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Effects of low-carbohydrate diets *v.* low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials

Nadia Mansoor[1]*†, Kathrine J. Vinknes[1]†, Marit B. Veierød[1,2] and Kjetil Retterstøl[1,3]

[1]*Department of Nutrition, Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo, PO Box 1046 Blindern, 0317 Oslo, Norway*
[2]*Oslo Centre for Biostatistics and Epidemiology, Institute of Basic Medical Sciences, University of Oslo, 0372 Oslo, Norway*
[3]*Lipid Clinic, Oslo University Hospital, Rikshospitalet, 0373 Oslo, Norway*

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Abstract

The effects of low-carbohydrate (LC) diets on body weight and cardiovascular risk are unclear, and previous studies have found varying results. Our aim was to conduct a meta-analysis of randomised controlled trials (RCT), assessing the effects of LC diets *v.* low-fat (LF) diets on weight loss and risk factors of CVD. Studies were identified by searching MEDLINE, Embase and Cochrane Trials. Studies had to fulfil the following criteria: a RCT; the LC diet was defined in accordance with the Atkins diet, or carbohydrate intake of <20 % of total energy intake; twenty subjects or more per group; the subjects were previously healthy; and the dietary intervention had a duration of 6 months or longer. Results from individual studies were pooled as weighted mean difference (WMD) using a random effect model. In all, eleven RCT with 1369 participants met all the set eligibility criteria. Compared with participants on LF diets, participants on LC diets experienced a greater reduction in body weight (WMD –2·17 kg; 95 % CI –3·36, –0·99) and TAG (WMD –0·26 mmol/l; 95 % CI –0·37, –0·15), but a greater increase in HDL-cholesterol (WMD 0·14 mmol/l; 95 % CI 0·09, 0·19) and LDL-cholesterol (WMD 0·16 mmol/l; 95 % CI 0·003, 0·33). This meta-analysis demonstrates opposite change in two important cardiovascular risk factors on LC diets – greater weight loss and increased LDL-cholesterol. Our findings suggest that the beneficial changes of LC diets must be weighed against the possible detrimental effects of increased LDL-cholesterol.

Key words: **Low-carbohydrate diets: Low-fat diets: Weight loss: Cardiovascular risk factors**

According to the World Health Organization[1], worldwide obesity has almost doubled since the 1980s. Globally, 35 % of people aged ≥20 years were overweight and 11 % were characterised as obese in 2008[1]. Overweight and obesity in adults are associated with CVD, type 2 diabetes and certain types of cancer[1,2]. A recent systemic analysis estimated that 3·4 million deaths in 2010 were caused by overweight and obesity[3]. Therefore, dietary measures that can most effectively contribute to reduce excess body weight and improve parameters of CVD should be further explored.

The low-carbohydrate (LC) diet, in which carbohydrates (CHO) are replaced by greater intake of fat and/or protein, is a popular weight-loss option compared with the conventional low-fat (LF) diet. However, concerns have been raised with regard to the macronutrient shift with an extreme CHO restriction and the liberal intakes of fats, which may present detrimental effects on CVD risk factors[4,5]. Increased intake of fat, particularly SFA, have been associated with an increase in LDL-cholesterol, and thus increased risk of CVD[4,6,7], whereas the LF approach has generally been supported by studies to have advantageous effects on CVD risk among high-risk patients[8,9]. The WHO recommends limiting SFA intake to <10 % of total energy intake, and other competent bodies such as the American Heart Association recommend restricting SFA intake to <7 %[4]. However, these recommendations have been challenged in a meta-analysis, where the authors concluded that there was no significant evidence that SFA was associated with increased risk of CHD and CVD[10].

Supporters of the LC diet point to studies where subjects on the LC diet produced greater weight loss, greater reduction of both total cholesterol (TC) and TAG and increased HDL-cholesterol compared with their LF diet counterparts[11,12]. However, studies also show significant increase or lack of reduction in LDL-cholesterol after consuming a LC diet[12–16], which potentially could be harmful, as LDL-cholesterol is an important risk factor for CVD morbidity and mortality[17–19]. Therefore, concern has been raised with regard to the use of the LC diet, especially by patients with known CVD, type 2 diabetes, dyslipidaemia and/or hypertension[20].

Abbreviations: CHO, carbohydrates; DBP, diastolic blood pressure; LC, low CHO; LF, low fat; RCT, randomised controlled trials; SBP, systolic blood pressure; TC, total cholesterol; WMD, weighted mean difference.

* **Corresponding author:** N. Mansoor, fax +47 22851398, email n.mauland.mansoor@gmail.com

† Both authors contributed equally to this work.

Due to the lack of consensus between previous meta-analyses[12,15,21], authors have cautioned against making recommendations for or against the LC diet[15,20], and thus the topic should be challenged and re-evaluated. The lack of consensus may be caused by the different inclusion and exclusion criteria used. For example, many previous meta-analyses have allowed a greater range in terms of CHO intake among subjects in the LC groups (ranging from 20–30 g/d upto 40–45 % of total energy), and in some studies all subjects in one group suffered from type 2 diabetes. In contrast, the present meta-analysis included adults with increased BMI, who in some cases had associated metabolic risk factors, but were altogether regarded as healthy. Studies where one intervention group consisted solely of subjects with established associated disease such as, but not limited to, type 2 diabetes and CVD were excluded. Furthermore, we have reduced factors that can contribute to variation by including studies with more comparable baseline values. In the present meta-analysis, we aimed to compare a typical LC diet defined as a CHO intake of 20–30 g/d in the first phase[22] or <20 % of total energy with traditional LF diets composed of <30 % of energy as fat and limited energy content[23], as well as determine the effects on long-term weight loss and several CVD risk factors in healthy adults by examining relevant randomised controlled trials (RCT).

Methods

Methods and literature search

The current meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement[24]. The protocol for the meta-analysis has been published with the registration number CRD42015020458 in the PROSPERO database and can be accessed at http://www.crd.york.ac.uk/PROSPERO.

We searched databases such as MEDLINE via Ovid, EMBASE and Cochrane Library in Trials (CENTRAL) for relevant RCT, with the last search date being 28 May 2015. In addition, references from the retrieved publications were thoroughly reviewed for potentially relevant citations not detected by the electronic search. The search terms were related to both groups of intervention ('low-carbohydrate diet' and 'low-fat diet') and primary and secondary outcomes ('weight loss' or 'cardiovascular disease' or 'cardiovascular risk'). Searches were restricted to RCT performed on humans, which were published in English. No restrictions were imposed on publication dates. The complete search strategy is available in the protocol published with the aforementioned registration number.

Study selection

As the present meta-analysis aimed to compare weight loss differences between two diet groups, only studies that met all of the following criteria were included: (1) the study was a RCT that compared a group of subjects on a LC diet with one or more groups on different variations of a conventional LF diet; (2) the LC diet was defined through a distinct reference to the Atkins diet, with an intake of only 20–40 g/d of CHO in the first phase or CHO intake of <20 % of total energy intake; (3) the dietary intervention consisted of at least twenty subjects/group in the first analysis or after drop out; (4) the subjects were previously healthy; and (5) the dietary intervention had a duration of 6 months or longer. RCT performed solely on subjects classified as severely obese with BMI $\geq 35\ kg/m^2$ were also excluded, as these subjects were not characterised as previously healthy. Likewise, studies involving supplementary medical therapy in addition to diet therapy were excluded. One investigator performed the searches and performed the screening. Studies with irrelevant titles and/or abstracts were excluded, whereas relevant studies were assessed in full text and included if they fulfilled the above-mentioned criteria. Another investigator also reviewed the selected studies with regard to whether they fulfilled all criteria.

