are grouped according to length (see text for details).
CI, confidence interval; M, months.

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