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Effects of carbohydrate restricted diets on low density lipoprotein-cholesterol levels in overweight and obese adults: a systematic review and meta-analysis of large randomised controlled trials of at least 6 months

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Abstract

Context

Carbohydrate restricted diets may increase low density lipoprotein-cholesterol and thereby cardiovascular risk.

Objective

A systematic review and meta-analyses was conducted to compare the effects of very low, low and moderate carbohydrate higher fat diets versus high-carbohydrate low-fat diets on low density lipoprotein-cholesterol and other lipid markers in overweight/obese adults.

Data Sources

Medline, PubMed, Cochrane Central, and CINAHL Plus were searched to identify large randomised controlled trials ($n > 100$) with duration ≥ 6 months.

Data Extraction

Eight randomised controlled trials (n = 1633, 818 carbohydrate restricted, 815 low fat diet) were included.

Data Analysis

Quality assessment and risk of bias, a random effects model, sensitivity and subgroup analysis based on the degree of carbohydrate restriction were performed using Cochrane Review Manager. Results were reported according to 'Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol'.

Results

Carbohydrate restricted diets showed a none significant difference in low density lipoprotein-cholesterol after 6, 12, and 24 months. While an overall pooled analysis statistically favoured low-fat diets [0.07 mmol/L; 95% CI 0.02, 0.13; p = 0.009] this was clinically insignificant. High density lipoprotein-cholesterol and plasma triglycerides at 6 and 12 months, favoured carbohydrate restricted diets [0.08 mmol/L, 95% CI 0.06, 0.11; $p < 1x10^{-5}$ and -0.13 mmol/L, 95% CI -0.19, -0.08; $p < 1x10^{-5}$] respectively. These favourable changes were more marked in the subgroup with very-low carbohydrate content (< 50 g/day) [0.12 mmol/L, 95% CI 0.10, 0.14; $p < 1x10^{-5}$ and -0.19 mmol/L, 95% CI -0.26, -0.12, p = 0.02] respectively.

Conclusions
Large randomised controlled trials of at least 6 months duration with carbohydrate restriction appear superior in improving lipid markers when compared to low-fat diets. Dietary guidelines should consider carbohydrate restriction as an alternative dietary strategy for the prevention/management of dyslipidaemia for populations with cardiometabolic risk.

Key words: low carbohydrate diet, low density lipoprotein cholesterol, lipid profile, cardiovascular disease, meta-analysis

Introduction

"All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time".

Austin Bradford Hill

The galloping global and upward trend in obesity/overweight prevalence and the epidemics of non-communicable diseases[1] is raising concern regarding the efficiency of existing dietary recommendations. Questions on the strength of the evidence on which these recommendations are based[2,3] as well as the role of saturated fatty acids (SFA), polyunsaturated fatty acids (PUFA), and refined carbohydrates in the on-set of cardiovascular disease (CVD) have historically been and continue to be debated.[4-9] Recently, an ample amount of evidence suggests that carbohydrate restricted diets (CRDs) including low, moderate, and very low carbohydrate ketogenic diets (LCD, MLCD, VLCD respectively) have the potential to improve various metabolic pathways with the added beneficial effects in treatment of overweight/obesity, and in amelioration of cardiometabolic risk markers.[9-14] VLCD are often interchangeable with the terminology, 'ketogenic diet' (KD). The underlying mechanism of a KD is reduction in the levels of circulating insulin along with increased levels of glucagon due

to scarcity of dietary carbohydrates, leading to a reduction in lipogenesis and fat accumulation.[15-17] This results in an increased mobilization of fatty acids from adipocytes and overproduction of ketone bodies, which are used as an alternative fuel to glucose by the extra-hepatic tissues such as the brain and the muscle.[15-18] Ketone bodies also reduce the catabolism of lean body mass, which in large explains the preservation of lean tissue observed during very low carbohydrate dieting.[12,19]

The main concern regarding CRDs, which are potentially high in total and SFA, is their theoretically adverse effect on low density lipoprotein-cholesterol (LDL-C) levels and presumably, CVD risk. Saturated fat per se is not associated with increased CVD risk, as concluded in several recent meta-analyses and systematic reviews[6,20,21] due, to some extent, to the differential effects of saturated fat on LDL subclass concentrations. Namely, cholesterol-enriched large buoyant LDL particles (lbLDL) have shown to be less atherogenic, while small dense (sdLDL) and medium sized LDL particles more strongly associate with CVD outcomes.[22-26] Data suggest that a shift towards lbLDL occurs among participants following a CRD, resulting in a decreased CVD-risk, while the opposite occurs among those on high-carbohydrate diets.[27] However, the role of low-carbohydrate ketogenic diets in the long-term management of obesity and cardiometabolic risk markers is not well established. Data from recent systematic reviews and meta-analyses regarding LDL-C are very contradictory. While some find an increased level,[28-30] others report non-significant changes[31] or decreased levels[32] of LDL-C in subjects following CRD compared to those on a low fat diets (LFD).

Due to the lack of consensus on the effects of CRD on LDL-C between these findings, authors have been very cautious in making recommendations for or against them. This has also led to deepening the disagreement among experts[2] and further uncertainty for the public especially regarding the long-term effectiveness of CRDs, pointing towards the need to further reconsider and evaluate the existing scientific evidence. The lack of consensus could be partially assigned

to the heterogeneity of the CHO content in interventions as definitions of CRDs differ,[14] and/or in inclusion and exclusion criteria used during the selection procedures of performed meta-analyses. For example, some meta-analyses include trials of both healthy and diabetic patients[32] and many report only the pooled net effect of large and small trials without stratification by duration of intervention or follow up.[28-30] Small studies may overestimate intervention effects, introduce higher heterogeneity and increase risk of selection bias[33-36] while larger studies are considered to have more power to detect differences in observed outcomes and are more likely to generate conclusions that can be generalised[37]. Based on these limitations, Santos *et al*.[38] performed a meta-analysis of randomised controlled trials (RCTs) with at least 100 overweight/obese healthy participants. This study reports an initial increase of LDL-C in the period 0-6 months, followed by a significant decrease at 12 and 24 months, and overall significantly favourable effect of the CRD on the main cardiometabolic risk markers. Though well designed and important, the limitation of this meta-analysis lies in the fact that the final effects are compared to the baseline values with no comparison against LFDs.

In light of these shortcomings and contradictory findings, the aim of this systematic review and meta-analysis is to compare the effects of CRD and LFD on LDL-C and other lipid markers in overweight/obese adults, using data obtained from large RCTs with at least 6 months' duration. This research also pertains to suggest the choice of diet that would be most effective for prevention and management of dyslipidaemia in population groups at higher risk of cardiovascular disease (e.g. obesity, overweight, metabolic syndrome, type 2 diabetes) and to contribute to the discussion about whether current dietary guidelines should be reconsidered and adapted to the latest evidence.