Data extraction and quality assessment

One investigator collected the following data: article title, primary author's name, year, country of origin, study design, blinding, dietary composition, dropout rate, intention-to-treat analysis, characteristics of the study population (sample size, age, sex and baseline levels of body weight and CVD risk factors) and the mean changes in end points from baseline to the end of intervention, with measures of variance. The main end point was weight loss and secondary end points were risk factors of CVD, including blood lipid levels (TAG, HDL-cholesterol, LDL-cholesterol), fasting insulin and glucose concentrations and systolic blood pressure (SBP) and diastolic blood pressure (DBP). If data were lacking, the authors were contacted to obtain additional information. For studies that had more than two intervention groups, the most appropriate one was chosen. If data were published as updates, results of the longest duration periods were included.

Methodological quality was evaluated by two authors using the Cochrane Collaboration's tool for assessing risk of bias[25] indicating the following bias categories: selection bias (random sequence generation, allocation concealment); performance bias (blinding of participants and personnel and blinding of the outcome assessments); attrition bias (incomplete outcome data); reporting bias (selective outcome reporting) and other biases. The nature of the trials required an open intervention with no blinding of the trial participants or the investigators. Any disagreement was resolved by consensus.

Statistical analysis

Raw data were first extracted from the selected studies. Data expressed in mg/dl were converted into mmol/l by multiplying with 0·0259 for cholesterol and 0·0113 for TAG. Insulin values in pmol/l were converted to mU/l by multiplying with 6·0. When only CI for the means were provided, standard deviations were calculated. When it was not possible to retrieve adequate data, standard deviations were imputed from studies in another meta-analysis (primary analyses)[26]; this was necessary for five studies[11,27–30] for one and upto maximum three variables. For each outcome measure of interest, a meta-analysis was performed to determine the pooled effect of the intervention in terms of weighted mean difference (WMD) from baseline to end of trial comparing LC with LF groups. Summary WMD with 95 % CI for the outcome measures were calculated using a random effect model[31].

To evaluate the influence of missing data on the summary estimate and the method used to calculate missing data, sensitivity analyses were carried out by removing studies not reporting standard deviation for mean differences. Heterogeneity between studies was tested using the Q test[32]. The I^2 index was used to quantify the extent of heterogeneity, with I^2 values >50 and >75 % being indicative of moderate and high heterogeneity, respectively. To further explore heterogeneity, we conducted sensitivity analyses to examine the influence of individual studies by omitting one study at a time. In addition, subgroup analyses were performed on studies sharing certain methodological features such as duration >12 months, low risk of bias, both men and women, intention-to-treat analyses and subjects with obesity-associated metabolic risk factors or disorders.

Publication bias was evaluated using funnel plots and Egger's regression test for each outcome[33]. Furthermore, when Egger's regression tests or funnel plots indicated publication bias, we used the trim-and-fill method to identify whether funnel plot asymmetry should be corrected. All the statistical analyses were carried out using Stata, version 13.1 software (StataCorp LP).

Results

Literature search

The flow and selection of studies from our search strategy are summarised in Fig. 1. Our searches warranted 740 potentially relevant records, of which 362 records remained after duplicates had been removed. After screening, forty-two records remained and were retrieved in full text, in order to be evaluated in accordance with the set inclusion and exclusion criteria. Of the forty-two records, thirty-one records were excluded as they failed to satisfy the set inclusion criteria. In addition, the references of the selected records were reviewed in an attempt to potentially find other relevant records, but none was found. Thus, a total of eleven RCT were included in the final meta-analysis.

Study and subject characteristics

The characteristics of the eleven studies are summarised in Table 1. All studies were parallel group RCT , but none was blinded because of the nature of the studies involving diet intervention. Intervention durations ranged from 6 to 24 months, with eight of them lasting for 12 months or longer[27,28,34–39]. The diet composition goal for the LC diets was intake of 20–40 g/d CHO in the first period with gradual increases or CHO intake of <20 % of total energy intake. The dietary goal for the LF diets was <30 % of total energy as fat. Furthermore, subjects on the LF diet were imposed a energy restriction, whereas subjects on the LC diet were mostly on an *ad libitum* diet, except in two studies where the LF and LC groups were isoenergetic[14,39]. However, in some of the studies, subjects on *ad libitum* LC diets also demonstrated a decrease in their energy intake, similar to subjects on the LF diet, although this was not required or encouraged at the outset[11,27,29,30,38]. Most studies offered group or individual sessions of dietary and supportive counselling, whereas one study had a self-help format with little contact with professionals[28]. In order to record and assure dietary adherence, subjects were encouraged to maintain dietary journals,

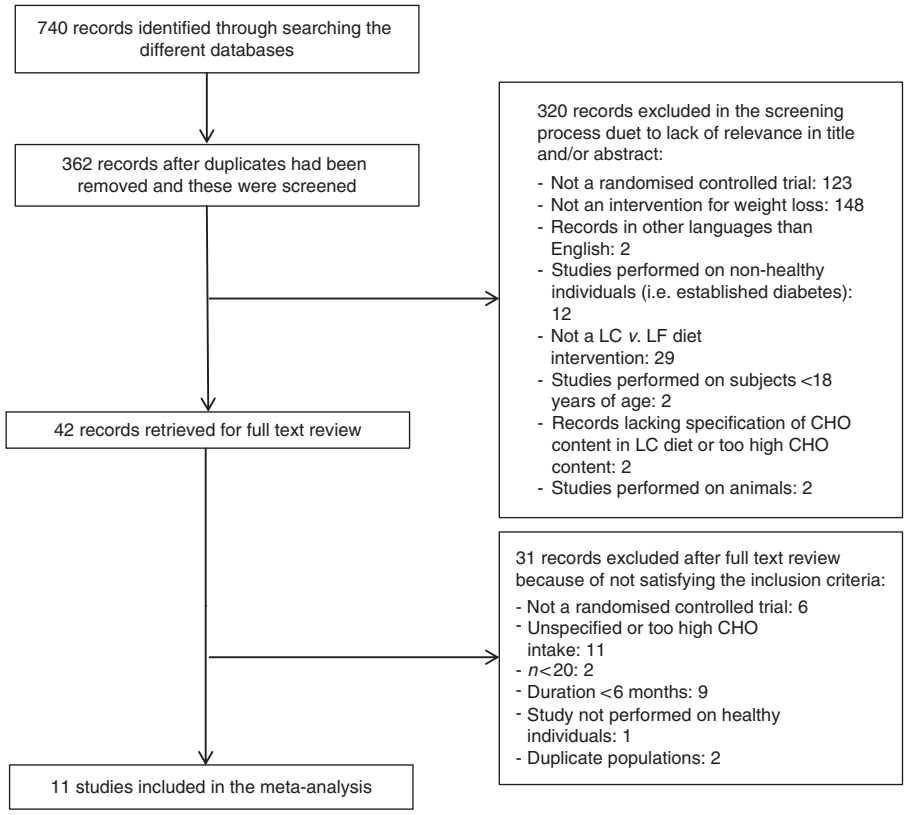


Fig. 1. Flow diagram of study selection for the meta-analysis. CHO, carbohydrate; LC, low-CHO; LF, low-fat.