Methods

This systematic review and meta-analysis is performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement[39] (Appendix S1) and the PICOS (Population, Intervention, Comparison, and Outcomes) (Table 1) criteria were used to define the following research question: Do long-term carbohydrate restricted, higher-fat diets have an adverse effect on LDL-C levels and presumably CVD risk among overweight/obese adults?

Search methods

The following databases were searched for relevant RCTs published between January 1970 and June 2017 with no restriction on language: Medline (EBSCO), PubMed, Cochrane Central, and CINAHL Plus. These databases were searched individually with advanced search strategies using various combinations of filters and controlled vocabulary in relation to both carbohydrate restricted diets and low fat diets in order to enhance precisions and sensitivity (Appendix 2. Furthermore, previous relevant meta-analyses, systematic reviews, and selected randomised controlled trials were manually searched for studies that met the inclusion/exclusion criteria.

Inclusion criteria and data abstraction

RCTs included in this research were required to compare the effects of carbohydrate restricted diets (CRD) (defined as ≤ 45% total energy intake (TEI) from CHO, including MLCD ≤ 45% - >26% TEI or 130 – 225 g, LCD as 10 - < 26% TEI or 50 – 130 g, and VLCD as < 10% TEI or < 50 g, and > 35% TEI from fat, fed ad libitum) versus a LFD (defined as ≤ 35% TEI from fat and ≥ 50% TEI from CHO, and restriction on total energy intake)[40,41] with outcomes on serum/plasma LDL-C and other lipid profile markers, namely total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C) and triglycerides (TG), published between 1970 and June, 2017. Large randomised controlled trials with duration of at least six months and with at

least 100 randomised adult participants (18-65 years) at the start of the dietary intervention, with a body mass index (BMI) > 25 kg/m^2 were included. The decision to include RCTs ≥ 6 months was based on the differential effects on LDL-C in shorter term versus longer term studies and lack of comparison to low fat diets at this duration, i.e. compared to baseline, LDL-C increases at 6 months but decreases at 12 and 24 months.[38]

Exclusion criteria

To increase power, reduce heterogeneity, and selection bias, [33-35,37], trials with a study population < 100 randomised participants were excluded. Trials with a specific pathology rather than obesity (such as diabetes, cancer, kidney or coronary heart disease), altered endocrinological state (such as pregnancy, lactation or menopause), trials with a duration < 6 months and trials which did not report standard deviation (SD) or 95% confidence intervals (CI) were also excluded.

Data extraction and quality assessment

In order to minimise potential bias during selection procedure, the duplicates of full articles retrieved for further assessment were independently read by two reviewers (T.G.H and R.A.B) to make a consent decision for inclusion. From studies with more than two interventions, the most suitable dietary interventions were chosen for comparison. The following data were collected: title, first author, year of publication, country, design of RCT (parallel, cross-over, factorial), blinding of participant and personnel (open, single, double), baseline characteristics of study participants such as age, sex, BMI, and total number of randomised participants, health status, and baseline LDL-C, HDL-C, TG and TC values, composition of diet, attrition, handling of missing data and overall and subgroup mean difference in outcomes with measures of variance (SD or 95% CI). The Cochrane Collaboration tool[42] was used for assessing methodological quality and risk of bias with the following categories: selection bias (random

sequence generation, allocation concealment), performance bias (blinding of participants and personnel and blinding of the outcome assessment), reporting bias (selective outcome reporting), and other biases. Publication bias was assessed with funnel plots. Disagreements were resolved by discussion and by seeking the opinion of the third independent reviewer (I.G.D.), as required by the PRISMA statement.[39]

Data synthesis and data analysis

Extracted data from eligible studies were first tabulated by outcome of interest and presented in mmol/L; data expressed in mg/dL were converted into mmol/L by multiplying the values with the factor 0.0259 for cholesterol and its fractions, and the factor 0.013 for conversion of TG. In studies reporting mean values and 95% CI, the SD was calculated. Intervention effects across trials were pooled to calculate weighted mean differences and the 95% CI for each continuous outcome (LDL-C, HDL-C, TG, TC) between baseline and 6, 12 and 24 months of intervention duration. The CRD arm was also divided into two subgroups based on the CHO-content: very low-carbohydrate diet (VLCD) with < 10% CHO TEI (< 50 g CHO) and moderate low-carbohydrate diet (MLCD) with 26-45% CHO TEI (130 – 225 g CHO).[43] Subgroup analyses were performed when possible in order to explore the potential effect of different CHO content on the primary and secondary outcome estimates. It is important to note that studies classified as low carbohydrate diets (LCDs) (10 – < 26% CHO TEI (50 – 130 g CHO)) which would fulfil the inclusion criteria were not identified. The Random Effects Model was used to account for heterogeneity in design and outcome variables, as the heterogeneity is incorporated in the total weighted efficacy of treatment, allowing for a greater variability of the estimate.[44] Heterogeneity and inconsistency (I^2) was calculated with the Cochran Q test. I^2 values > 50% and > 75% indicated moderate and high heterogeneity respectively.[42] In order to evaluate the relative influence on the pooled estimated effects, a sensitivity analysis was conducted by excluding studies that had less than 70% completion

rate, studies with a very low-fat diet, studies that were performed on women only, and on those with the lowest mean age of participants. For detecting the existence of publication bias and its possible effect on the performed meta-analysis, funnel plots as the most common method were used. All statistical analyses were performed using Review Manager (RevMan 5.3.5).

Results

Literature search

The flow of the study selection procedure which followed the literature search is summarised in Figure 1. Potential relevant records (308) were identified during the search of the databases and additional 17 were identified from screening of references. After initial screening and duplicate removal 252 records remained, of which 205 were excluded on the bases of interrogation of abstracts, and 47 full-text articles were retrieved for detailed review. Thirty-nine full-text records did not fulfil the set inclusion criteria and, after their removal, 8 RCTs remained eligible to be included in the meta-analysis. The reasons for exclusion of the 39 full-article trials are presented in Table 2[45-83]. Five trials[45-49] did not include LDL-C as an outcome; ten trials[50-59] were performed on participants with Diabetes mellitus and/or CVD; eleven trials[60-70] had less than 100 randomised participants; three[71-73] had duration < 6 months; two trials[74,75] did not report on SD or 95% CI; seven trials[76-82] were irrelevant with inappropriate intervention; and one trial[83] was dismissed based on high attrition rate and high risk of bias.

Study and participant characteristics

The main characteristics of the eight published articles eligible for meta-analysis are summarised in Table 3[84-91]. All eight RCTs were open and parallel group trials with no possibility for blinding of participants due to the polarity of diets. Intervention duration ranged from 6 to 24 months. Most of the trials offered some form of supportive dietary sessions and

213 professional contact and participants were encouraged to engage and maintain a certain level of
214 physical activity. However, none reported any record of the level of physical activity. Trials
215 were conducted on both sexes with a higher proportion of female participants, except for the
216 study by Gardner *et al*.[88] which was performed only on women. The mean age and BMI of
217 participants varied from 28.2 - 51.5 years, and 31.4 – 36.1 kg/m^2 respectively. All 8 trials[84-91]
218 with a total of 1633 participants (n = 818 on CRD, n = 815 on LFD) reported 6 months follow
219 up; 5 trials with a total of 1010 participants (n = 505 on CRD, n = 505 on LFD) reported 12
220 months outcome measures[84,86,87,89,90] and 2 studies with a total of 715 (n = 357 on CRD, n =
221 358 on LFD) reported data for 24 months.[86,91] According to the CHO content, the CRD
222 intervention was divided into two subgroups: VLCD and MLCD (Table 3). The VLCD-
223 subgroup consisted of four trials: three trials[86,88,90] followed the Atkins diet (Dr. Atkins New
224 Diet Revolution, 1998)[92], defined as < 20 g/d of CHO for the first three months, with a gradual
225 increase of 5 g/d after the third month up to 50 g/d CHO, while in one trial[84] the CHO intake
226 was restricted to < 40 g of CHO daily. The other 4 trials[85,87,89,91] restricted the CHO
227 consumption to about 35-40% of the total daily energy, making up the MLCD subgroup. CRD
228 interventions were *ad libitum* in all trials regarding energy intake, but some studies reported a
229 spontaneous reduction of energy intake.[87,88,90] LFD interventions permitted 50-65% of energy
230 from CHO and 20 - < 35% of energy deriving from fat across all trials, except for the trial of
231 Gardner *et al*.[88] with a very low fat (< 10%) high CHO (70%) intervention (Ornish) diet.[93]

232 Diet compliance was measured via three 24 h dietary recalls[84,87,88,91] or 7-day food
233 diaries.[86,89,90] In the study of Due *et al*.[85] dietary intake and compliance was assessed by fat
234 biopsy, while food was available from a custom made supermarket for the purpose of the trial
235 with supervised shopping. Attrition rate showed large variation, with dropout rates ranging
236 from 12-44%. All studies had applied Intention-to-treat analysis for the missing data. (Table
237 3). Reported baseline mean levels of LDL-C, HDL-C, TG, and TC varied across trials and

intervention, but were well balanced in both the CRD and LFD arm of intervention in each study (Table 4[84-91]).

LDL-C concentrations were directly measured except in the trials of Bazzano *et al*.[84] and Due et al.[85] where it was calculated using the Friedewald formula.[94] In the study of Klemsdal *et al*.[89] the assessment of LDL-C was not clearly stated. Three studies evaluated additional lipid profile markers that are of interest to the primary outcome: changes in LDL-peak density (g/L) reported by Morgan *et al*.[90], apolipoprotein-B concentration in the trial of Klemsdal *et al*.,[89] and concentration of the very low density lipoprotein cholesterol (VLDL-C) fraction in the study of Foster *et al*.[86]

Quality assessment and risk of bias

The quality and the risk of bias (%) across all included studies were assessed using the Cochrane Risk of Bias Tool and are presented in Figures 2 & 3[84-91]. Three studies did not clearly report on the sequence generation[89-91] and allocation concealment[86,89,90] used. Blinding of participants was impossible due to the nature of the trial. In addition, there was no blinding of the outcome assessors reported, but considering the fact that all outcomes are objective, it is unlikely that this has influenced the results of the RCTs. There was no evidence of selective reporting and five trials[84-88] showed low risk of attrition bias. Four studies[86,89-91] were judged to have a low risk of bias and no study received an overall score of 'high' in any assessed risk of bias category.

Meta-analyses

Effects of CRD and LFD on LDL-Cholesterol levels

Results from the primary meta-analysis regarding the mean difference of LDL-C concentration between CRD and LFD intervention at 6, 12, and 24 months (compared to baseline) are

presented in Figure 4[84-91] & Table S1. Although participants on the CRD intervention experienced a greater increase in LDL-C compared to the LFD, these changes are statistically non-significant regardless of intervention duration [6 months: 0.08 mmol/L; 95% CI -0.01, 0.18; P = 0.08], [12 months: 0.04 mmol/L; 95% CI -0.04, 0.12; P = 0.37] and [24 months: 0.10 mmol/L; 95% CI -0.01, 0.21; P = 0.06]. However, analysis of the global pooled effect between CRD and LFD interventions on LDL-C levels shows a significant weighted mean difference in favour of the LFD [0.07 mmol/L; 95% CI 0.02, 0.13; P = 0.009]. Significant (moderate) heterogeneity (I^2 = 58%; P = 0.009) for the estimated difference of LDL-C between both diets was observed only at 6 months. Sensitivity analysis (exclusion of studies one by one) was carried out to identify the possible studies that could explain this heterogeneity. After exclusion of the study of Foster *et al*.,[86] which had the highest weight effect, the heterogeneity considerably decreased (I^2 = 28%, P = 0.22), but did not significantly change the weighted mean difference of LDL-C (P = 0.25). However, exclusion of the study of Due *et al*.,[85] did not change the heterogeneity, but resulted with a statistically significant mean difference of LDL-C at 6 months in favour of the LFD (I^2 = 58%, P = 0.04). This is possibly because it is the smallest study and/or has the lowest mean age of participants of 29.8 (Table 3).

Subgroup analyses were performed to explore the possible influence of the CHO-content of the CRD intervention on LDL-C levels compared to the LFD-interventions. The very low carbohydrate subgroup (VLCD) with < 10% CHO TEI (Figure 5[84,86,88,90] & Table S2) and the moderate carbohydrate subgroup (MLCD) with 35–45% CHO TEI (Figure 6[85,87,89,91] & Table S3) did not cause any significant difference of LDL-C compared to the LFD regardless of duration of intervention. Both CRD-interventions, the VLCD and the MLCD, resulted with an overall non-significant mean change of LDL-C compared to the LFD-intervention and values were similar to the primary meta-analysis [for VLCD: 0.07 mmol/L; 95% CI -0.05, 0.18; P=0.27 and for the MLCD: 0.05 mmol/L; 95% CI -0.02, 0.12; P=0.16].