Table 1. Characteristics of eleven randomised controlled trials included in the meta-analysis

First author, year (reference no.)	Country	Duration of intervention (months)	Diet composition		Drop out (%)	
			LC	LF	LC	LF
Bazzano, 2014[34]	USA	12	CHO intake <40 g/d. *Ad libitum* diet with no set energy goal	<30 % of total fat intake as fat, and <7 % as SFA. 55 % of total energy intake as CHO. No energy restriction	21	18
Brehm, 2003[11]	USA	6	*Ad libitum* diet with <20 g/d as CHO. After 2 weeks, permission to increase CHO to 40 – 60 g/d	55 % of total energy as CHO, 15 % as protein and 30 % as fat	15	26
Brinkworth, 2009[35]	Australia	12	4 % of total energy as CHO, 35 % as protein, 61 % fat (20 % SFA). Restriction of CHO to <20 g/d the first 2 months and then <40 g/d for the remainder of the intervention period	30 % as fat (8 % or 10 g/d as SFA), 46 % as CHO and 24 % as protein	40	31
Dansinger, 2005[36]	USA	12	CHO intake <20 g/d, with gradual increase towards 50 g/d	10 % of energy from fat, vegetarian diet	48	50
Foster, 2003[28]	USA	12	CHO intake <20 g/d for the first 2 weeks, with gradual increase until stable and desired weight was achieved. Instructed to follow the Atkins diet	60 % of total energy as CHO, 20 % as fat and 10 % as protein. Energy intake limited to 5021–6276 kJ (1200–1500 kcal/d) for women and 6276–7531 kJ (1500–1800 kcal/d) for men	39	43
Foster, 2010[37]	USA	24	<20 g CHO for the first 3 months, thereafter gradual increase in CHO intake (5 g/d per week). Participants followed guidelines as described in Dr Atkins' New Diet Revolution	55 % of energy from CHO, 30 % from fat and 1 % from protein. Energy intake was limited to 5021–6276 kJ (1200–1500 kcal/d) for women and 6276–7531 kJ (1500–1800 kcal/d) for men	42	32
Gardner, 2007[38]	USA	12	CHO intake of 20 g/d or less in the induction phase (2–3 months), and ≤50 g/d or less for the subsequent ongoing weight loss phase	<10 % of total energy from fat	12	22
Lim, 2010[39]	Australia	15	4 % of energy as CHO, 35 % as protein and 60 % fat (20 % SFA).	70 % of energy as CHO, 20 % protein and 10 % fat (3 % SFA)	37	36
Morgan, 2009[29]	UK	6	LC diet prescribed as Atkins diet after Dr Atkins' New Diet Revolution	LF diet prescribed after Rosemary Conely 'Eat yourself slim' Diet and fitness plan-an energy-controlled and low-fat healthy eating diet and group exercise class	42	29
Shai, 2008[27]	Israel	24	CHO intake limited to 20 g/d for first 2 months, with gradual increase to maximum 120 g/d. Intake of total energy, protein and fat were not limited	30 % fat (10 % SFA) and 300 mg cholesterol/d. Restricted energy intake: 5021 kJ (1500 kcal/d) for women and 7531 kJ (1800 kcal/d) for men	22	10
Yancy, 2004[30]	USA	6	CHO intake limited to <20 g/d. Increase of 5 g/week until body weight was maintained	<30 % of total energy as fat, <10 % SFA and <300 mg cholesterol daily	24	43

CHO, carbohydrates; LC, low-CHO diet; LF, low-fat diet.

24 h recalls were made and 3-, 5- or 7-d food records were collected. Adherence decreased over time, but studies that provided more extensive behavioural treatment and close follow-up had better dietary adherence than studies with less follow-up. Mostly, subjects were encouraged to maintain a certain level of physical activity, although none of the studies provided records of the subjects' physical activity level. There was a large variation in attrition rates, with drop out ranging from 12 to 50 %. We collected data from analyses that included only subjects who completed the intervention, except for two studies that only presented data from intention-to-treat analysis[30,37]. However, one of the studies reported that the results from the intention-to-treat analysis did not significantly differ from the results of completers data only[37]. Likewise, two other studies provided data for both intention-to-treat and completers analyses, and similarly reported no significant differences at the end of the intervention[28,36].

The baseline subject characteristics are presented in Table 2. A total of 1369 subjects (LC, *n* 688 and LF, *n* 681) were included in the eleven studies that met the eligibility criteria. Most of the studies had a higher proportion of women than men, and two studies included only women. The mean age of participants varied between 40 and 52 years.

Reported mean BMI and baseline levels of cardiovascular risk factors (TAG, HDL-cholesterol, LDL-cholesterol, TC, SBP, DBP, glucose and insulin) varied among studies but were similar in the LC and LF groups in each study.

Quality assessment: risk of bias

Results from the quality assessment are provided in Table 3. Some studies did not report on the sequence generation used, and most studies did not report on allocation concealment. Blinding was impossible. One study was considered to have high risk in terms of incomplete outcome data. No evidence of selective reporting was found in any of the studies. Of the eleven studies, one study received an overall score of 'high' in terms of risk of bias.

Meta-analyses

The results from the primary meta-analyses are presented in Fig. 2 and online Supplementary Table S1. The WMD comparing the LC *v.* LF diets was significant for body weight (WMD = –2·17 kg; 95 % CI –3·36, –0·99) and TAG (WMD = –0·26 mmol/l; 95 % CI –0·37, –0·15). Furthermore, subjects on the LC diets experienced a significantly greater increase in both HDL-cholesterol (WMD = 0·14 mmol/l; 95 % CI 0·09, 0·19) and LDL-cholesterol (WMD = 0·16 mmol/l; 95 % CI 0·003, 0·33) compared with subjects on LF diets. Only four studies provided data on TC, which showed no significant difference between the groups. Similarly, WMD for SBP, DBP and glucose and insulin concentrations between the LC *v.* LF groups were not significant. We imputed standard deviation calculated from studies in our meta-analysis, which produced similar results to the primary analyses with standard deviation imputed from another meta-analysis[12]. Likewise, excluding all studies not reporting standard deviation for mean differences or those with imputed standard deviation from another meta-analysis showed similar results, except non-significant results for LDL-cholesterol due to fewer studies being included in the analyses.

Moderate-to-high heterogeneity was observed for all variables, with I^2 values ranging from 63 to 92 % (Fig. 2 and online Supplementary Table S1). We carried out sensitivity analyses to identify possible studies explaining the heterogeneity. The exclusion of each study one at a time did not significantly alter the results or the heterogeneity for body weight and insulin. However, for TAG, the heterogeneity dropped considerably when we excluded the study by Foster *et al.*[37] ($I^2 = 30{\cdot}2$; $P = 0{\cdot}17$) or Brinkworth *et al.*[35] ($I^2 = 40{\cdot}8$; $P = 0{\cdot}09$), but did not change the WMD. For TC, HDL-cholesterol, LDL-cholesterol and DBP, the heterogeneity decreased when the study by Brinkworth *et al.*[35] was excluded ($I^2 = 35{\cdot}1$; $P > 0{\cdot}10$ for all), but WMD did not change. The study by Gardner *et al.*[38] was responsible for the heterogeneity in the sensitivity analysis for SBP, although exclusion of this study did not change the results.

In the subgroup analysis, we excluded studies with duration <12 months, with high or unclear risk of bias, with 100 % women or only presenting intention-to-treat analyses. The WMD were similar for almost all variables (data not shown), except for LDL-cholesterol, which did not remain significantly different between the LC and LF diets, probably due to reduction of included studies from 11 to 8 or 9. In addition, body weight did not remain significant, whereas DBP became significantly different between LC and LF diets after excluding studies with unclear or high risk of bias[29,30,35,39]. Heterogeneity was reduced for TAG, TC, HDL-cholesterol, LDL-cholesterol and DBP when studies with unclear or high risk of bias were excluded. Similarly, heterogeneity was reduced for TAG when studies only presenting intention-to-treat analyses were excluded. In addition, heterogeneity was reduced for SBP and glucose levels when studies with only women were excluded.