Effects of CRD and LFD on HDL-C and Triglycerides levels

The pooled global mean differences for HDL-C [HDL-C: 0.08 mmol/L, 95% CI 0.06, 0.11; P < $1x10^{-5}$] (Figure 7[84-91] & Table S1) and TG [-0.13 mmol/L, 95% CI -0.19, -0.08; P < $1x10^{-5}$] (Figure 8[84-91] & Table S1) showed an overall more favourable total effect of the CRD intervention. However, the mean differences for both parameters were significant at 6 months [HDL-C: 0.09 mmol/L, 95% CI 0.06, 0.12; P < $1x10^{-5}$ and TG: -0.18 mmol/L, 95% CI -0.25, -0.11; P < $1x10^{-5}$] and 12 months [HDL-C: 0.09 mmol/L, 95% CI 0.02, 0.15; P = 0.008 and TG: -0.11 mmol/L, 95% CI -0.18, -0.03; P = 0.005], but non-significant at 24 months [HDL-C: 0.05 mmol/L, 95% CI -0.00, 0.11; P = 0.06] and [TG: 0.01 mmol/L, 95% CI -0.12, 0.13; P=0.93]. High heterogeneity of 74% was observed for HDL-C at 12 months, which was considerably decreased after removal of the trial of Frisch *et al.*[87] without affecting the significance of the weighted mean difference (I^2 = 45%; P < $1x10^{-4}$).

The VLCD (Figure 9[84,86,88,90] & Table S2) showed a greater increase of HDL-C compared to the LFD throughout the entire observed period [for 6 months: 0.13 mmol/L, 95% CI 0.09, 0.16; P = $1x10^{-5}$; for 12 months: 0.13 mmol/L, 95% CI 0.09, 0.17; P = $1x10^{-5}$ and for 24 months: 0.08 mmol/L, 95% CI 0.02, 0.14; P = 0.01]. Regarding TG concentration, the VLCD was more favourable at 6 months [-0.24 mmol/L, 95% CI -0.32, -0.16; P = $1x10^{-5}$] and 12 months [-0.16 mmol/L, 95% CI -0.25, -0.06; P = 0.002] of the diet intervention, levelling its effect with the LFD group at 24 months [0.02 mmol/L, 95% CI -0.16, 0.02; P = 0.82] (Figure 10[84,86,88,90] & Table S2). Compared to the LFD, the MLCD showed more favourable effects regarding HDL-C and TG only for the initial period of 6 months of intervention duration respectively [HDL-C: 0.06 mmol/L, 95% CI 0.02, 0.10; P = 0.002] and [TG: -0.09 mmol/L, 95% CI -0.18, 0.0; P = 0.05] (Figures 11[85,87,89,91], 12[85,87,89,91], & Table S3). Based on the overall total effect, the subgroup analyses showed that the VLCD was more effective than the

MLCD for HDL-C and TG, suggesting that the amount of CHO in CRD interventions plays an important role and its effect depends on the duration of intervention (Table S2 & S3).

Effects of CRD and LFD on Total Cholesterol levels

TC as an outcome was reported only in six studies[84-87,89,91], which did not permit a meaningful subgroup analyses based on the CHO content of CRD interventions. The primary meta-analysis for the estimated mean difference of total cholesterol level (Figure 13)[84-87,89,91] & Table S1 revealed a negligible, but nevertheless more favourable significant effect of the CRD in the initial 6 months period [-0.01 mmol/L, 95% CI -0.01, -0.00; P = 0.02]. It is worth noting that though the estimated mean difference at 12 months was identical to the 6 month value, it showed to be statistically insignificant [-0.01 mmol/L, 95% CI -0.04, 0.3; P=0.78]. Both diets seemed to show no effect on total cholesterol level after 24 months of intervention [-0.00 mmol/L, 95% CI -0.01, 0.00; P = 0.66]. The combined total effect of all studies was statistically in favour of the CRD intervention but clinically meaningless [-0.00 mmol/L, 95% CI -0.01, 0.00; P = 0.002].

Effects of CRD and LFD on lipid markers not included in the meta-analysis

Results of the LDL-peak density in the trial of Morgan *et al*.[90] showed that after six months of intervention, this variable decreased within both dietary groups included in this RCT. However, the decrease of the LDL-peak density indicating an increase in LDL particle size was significantly greater than the control (no intervention group) only among participants on the VLCD diet. No significant changes of apolipoprotein-B after 12 months were found within and between dietary intervention groups in the trial of Klemsdal *et al*.[89] Decreases in VLDL-C levels reported by Foster *et al*.[86] were significantly greater in the CRD than in the LFD group at 6 months [LFD: -0.12 mmol/L; 95% CI -0.17, -0.08 vs CRD: -0.23 mmol/L; 95%CI -0.27, -0.19; P < 0.001] and 12 months [LFD: -0.09 mmol/L; 95% CI -0.16, -0.02 vs CRD: -0.21

mmol/L; 95% CI -0.27, -0.19; P = 0.009], but non-significant differences were found at 24 months [LFD: -0.05 mmol/L; 95% CI -0.12, -0.004 vs CRD: -0.05 mmol/L; 95%CI -0.12, -0.0007; P = 0.99]

Funnel Plots and Publication Bias

Upon visual inspection, all three funnel plots (Figures S1-3) appeared to be approximately symmetrical, therefore no evidence of publication bias was found. However, the small number of studies included in this meta-analysis means that the funnel plots must be interpreted very cautiously, and the possibility of publication bias cannot be ruled out.

Discussion

The present meta-analysis of large randomised controlled trials with duration of at least six months compared the effects of CRDs with different CHO content versus LFD on LDL-C levels as a primary outcome, and HDL-C, TG and TC as secondary outcomes. The primary meta-analysis of the effects of CRDs and LFD on LDL-C levels showed an overall significant weighted mean difference in favour of the LFD despite the non-significant changes at 6, 12 and 24 months of intervention duration (Figure 4). However, the subgroup analysis of LDL-C levels based on the CHO content of the CRD arm (Figures 5 & 6), showed non-significant net changes for both the VLCD and the MLCD diets throughout the whole observed period (6, 12 and 24 months). Further, participants on CRDs experienced negligible changes of TC levels after 6 months (Figure 13) and more favourable changes on HDL-C and TG at 6 and 12 months (Figures 7 & 8) resulting in overall more favourable net effects of CRDs compared to the LFD regarding these lipid markers. The comparison between VLCD and MLCD subgroups revealed the VLCD showed a marked increase and decrease of HDL-C and TG respectively (Figures 9-12). It is worth noting, however, that the analyses with a follow up of 24 months included only two trials.

The more favourable changes in several lipid parameters (HDL-C and TG) and non-significant changes of LDL-C in both the VLCD and MLCD subgroup analysis, despite the slight global increase in LDL-C, support the view that carbohydrate restriction, especially the VLCD, is more effective in improving investigated CVD risk markers. The presented findings with regard to LDL-C, HDL-C and TG weighted mean changes are relatively consistent with the findings of several other meta-analyses,[28,32,95] all concluding that CRDs are at least as beneficial as the LFD and thus proposing CRDs as an alternative tool for treatment of metabolic risk and obesity. These findings are also in line with the most recent meta-analyses by Mansoor *et al*.[29] and Lu *et al*.[30] investigating the effects of a CRD vs LFD on cardiovascular risk markers. While the Lu *et al*.[30] study showed an increase in LDL-C of 0.11 mmol/L (95% CI 0.205, 0.026) with the CRD, the authors emphasised the beneficial HDL-C raising effect of the CRD of 0.066 mmol/L (95% CI, 0.10, 0.033) equating to a 7.45% reduction in relative risk of CVD. However, Mansoor *et al*.[29] found an overall increase in LDL-C level of 0.16 mmol/L (95% CI 0.003, 0.33) with the CRD and highlighted its possible detrimental effect on CVD, stating this may outweigh the benefits of the increased HDL-C and decreased TG levels observed. The results of the present study show the inverse; the overall increase in LDL-C of 0.07 mmol/L (95% CI 0.02, 0.13) with the CRD in the primary meta-analysis equates to a 1.54% relative risk reduction in cardiovascular events.[96] With HDL-C the pooled increase of 0.08 mmol/L (95% CI 0.06, 0.11) reduces relative risk by 4.6% (using the latest evidence from the European Atherosclerosis Society).[97] Furthermore, the lack of significant difference for LDL-C at 6, 12 and 24 months and in the VLCD and the MLCD-subgroup analysis supports a negated risk of CVD from LDL-C. These differences are presumably due to the different inclusion/exclusion criteria during the selection process between the current and the two previous meta-analyses.[29,30]

Targeting LDL-C has been a conventional strategy in prevention and treatment of CVD and reduction of mortality rate[98,99] using statins that inhibit the 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase activity which decreases hepatic cholesterol production and upregulation of the LDL-receptor.[100] However, the reduction of CVD risk accomplished with this strategy, as it has been reported in several clinical trials,[101,102] is no more than 30%. The main limitations of this strategy lies in the observed atherosclerotic complications among participants even after reaching acceptable LDL-C goals[103] which is indicative of the presence of other risk factors beyond LDL-C that should be considered.

Extensive evidence has shown that parameters which take into consideration the role of triglyceride-rich remnant lipoproteins or non-HDL-C as an indicator of cholesterol within all the apolipoprotein-B (apo-B) particles (including LDL, VLDL, Lp(a), and to some extent, intermediate-density lipoprotein, chylomicrons, and chylomicron remnants) are superior to LDL-C in quantifying the atherogenic properties of lipoproteins.[104,105] In that context, non-HDL-C, TG, and the TC/HDL-C ratio are more strongly associated with increased CVD risk than LDL-C, as depicted in several prospective studies such as: the Lipid Research Clinics Program Longitudinal Follow-up Study with over 19 years of follow-up of CVD risk and mortality rate[106]; the Framingham Offspring Study[107]; the 11 year follow up of the EPIC (European Prospective Investigation Into Cancer and Nutrition) Norfolk prospective population study.[108] This study quantified the risk associated with these lipid parameters for each level of LDL-C, from low (< 2.59 mmol/L (100 mg/dL)) to high (> 4.14 mmol/L (160 mg/dL)) in non-fasting samples.[108] In addition, analysis of pooled data from nine RCTs on subjects with coronary artery disease undergoing serial intravascular ultrasonography, reports that the lower TC/HDL-C ratio lowers the risk of major adverse cardiovascular events and lower coronary atheroma progression rates.[109] The above evidence points to the residual risk when LDL-C lowering treatments have failed to reduce cardiovascular events, and recent

review articles suggest focus should turn to drug or diet treatment other than LDL-C lowering.[110,111] In the light of these consistent findings, it has been proposed that non–HDL-C be routinely used as a cost effective target in prevention and treatment of CVD risk.[109,112] Thus, when assessing the CVD risk of this negligible increase in total LDL-C concentration produced by the CRDs, the marked increase in HDL-C in parallel to a marked decrease of TG with an overall neutral effect on TC, as found in the current meta-analysis, must be acknowledged.

The strategy to target LDL-C concentration as a primary CVD risk marker also disregards the heterogeneity of LDL-particle number (LDL-P) and size as a function of atherogenecity, an important indicator particularly when LDL-C is not elevated. Namely, sdLDL particles (phenotype B) are more strongly associated with CVD outcomes than the lbLDL particles (phenotype A).[24,25,113,114] sdLDL particles are characterised by a longer plasma residence time, which results in higher particle oxidation and glycation, further reduction in size and increased accumulation within arterial intima.[26,113] Increased concentrations of sdLDL particles produced by delipidated larger atherogenic VLDL and large LDL, and direct de novo hepatic production, correlate with increasing TG and decreasing HDL-C levels.[25] Hence, increased TG concentration and higher TG/HDL-C ratios are superior predictors of an increasingly atherogenic LDL phenotype (phenotype B) than LDL-C, as it indicates higher levels of remnant lipoprotein particle cholesterol along with higher non-HDL-C and LDL density.[114,115]

Further, recent evidence suggests that apo-B and LDL-P concentration are superior to LDL-C and non-HDL-C for assessment of CVD risk,[116] particularly among subjects with metabolic syndrome and insulin resistance, as found in the Framingham Heart Study[117] and in the cohort of the Quebec Cardiovascular Study.[118] The concordance/discordance analysis of plasma apo-B and LDL-P in two large retrospective cohorts shows that the discordance of LDL-P > apo-B is associated with sdLDL particle size, insulin resistance and increased systemic

inflammation.[119] Evidence regarding the effect of CRDs on LDL-P size and apo-B in the published literature is scarce, which was also revealed during this study. In the presented systematic review, decreased LDL-peak density were reported by Morgan *et al*.[90] only among participants following the Atkins diet when compared to the control, while decreased VLDL-C concentrations were found by Foster et al.[86] These findings, though in favour of the VLCD, are not yet sufficient to make a meaningful judgement, as more large RCTs with longer duration are necessary in order to compare and critically discuss these variables. However, the results of the RCT conducted by Sharman *et al*.[120] show that a short-term (6 week) hypoenergetic VLCD (< 10% CHO TEI) led to improvement of cardiometabolic risk factors: increased mean and peak LDL-P size along with fasting serum TG, TG/HDL-C ratio, postprandial lipaemia, serum glucose and insulin resistance in overweight men.[120] Similar findings, namely, increase in peak LDL-P size, a shift towards lbLDL in participants who started with a predominance of sdLDL-P, and overall improvement of CVD and diabetic risk markers after a 6 week KD-intervention in normolipidaemic men with normal body weight[121] and after 12 weeks in subjects with atherogenic dyslipidaemia[11] were found.