Another subgroup analysis was performed to explore whether studies including subjects with metabolic risk factors or disorders were associated with changes in WMD and heterogeneity for the different variables[27,30,35,36,39]. WMD was similar as in the primary meta-analysis for body weight (five studies), TAG (five studies), TC (three studies) and HDL-cholesterol (five studies), whereas WMD for LDL-cholesterol turned out to be non-significant (data not shown). Heterogeneity was no longer significant for TAG, SBP, DBP, glucose and insulin. In analyses that excluded studies including subjects with associated metabolic disorders[11,28,29,34,37,38], the WMD was similar as in the primary meta-analysis for body weight (six studies), TAG (six studies), TC (one study), HDL-cholesterol (six studies) and LDL-cholesterol (six studies). The heterogeneity was reduced for TAG, HDL-cholesterol and LDL-cholesterol.

We explored the possibility of publication bias by plotting mean differences against standard errors in body weight and cardiovascular risk factors (online Supplementary Fig. S1). Using Egger's linear regression test, possible publication bias was detected for body weight ($P = 0{\cdot}03$, eleven studies), TC ($P = 0{\cdot}03$, four studies), LDL-cholesterol ($P = 0{\cdot}03$, eleven studies) and DBP ($P = 0{\cdot}05$, eight studies). Visual inspection of the funnel plots (online Supplementary Fig. S1) suggests that publication bias may also be present for SBP (eight studies) and glucose (seven studies). The trim-and-fill method was used, but no trimming was performed, and the WMD estimates were unchanged.

Table 2. Baseline characteristics of eleven randomised controlled trials included in the meta-analysis*
(Percentages; mean values and standard deviations)

								Cardiovascular risk factors													
				Age (years)		BMI (kg/m^2)		TAG (mmol/l)		HDL-cholesterol (mmol/l)		LDL-cholesterol (mmol/l)		TC (mmol/l)		SBP (mmHg)		DBP (mmHg)		Glucose (mmol/l)		Insulin (mU/l)	
First author, year, (reference no.)	Diet	No.	Women (%)	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Bazzano, 2014[34]	LC	75	88	45·8	9·9	35·2	3·8	1·3	0·6	3·8	1·0	3·2	0·9	5·1	1·1	120	12·8	78	9·0	5·2	0·6	17·1	10·7
	LF	73	89	47·8	10·4	35·6	4·5	1·4	0·9	3·8	1·0	3·2	1·0	5·3	1·1	125	13·8	79	8·3	5·2	0·5	17·6	9·2
Brehm, 2003[11]	LC	22	100	44·2	6·84	33·17	1·83	1·68	0·15	1·34	0·07	3·23	0·14	5·34	0·17	116	3·23	79	2·69	5·51	0·14	16·9	1·8
	LF	20	100	43·1	8·6	34·04	1·83	1·23	0·11	1·26	0·06	2·95	0·16	4·78	0·16	115	2·47	75	1·99	5·06	0·12	23·9	2·34
Brinkworth, 2009[35]	LC	33	67	51·5	7·7	33·6	0·7	1·67	0·14	1·45	0·05	3·2	0·1	5·4	0·2	132·7	2·3	72·3	1·8	5·7	0·1	7·9	0·6
	LF	36	61	51·4	6·5	33·7	0·7	1·80	0·14	1·36	0·06	3·2	0·1	5·5	0·1	135·2	2·1	77·1	1·8	5·6	0·1	9·8	0·6
Dansinger, 2005[36]	LC	40	53	47	12·0	35	3·5	1·7	1·11	1·24	0·41	3·52	0·80	5·53	0·80	129	17	77	9	7·06	4·44	22	16
	LF	40	43	49·0	12·0	35	3·9	1·96	1·47	1·16	0·05	3·52	0·89	5·53	0·88	133	17	76	9	6·72	3·06	30	18
Foster, 2003[28]	LC	33	64	44·0	9·4	33·9	3·8	1·48	1·28	1·21	0·29	3·35	0·78	5·19	0·87	120·5	11·0	74·6	8·5				
	LF	30	73	44·2	7·0	34·4	3·1	1·38	0·93	1·28	0·32	3·10	0·78	5·02	0·83	123·3	14·1	77·6	10·8				
Foster, 2010[37]	LC	153	67	46·2	9·2	36·1	3·59	1·28	0·62	1·20	0·35	3·11	0·67	4·88	0·78	124·3	14·1	73·9	9·4				
	LF	154	68	44·9	10·2	36·1	3·46	1·40	0·83	1·18	0·30	3·21	0·76	4·98	0·85	124·6	15·8	76·0	9·7				
Gardner, 2007[38]	LC	77	100	42	5·0	32	4	1·41	0·88	1·37	0·36	2·82	0·75			118	11	75	8	5·11	0·50	10	7
	LF	76	100	42	6·0	32	3	1·33	0·70	1·29	0·28	2·87	0·70			116	10	75	8	5·12	0·72	10	8
Lim, 2010[39]	LC	30	80	48·3	7·6	32·3	3·1	1·8	1·0	1·3	0·3	3·1	1·7	5·9	1·0	120·8	15·1	77·2	13	5·4	0·6	10·9	5·8
	LF	30	80	48·6	11·3	30·5	9·5	1·6	0·6	1·4	0·4	2·7	1·9	5·7	1·2	129·4	12	76·4	9·6	5·3	0·6	8·4	3·7
Morgan, 2008[29]	LC	57	74	40·9	9·7	31·9	2·2	1·65	0·70	1·22	0·23	3·72	0·52			135·0	15·1	83·0	10·7	5·59	0·56	12·2	5·85
	LF	58	72	40·6	10·3	31·6	2·6	1·59	0·83	1·22	0·30	3·59	0·67			130·0	14·8	82·0	10·3	5·66	0·66	12·6	7·95
Shai, 2008[27]	LC	109	9	52·0	7·0	30·8	3·5	2·05	1·32	0·97	0·22	3·03	0·89			130·8	15·1	79·4	9·1	5·14	1·58	14·1	10·2
	LF	104	14	51·0	7·0	30·6	2·2	1·77	0·7	1·00	0·25	3·03	0·92			129·6	13·2	79·1	9·1	4·83	1·44	13·3	6·8
Yancy, 2004[30]	LC	59	75	44·2	10·1	34·6	4·9	1·78	1·20	1·43	0·39	4·07	0·80	6·32	0·91	132	16	82	8				
	LF	60	78	45·6	9·0	34·0	5·2	2·15	1·20	1·40	0·39	3·83	0·70	6·20	0·91	133	16	82	9				

TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; LC, low-carbohydrate diet; LF, low-fat diet.
* To convert from SI units: multiply TC, LDL-cholesterol and HDL-cholesterol (mg/dl) × 0·0259 = mmol/l; multiply TAG (mg/dl) × 0·01129 = mmol/l.

Table 3. Assessment of risk of bias of the studies included in the meta-analysis

	Selection bias	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	
Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall
Bazzano *et al.*[34]	Low	Low	Low	Low	Low	Low	Low
Brehm *et al.*[11]	Low	Unclear	Low	Low	Low	Low	Low
Brinkworth *et al.*[35]	Unclear	Unclear	Low	Low	Low	Low	Low
Dansinger *et al.*[36]	Low	Low	Low	Low	Low	Low	Low
Foster *et al.*[28]	Low	Unclear	Low	Low	Low	Low	Low
Foster *et al.*[37]	Low	Unclear	Low	Low	Low	Low	Low
Gardner *et al.*[38]	Low	Low	Low	Low	Low	Low	Low
Lim *et al*[39]	Unclear	Unclear	Low	Low	Low	Low	Low
Morgan *et al*[29]	Unclear	Unclear	Low	Low	Unclear	Low	Low
Shai *et al.*[27]	Low	Unclear	Low	Low	Low	Low	Low
Yancy *et al.*[30]	Low	Unclear	Low	Low	High	Low	High

Discussion

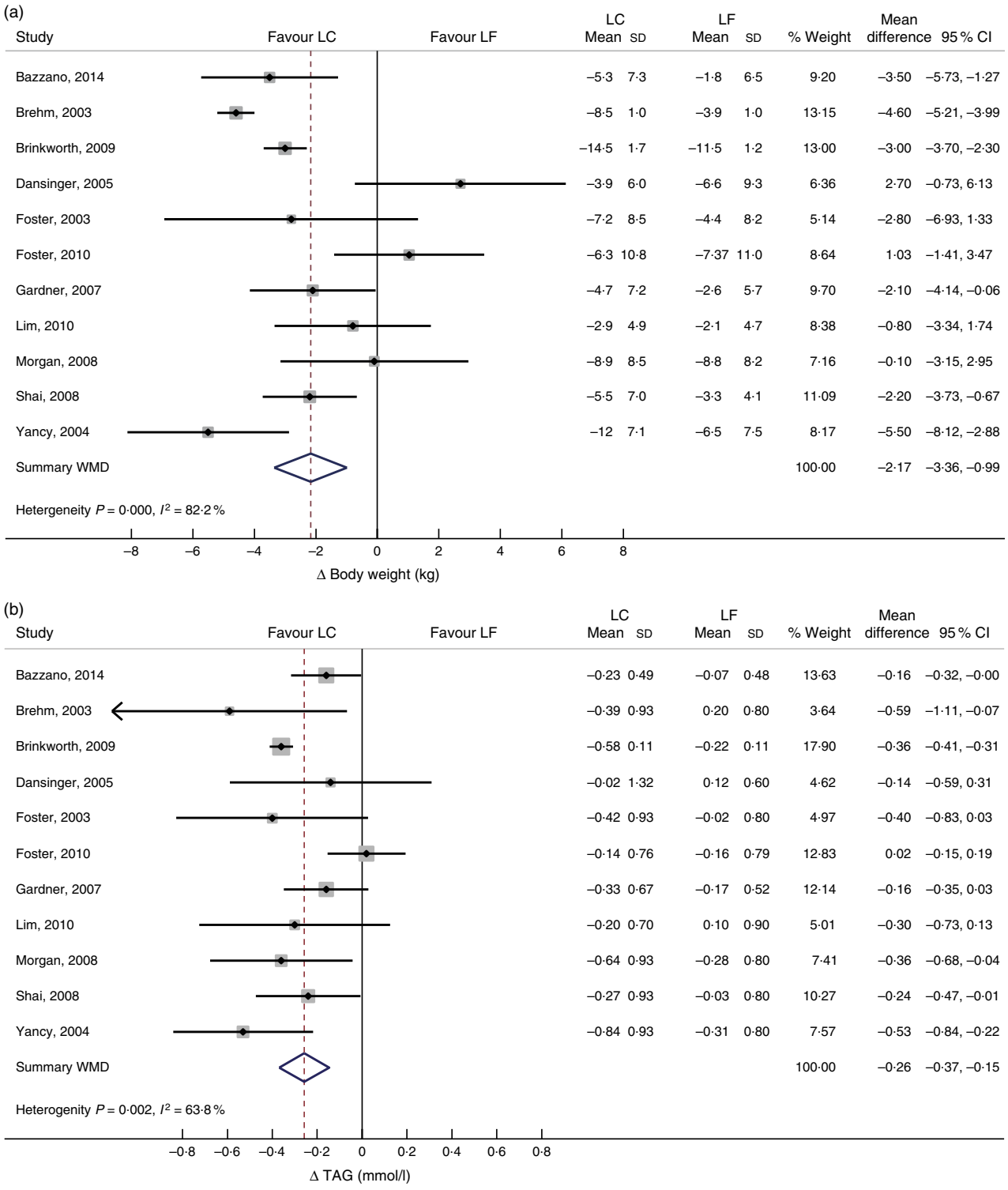
In this meta-analysis, we compared the effects of LC diets with LF diets on weight loss and CVD risk factors. Compared with subjects on LF diets, subjects on LC diets experienced significantly greater weight loss, greater TAG reduction and greater increase in HDL-cholesterol after 6 months to 2 years of intervention. Despite significant weight loss, subjects on the LC diet experienced a significant increase in LDL-cholesterol compared with their counterparts consuming an LF diet. Our findings suggest that the beneficial changes of LC diets must be weighed against the possible detrimental effects of increased LDL-cholesterol.

It is still uncertain how the beneficial effects of the LC diet such as weight loss, TAG reduction and HDL-cholesterol increase[12,21] translate into possible prevention of CVD. In epidemiological studies, HDL-cholesterol levels are inversely related to the risk of CHD[40], whereas results from studies on treatment that increase HDL-cholesterol levels have so far been disappointing[41]. Further, large Mendelian randomisation studies indicate that increased HDL-cholesterol cannot be translated into a reduction in CVD risk[42,43]. Thus, whether an increase in HDL-cholesterol levels is directly related to the reduction in risk of CHD is yet to be demonstrated[15]. On the other hand, increased levels of LDL-cholesterol are clearly associated with increased risk of CVD[18,19]. A number of studies have previously reported increased LDL-cholesterol levels in subjects on LC diets, recognising the concerns associated with this change in LDL-cholesterol concentration[12,14,15,35]. Consequently, a LC diet may not be appropriate for subjects at increased risk for CVD[11,28,36].

Blood concentrations of LDL-cholesterol are expected to decrease with moderate weight loss[44]. The significant weight loss and increase in LDL-cholesterol in the LC *v.* LF groups in the present meta-analysis are consistent with several other meta-analyses[12,15,16], but not all report significant differences in weight loss between the LC and the LF groups[15]. Hu *et al.*[21] concluded that dieters on a LC diet experienced less reduction of LDL-cholesterol, although both groups experienced similar weight loss. Concerns regarding lack of decrease and the great individual variability in LDL-cholesterol levels among dieters on the LC diet have been raised[13,14,28,37].

Furthermore, the role of a greater decrease in TAG concentrations among LC dieters is uncertain, as reduction of TAG below a specific target has in itself not been proven to reduce risk of CVD[23]. In addition, the associated alteration of the LDL-cholesterol phenotype from small dense LDL to greater LDL has been associated with reduced atherogenicity[18,19]. Notably, large, dense LDL-cholesterol particles are also associated with increased CVD risk, especially together with low TAG levels[18]. Morgan *et al.*[29] reported that the LC and LF diets produced different effects on the LDL-cholesterol particle size, depending on the subjects' initial LDL-cholesterol phenotype, but with greater and less-dense LDL-cholesterol particles in subjects following the LC diet. Others have shown that subjects with large LDL-cholesterol particle size (pattern A) had small, dense LDL-cholesterol particle size (pattern B) after being on a LF diet[45]. Importantly, the lack of evidence that a change from pattern B to pattern A leads to reduced CVD risk weakens the impact of this discussion for the general population. Only one study in the current meta-analysis investigated LDL-cholesterol particle size[29]. The authors reported that subjects on both LC and LF diets achieved an increase in LDL-cholesterol particle size, but it was difficult to establish a relationship between the dietary effects on LDL-cholesterol and shift in particle size[29]. This supports the view that weight reduction itself leads to a shift towards pattern A. The dietary effects on LDL-cholesterol particle size warrant further investigations, especially with regard to establishing whether some individuals can benefit from one diet over another.