The main argument against low-carbohydrate high-fat diets is the potential adverse effect on the TC and LDL-C levels as a result of a relative or absolute increase in dietary SFA due to CHO restriction,[4,7,14] although the magnitude of the effect shows variations in constellation to the specific diet quality and individual susceptibility.[5,122,123] Macronutrient dietary content with SFA intake is almost unavoidable, because these fatty acids are present in all fat-containing foods (dairy products, meats, egg yolk, and in some vegetable fats and oils). SFA are non-uniform compounds and their metabolic effects and potency to alter plasma lipids and lipoproteins depend on the composition of SFA in their structure. As an illustration, evidence suggests that palmitate increases LDL-C and the LDL-C/HDL-C ratio and may enhance thrombogenesis, while stearate does not affect these lipoproteins; laurate increases LDL-C and

457 HDL-C levels, and decreases TG concentrations and the TC/HDL ratio.[124,125] Despite the
458 persisting belief, saturated fats per se are not robustly linked with increased all-cause mortality,
459 CVD risk, ischemic stroke or type 2 diabetes, as concluded in several recent meta-analyses and
460 systematic reviews.[6,20,21] Though associated with increased LDL-C concentration, higher SFA
461 intake mainly increases the less atherogenic lbLDL,[126,127] confirmed also in a RCT among
462 participants assigned to a high-fat (46% fat) compared to a low-fat (24% fat) diet for 6
463 weeks.[128] Conversely, partial replacement of dietary SFA with CHO, particularly with fructose
464 and sucrose, results with production of elevated sdLDL-P and overall unfavourable effects on
465 the lipid profile, impaired glucose tolerance and insulin resistance[14,122,129,130]. In other words,
466 by shifting sdLDL-P towards lbLDL (phenotype B to A), dietary SFA seem to be protective
467 against the effect of CHO.

468 There is very little data available on the effects of different amounts of SFA on
469 cardiometabolic risk factors in participants following a CRD. Krauss *et al*.[71] found initial
470 reduction in TG, apo-B, LDL-C, sdLDL and TC/HDL cholesterol and increased LDL peak
471 diameter in subjects undergoing low/moderate carbohydrate intake (26% CHO) with different
472 amounts of SFA (7-9% and 15%) during weight-loss. However, after subsequent weight loss
473 and weight stabilisation, authors reported that improvements of these parameters were
474 significantly greater with the 54% CHO diet. Nevertheless, this clearly confirms that a
475 moderate short-term CHO restriction still has the potential to improve atherogenic
476 dyslipidaemia, even in the absence of weight loss or in the presence of SFA, while the LFD
477 seems to require weight loss for its effective improvement, as argued by Feinman & Volek.[27]
478 Hence, based on the above supporting evidence, the fear that CRDs might have adverse health
479 effects due to increased consumption of saturated fats in particular, would appear to be
480 groundless. This is also pointed out in several reviews.[7,9,14]

Dietary guidelines do not only shift the population away from SFA and towards increased CHO intake, but also encourage replacement of SFA with PUFA, without stating any specific type of PUFA. The pooled effects of a meta-analysis of RCTs[131] and 11 cohort studies[132] indeed provide evidence that substituting SFA with PUFA significantly reduces CVD events. However, substitution of SFA and trans-fats with n-6 PUFA without increasing n-3 PUFA, decreases HDL-C and increases oxidised LDL, resulting with an increased risk of all-cause mortality (mainly cancer, CVD and coronary heart disease), as reported in the meta-analysis of Ramsden *et al.*[133] Thus, research and concerns should be more focused on the dietary guidelines that suggest replacing SFA with a specific dietary PUFA, as the beneficial claims regarding PUFAs in general may be even harmful as recently suggested.[14,122,130] The macronutrient content of both CRDs and the LFDs in the RCTs included in this meta-analysis is not clearly described as they are performed on free living adults, fed *ad libitum*. Nevertheless, the findings of this meta-analysis in light of the presented to date available evidence demonstrate lower non-HDL-C, and lower TG/HDL-C and TC/HDL-C ratios, supporting the claim that CRDs, especially the VLCD arm are more effective in the long-term reduction of CVD risk markers. Moreover, findings also suggest that the LFD in fact presents a potential risk as it contributes towards increased atherogenic dyslipidaemia.

Strengths and Limitations of the study

This is the first meta-analysis that compares the long-term effects between CRD vs LFD on LDL-C levels in adults. Its strength lies in the inclusion of large RCTs (n > 100 of randomised participants) as they have more power to detect intervention effects and are more likely to generate conclusions that can be generalised. Further, the duration of follow-up was 6-24 months, which enabled comparison of intervention effects at three points (6, 12 and 24

months) compared to the baseline values. Separating the CRD arm into VLCD and MLCD allowed the estimation, when possible, of the long-term effects of CRDs with different CHO content on LDL-C and other lipid parameters. However, this study has several limitations. The trials were performed on free living participants; hence the macronutrient content of both the CRD and the LFD arms remains unknown, making it impossible to separately investigate the effects of the macronutrient groups (CHO, lipids and proteins) and/or their subgroups on the outcomes of interest. Diet compliance was assessed via food diaries and 24 h diet recalls which may result in biased association due to inaccurate reporting in the trials[134,135] and subsequent discrepancies in effect estimates in the meta-analysis[136] which cannot be detected via the Cochrane Risk of Bias Tool.

Attrition rates between the CRD and the LFD were relatively similar, although adherence was decreasing after 6 months regardless of the type of intervention. This to some extend might explain the more distinct changes of all parameters during the first six months of intervention as subjects tend to return to their baseline dietary habits, which was outlined in the long-term RCTs included in this research.[86-88] This has also been confirmed in the three-year follow-up of a RCT[51], that found non-significant differences in carbohydrate consumption after 36 months between participants following either a CRD or a LFD. Hence, behavioural treatments to increase long-term compliance appear to be as important as the composition of the diet in prevention and treatment of CVD risk. Lastly, increased LDL-C may be an artefact due to the overestimation in trials where it is calculated by the Friedewald formula[94]; in cases when the TG level falls, as it happens amongst subjects on CRDs, even if TC and HDL-C remain unchanged, calculated LDL-C shows an increased level.[137]

Conclusions and Implications for future research

Undoubtedly, the overall 'picture' of this study demonstrates that carbohydrate restriction, especially the VLCD, shows superiority over the LFD in improving cardiometabolic risk markers due to the superior effects on HDL-C and TG with only negligible effect on LDL-C and no effect on TC. These favourable outcomes from the CRD, should be considered for the prevention and management of dyslipidaemia in population groups at higher risk of cardiovascular disease (e.g. obesity/overweight, metabolic syndrome, prediabetes and type 2 diabetes). The results of the presented meta-analysis suggest that the current guidelines should consider the latest evidence and carbohydrate restriction should be included as an alternative for individuals with increased cardiometabolic risk. In general, the number of well-designed large RCTs that would compare the long-term effects between the CRD and LFD on cardiometabolic risk markers in overweight and obese adults is very small. Large and long-term RCTs with emphasis on psychosomatic experiences of patients and their views on motivation to undergo diet-change, focus on the quality and quantity of dietary macronutrients, more accurate assessment of the lipid profile (LDL and HDL subfractions and particle number, concentration of apolipoproteins) and inflammatory markers are warranted. In addition, metabolomics analysis linking to the hallmark metabolite concentrations would provide an insight on a molecular level regarding inter-individual variation in response to the same dietary exposure and understanding of contradictions in data findings. Considering the epidemics of obesity and obesity related comorbidities, new nutritional approaches and more focused innovative interventions are needed in order to achieve lasting behavioural changes among population groups at higher cardiometabolic risk (obesity/overweight, metabolic syndrome, prediabetes, type 2 diabetes, and CVD).

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Supporting Information

Appendix S1 PRISMA checklist

Appendix S2 Search strategy

Table S1 Weighted mean difference of LDL-C, HDL-C, TG, and TC between CRD and LFD at 6, 12 and 24 months compared to baseline (mmol/L)

Table S2 Weighted mean difference of LDL-C, HDL-C and TG between VLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L)

Table S3 Weighted mean difference of LDL-C, HDL-C and TG between MLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L)

Figure S1 Funnel plot of the mean LDL-C differences (mmol/L) between CRD and LFD across trials (n=8)

Figure S2 Funnel plot of the mean HDL-C differences (mmol/L) between CRD and LFD across trials (n=8)

Figure S3 Funnel plot of the mean TG differences (mmol/L) between CRD and LFD across trials (n=8)

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Table 1: PICOS criteria for inclusion of studies

Parameter	**Inclusion criteria**
Population	Overweight/obese adult population (18-65) no restriction for sex
Intervention	Carbohydrate restricted diets
Comparison	Intervention vs Low-fat high-carbohydrate diet
Outcome: Primary	Low density lipoprotein-cholesterol
Secondary	High density lipoprotein-cholesterol, triglycerides, total cholesterol
Setting	Randomised controlled trials with at least 100 randomised participants and duration of at least 6 months

Table 2: Reasons for exclusion of full-text trials (n = 39)

Reason for exclusion	Authors
No LDL-C reported	Hu *et al*(2015)[45] McManus *et al*(2001)[46] Viegener *et al*(1990)[47] Zelicha *et al*(2017)[48] Blüher *et al*(2012)[138]
D. mellitus and/or CVD	Shai *et al* (2008)[50] Cardillo *et al* (2006)[51] Tsai *et al* (2005)[52] Stern *et al* (2004)[53] Dyson *et al* (2007)[54] Samaha *et al* (2003)[55] Yancy *et al* (2010)[56] Hu *et al* (2016)[57] Turer *et al* (2012)[58] Qi *et al* (2015)[59]
<100 participants on start	Lim *et al* (2010)[60] Das *et al* (2007)[61] Foster *et al* (2003)[62] Seshadri *et al* (2004)[63] Brehm *et al* (2003)[64] Keogh *et al* (2007)[65] Ebbeling *et al* (2007)[66] Bradley *et al* (2009)[67] Tay *et al* (2008)[68] Dansinger *et al* (2005)[69] Leichtle *et al* (2011)[70]
Short duration (<6 months)	Krauss *et al* (2006)[71] Petersen *et al* (2006)[72] Harvie *et al* (2013)[73]
No SD / 95% CI reported	Yancy *et al* (2004)[74] Westman *et al* (2006)[75]
Inappropriate intervention, irrelevant outcomes	Jenkins *et al* (2007)[76] Merra *et al* (2017)[77] Juanola-Falgarona *et al* (2013)[78] Wan *et al* (2017)[79] Le *et al* (2016)[80] Juanola-Falgarona *et al* (2014)[81] Rock *et al* (2016)[82]
High risk of bias, high dropout rate	Brinkworth *et al* (2009)[83]

LDL-C, low density lipoprotein-cholesterol; CVD, cardiovascular disease; SD, standard deviation; CI, confidence intervals.

Table 3. Characteristics of included trials

Author Country	Number CRD / LFD	Mean Age Sex	BMI	Duration (months)	Intervention CRD	Intervention LFD	Completed % CRD/LFD	Missing data
Bazzano *et al*(2014)[84]* USA	75/73	50 Both	35.4	12	<40 g/d CHO, ad libitum*	55% of energy from CHO, <30% fat	88/79	ITT analysis
Due *et al* (2008)[85]** Denmark	52/48	28.2 Both	31.4	6	<45% energy from CHO, 35-45% from fat, >20% of MUFA**	20-30% energy from fat, 50-55% energy from CHO	56/73	ITT analysis
Foster *et al* (2010)[86]* USA	153/154	45.5 Both	36.1	24	Atkins 20 g/d CHO, after 3 months gradual increase of CHO of 5 g/d, ad libitum*	55% of energy from CHO, <30% fat, limited energy intake	58/68	ITT analysis
Frisch *et al* (2009)[87]** Germany	100/100	47 Both	33.5	12	<40% energy from CHO, >35% from fat**	>55% CHO, < 35% energy from fat	95/89	ITT analysis
Gardner *et al* (2007)[88]* USA	77/76	41.3 F	32	12	Atkins 20g/d CHO, after 3 months gradual increase of CHO of 5g/d*	Ornish diet (70% CHO, 10% energy from fat)	88/78	ITT analysis
Klemsdal *et al* (2010)[89]** Norway	100/102	46.8 Both	35.4	12	35-40% energy from fat, 35% from CHO**	<30% energy from fat, 55-60% from CHO	78/84	ITT analysis
Morgan *et al* (2009)[90]* UK	57/58	40.7 Both	31.6	6	Atkins New Diet Revolution 20g/d CHO, after 3 month <50 g/d CHO**	Eat Yourself Slim – controlled low fat healthy diet + fitness	72	ITT analysis
Sacks *et al* (2009)[91]** USA	204/204	51.5 Both	33	24	40% energy from fat, 40% from CHO**	65% CHO and 20% fat, average protein	82/83	ITT analysis

*very low carbohydrate diet intervention; ** moderate low carbohydrate diet intervention
BMI, body mass index; CRD, carbohydrate restricted diet; LFD, low fat diet; CHO, carbohydrate; MUFA, monounsaturated fatty acids; ITT, Intention-to-treat

Table 4. Baseline lipid variables (mmol/L) among study participants by dietary intervention