Several studies showed that macronutrient composition did not seem to be the determining factor in the effectiveness of losing weight when energy intake is also decreased[14,29,36,38]. LC dieters reduced the energy intake upto 30 %, which was a significant reduction compared with baseline intake and comparable with subjects on the LF diet[11,27–29,30,36,38]. These findings support the assumption that the weight loss observed among LC dieters is mainly due to reduction in energy intake rather than macronutrient composition[44,46]. All the information available on energy intake in the LC and LF groups is presented in Table 1. Unfortunately, there is a general lack of information detailing actual energy intake



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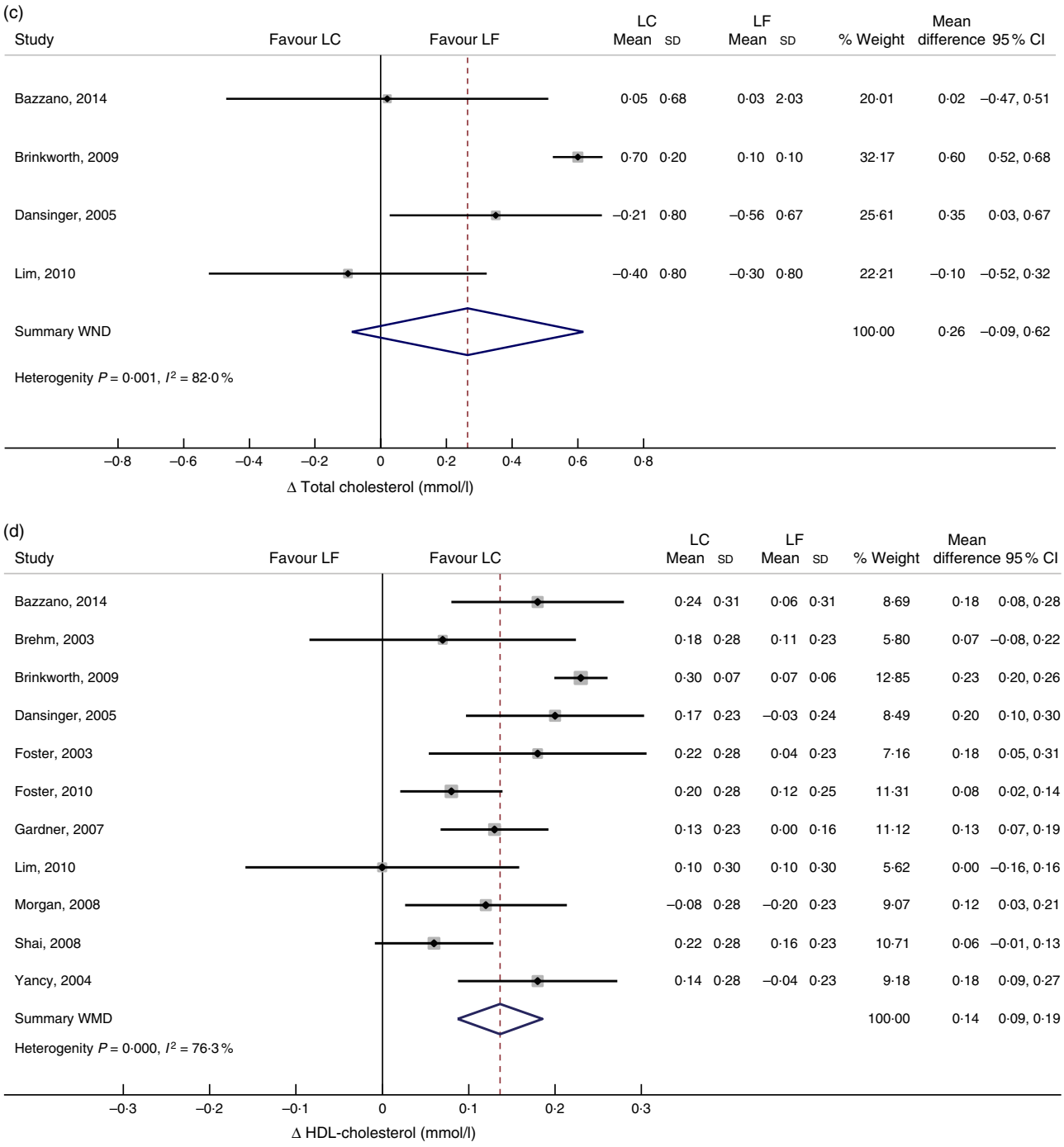
among subjects, and therefore some uncertainty is associated with the effect of macronutrient composition *v.* energy intake on weight loss and on other CVD risk factors. Plausible causes for reduced energy intake on a LC diet are increased satiety due to high intake of fat and protein and increased attention to dietary behaviour[28,30,46].

A strength of this meta-analysis is the inclusion criteria, particularly the strict definition of the LC diet in an attempt to achieve consensus between the different studies. Previous meta-analyses have included studies with CHO ranging from 20 g/d upto 40–45 % at the beginning of the intervention[15,21], whereas our meta-analysis included only studies with an intake



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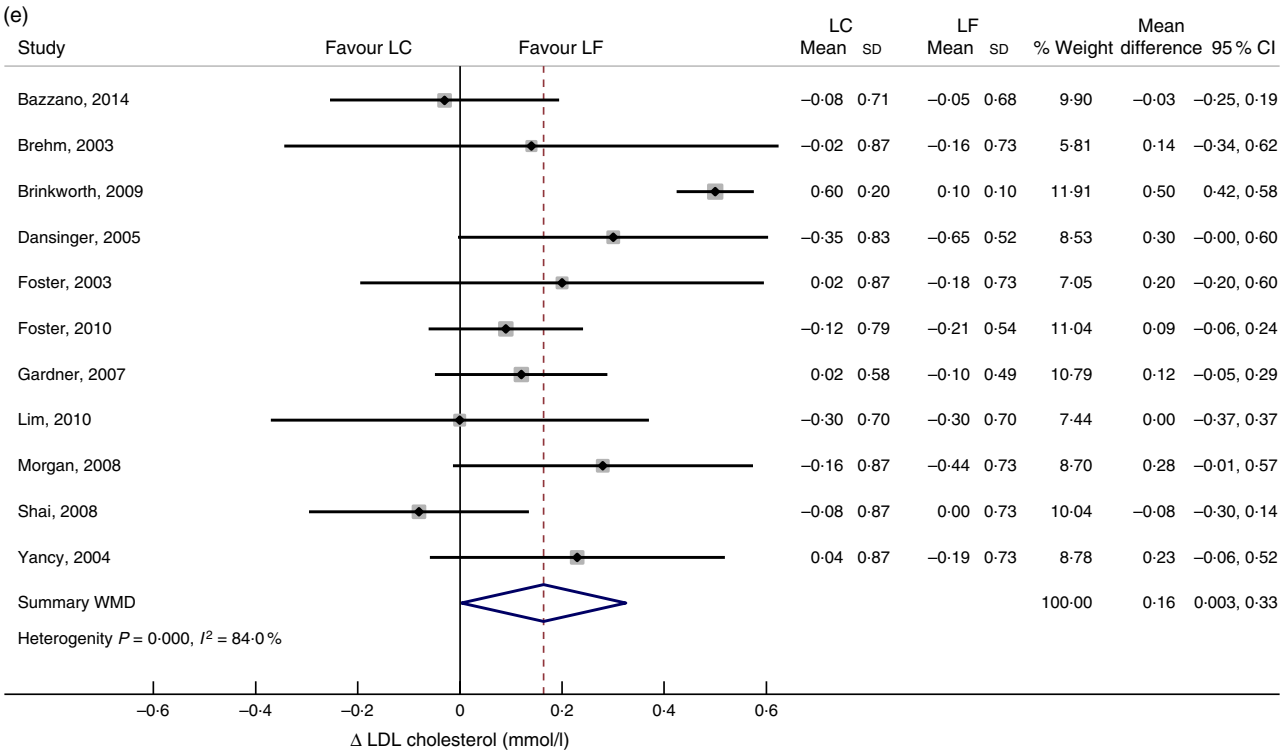
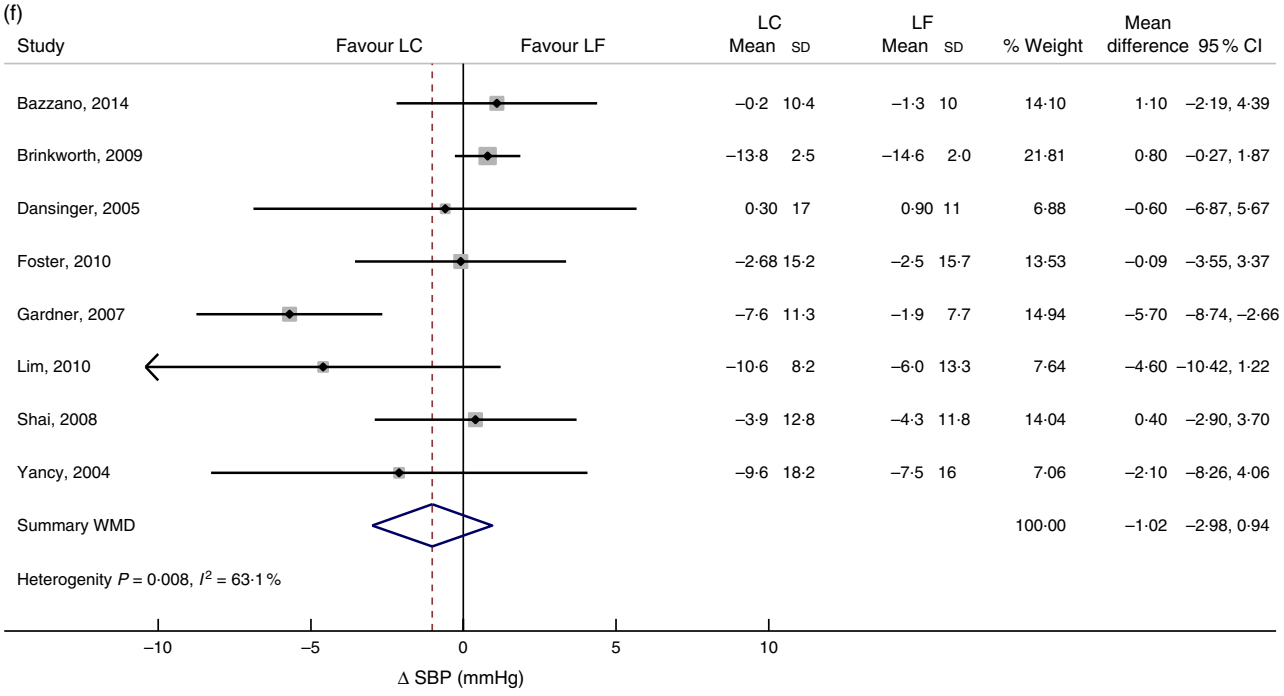
of no more than 20–30 g/d of CHO in the first phase or CHO intake of <20 % of total energy intake. Another strength is the inclusion of only RCT performed in healthy adult subjects with intervention ≥6 months. Six months is too short when speaking of long-term effects, but as a few studies have longer duration, we believe that this inclusion criterion was as close as possible to study the long-term effect on changes in CVD risk factors, such as lipid values and body weight.

The current meta-analysis has several limitations. First, heterogeneity was moderate to high for all variables. Sensitivity analyses suggested influence of some of the individual studies for some variables, although the WMD results remained near similar after their exclusion. Second, the observed asymmetry in some of the funnel plots raises the possibility of publication bias. Presence of publication bias could be due to unpublished studies or if some findings have been suppressed, distorted or emphasised in a scientifically unjustified manner, resulting in an inaccurate measure of the effect of LC diets on weight loss and CVD risk factors. However, the trim-and-fill analysis did not change the estimates, indicating that the effect of publication





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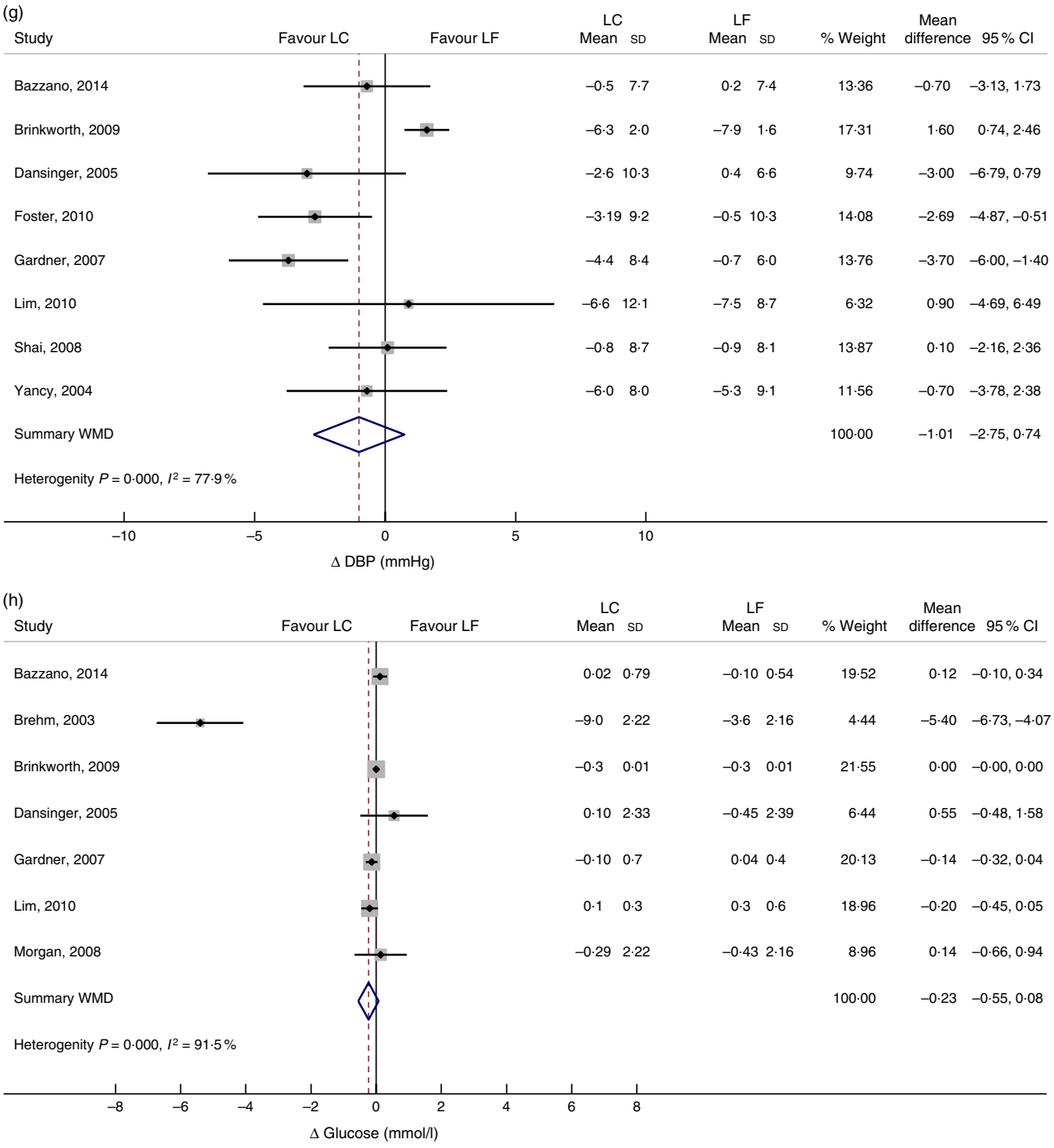
bias in the present meta-analysis could be minor. Importantly, the Egger's test has low power when there are <10 studies in the meta-analysis[47]. Our analyses included eleven studies for body weight, TAG, HDL and LDL, but less than ten studies for TC, SBP, DBP, glucose and insulin, which may have resulted in too low power to detect asymmetry. However, the majority of published meta-analyses contain ten or fewer studies[48]. Third, the high dropout rates of the included studies, with an average of 31 % for both the LC and LF groups must be taken into consideration. Different follow-up systems were used in the studies, ranging from self-help format to intensive dietary counselling. Studies have shown that close follow-up and support in a weight-loss process increases chances of greater weight loss[27,36,49]. Several studies in this meta-analysis pointed



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out significant weight loss at certain times during the intervention, but not at the end of the intervention, which can possibly be attributed to weak adherence[15,27–29,37,38]. Seven studies in our meta-analysis reported the macronutrient consumption at the end of the intervention, where CHO intake ranged from 9–40 % of total energy intake[27,35]. Furthermore, from studying the data provided, LC dieters seemed to compensate with increased fat intake, ranging from 37–54 % of total energy at the end of the intervention, and generally a slight increase in protein intake. It is clear that, although similar diets were prescribed at the outset, some differences in macronutrient composition are undoubtedly inevitable when subjects were not given any further directions in terms of dietary intake. The large variations in the reported CHO intake (reflecting limited adherence) and differences in macronutrient composition could limit the generalisability and validity of the presented data. It is difficult to conduct a dietary intervention on free-living subjects and one cannot expect 100 % dietary adherence. Even if

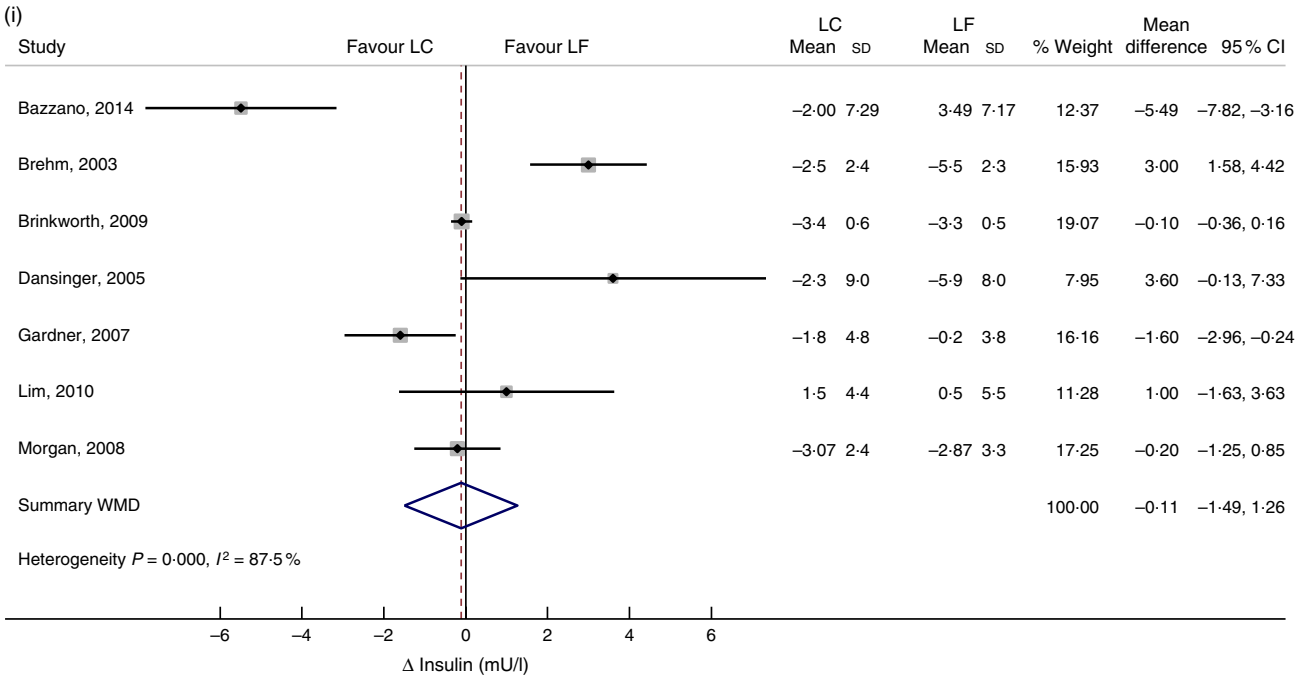

Fig. 2. Forest plots showing weighted mean differences (WMD) and 95 % CI. (a) Body weight (eleven studies); (b) TAG (eleven studies); (c) total cholesterol (four studies); (d) HDL-cholesterol (eleven studies); (e) LDL-cholesterol (eleven studies); (f) systolic blood pressure (SBP) (eight studies); (g) diastolic blood pressure (DPB) (eight studies); (h) glucose (seven studies); and (i) insulin (seven studies). The size of the square represents the weight that the corresponding study exerts in the meta-analysis. Studies are listed in alphabetical order. LC, low-carbohydrate diet; LF, low-fat diet.

macronutrient and energy settings were carefully imposed in dietary interventions, it is a limitation when subjects are left to report the food intake themselves. In addition, collection of dietary data differed between the included studies, and dietary assessment methods have limitations and involve significant measurements errors, such as under-or over-reporting of certain types of foods, people may forget to report certain foods or they report what is expected rather than their actual food intake. This is and remains one of the greatest limitations for all dietary interventions, and for this meta-analysis it is not an exception. Some of the uncertainty may, however, be reduced by including studies with approximately the same macronutrient content at the outset, which has been attempted in this meta-analysis, reflected by the strict inclusion criteria with regard to CHO intake. Moreover, as the studies were performed on overweight individuals, regarded as otherwise healthy, the results may not be applicable to individuals with obesity-related conditions such as diabetes, CVD and disturbances in lipid metabolism. Finally, multiple testing was not adjusted for, but each association was evaluated on its own merits and with respect to results in the literature.

In the present meta-analysis that included dietary interventions on individuals with increased BMI, but regarded as otherwise as healthy, we found a greater weight loss in subjects on the LC diet compared with subjects on the LF diet, more favourable changes in HDL-cholesterol and TAG levels and less favourable changes in LDL-cholesterol levels. However, none of the studies examined effects of the LC diet on hard end points, such as CHD and mortality, and it is therefore impossible to draw conclusions in this regard. Nevertheless, as LDL-cholesterol is highly atherogenic, we raise the question whether LC diets may increase morbidity and mortality in the long term. Thus, there is a need for studies of longer duration investigating effects on hard end points. Further investigations are needed, and may contribute to an improved understanding of the large variability in individual response to dietary intervention.

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K. J. V., N. M. and K. R.: designed the research; N. M. and K. J. V.: conducted the database searches, selected, screened, reviewed the articles and drafted the paper; K. J. V. and M. B. V.: analysed data and performed statistical analyses; M. B. V. and K. R.: critically revised the manuscript for important intellectual content; and N. M., K. J. V. and K. R.: had primary responsibility for the final content. All the authors read and approved the final version of the manuscript.

None of the authors has any conflicts of interest to declare.

Supplementary material

For supplementary material/s referred to in this article, please visit http://dx.doi.org/doi:10.1017/S0007114515004699

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