Intervention	CRD				LFD			
Parameter mmol/L	LDL-C (SD)	HDL-C (SD)	TG (SD)	TC (SD)	LDL-C (SD)	HDL-C (SD)	TG (SD)	TC (SD)
Bazzano *et al* (2014)[84]	3.20 (0.9)	1.40 (0.32)	1.30 (0.6)	5.1 (1.1)	3.30 (1.0)	1.22 (0.3)	1.40 (0.9)	5.3 (1.1)
Due *et al* (2008)[85]	2.75 (0.8)	1.22 (0.6)	1.02 (0.37)	4.44 (0.74)	2.78 (0.9)	1.23 (0.42)	1.15 (0.8)	4.52 (1.04)
Foster *et al* (2010)[86]	3.11 (0.67)	1.20 (0.35)	1.28 (0.62)	4.88 (0.78)	3.21 (0.76)	1.18 (0.30)	1.40 (0.83)	4.98 (0.85)
Frisch *et al* (2009)[87]	3.54 (0.8)	1.49 (0.37)	1.31 (0.56)	5.50 (0.93)	3.56 (0.91)	1.46 (0.37)	1.59 (0.65)	5.54 (1.10)
Gardner *et al* (2007)[88]	2.82 (0.75)	1.37 (0.36)	1.41 (0.88)	na	2.87 (0.70)	1.29 (0.28)	1.3 (0.7)	na
Klemsdal *et al* (2010)[89]	3.76 (0.94)	1.28 (0.37)	1.93 (1.21)	5.8 (0.97)	3.84 (1.01)	1.29 (0.37)	1.91 (1.13)	6.0 (1.04)
Morgan *et al* (2009)[90]	3.72 (0.52)	1.22 (0.23)	1.65 (0.7)	na	3.59 (0.67)	1.22 (0.3)	1.59 (0.83)	na
Sacks *et al* (2009)[91]	3.21 (0.85)	1.27 (0.39)	1.52 (0.92)	5.26 (0.96)	3.31 (0.83)	1.24 (0.1)	1.66 (1.05)	5.15 (0.98)

CRD, carbohydrate restricted diet; LFD, low fat diet; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol, TG, triglycerides; TC, total cholesterol; SD, standard deviation.

Figure 1. Flow diagram of literature search

Figure 2. Quality assessment of each included study (n = 8) using the Cochrane Risk of Bias Tool

Figure 3. Risk of bias (%) across included studies (n = 8) using the Cochrane Risk of Bias Tool: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.

Figure 4. Forest plot for LDL-C changes between CRD and LFD at 6, 12, and 24 months compared to baseline (mmol/L). *Abbreviations:* CRD, carbohydrate restricted diet; LFD, low fat diet; LDL, low density lipoprotein.

Figure 5. Forest plot for LDL-C changes between VLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). *Abbreviations*: VLCD, very low carbohydrate diet; LFD, low fat diet; LDL, low density lipoprotein.

Figure 6. Forest plot for LDL-C changes between MLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). *Abbreviations*: MLCD, moderate low carbohydrate diet; LFD, low fat diet; LDL, low density lipoprotein.

Figure 7. Forest plot for HDL-C changes between CRD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). *Abbreviations*: CRD, carbohydrate restricted diet; LFD, low fat diet; HDL, high density lipoprotein.

Figure 8. Forest plot for TG changes between CRD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). *Abbreviations*: CRD, carbohydrate restricted diet; LFD, low fat diet; HDL, high density lipoprotein.

Figure 9. Forest plot for HDL-C changes between VLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). *Abbreviations*: VLCD, very low carbohydrate diet; LFD, low fat diet; HDL, high density lipoprotein.

Figure 10. Forest plot for TG changes between VLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). *Abbreviations*: VLCD, very low carbohydrate diet; LFD, low fat diet; TG, triglycerides.

Figure 11. Forest plot for HDL-C changes between MLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). *Abbreviations*: MLCD, moderate low carbohydrate diet; LFD, low fat diet; HDL, high density lipoprotein.

Figure 12. Forest plot for TG changes between MLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). *Abbreviations*: MLCD, moderate low carbohydrate diet; LFD, low fat diet; TG, triglycerides.

Figure 13. Forest plot for Total Cholesterol changes between CRD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). *Abbreviations*: CRD, carbohydrate restricted diet; LFD, low fat diet.

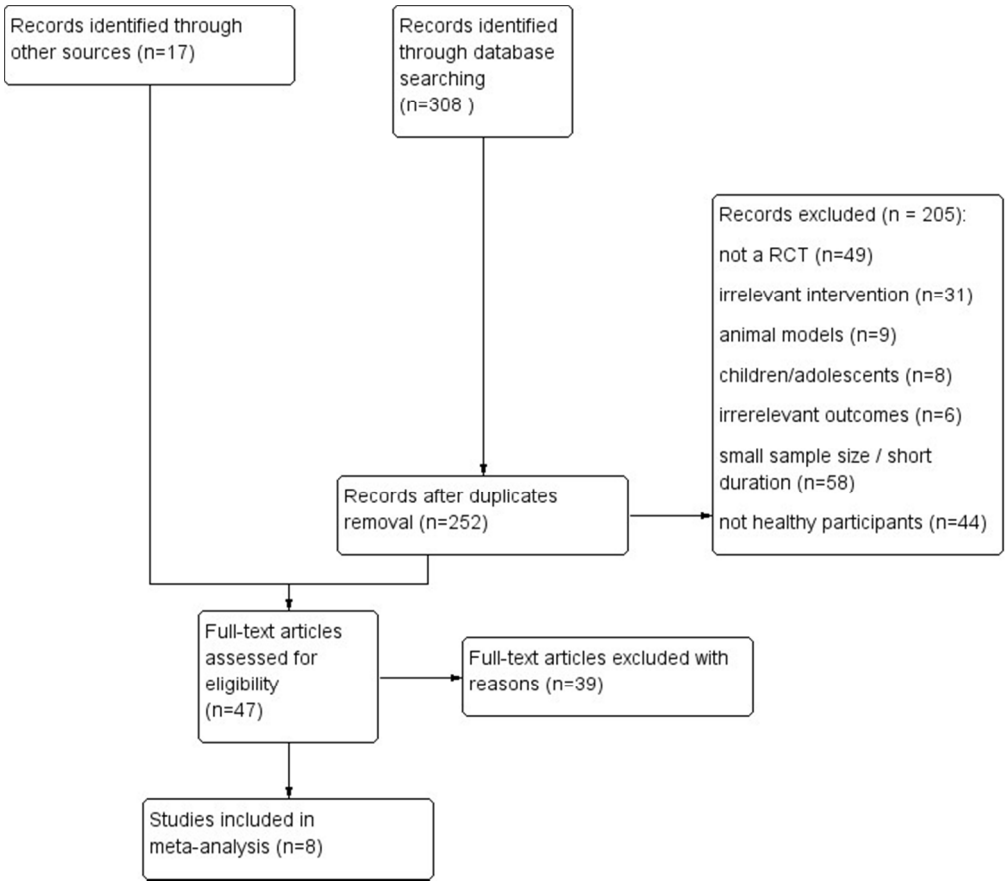

Figure 1. Flow diagram of literature search

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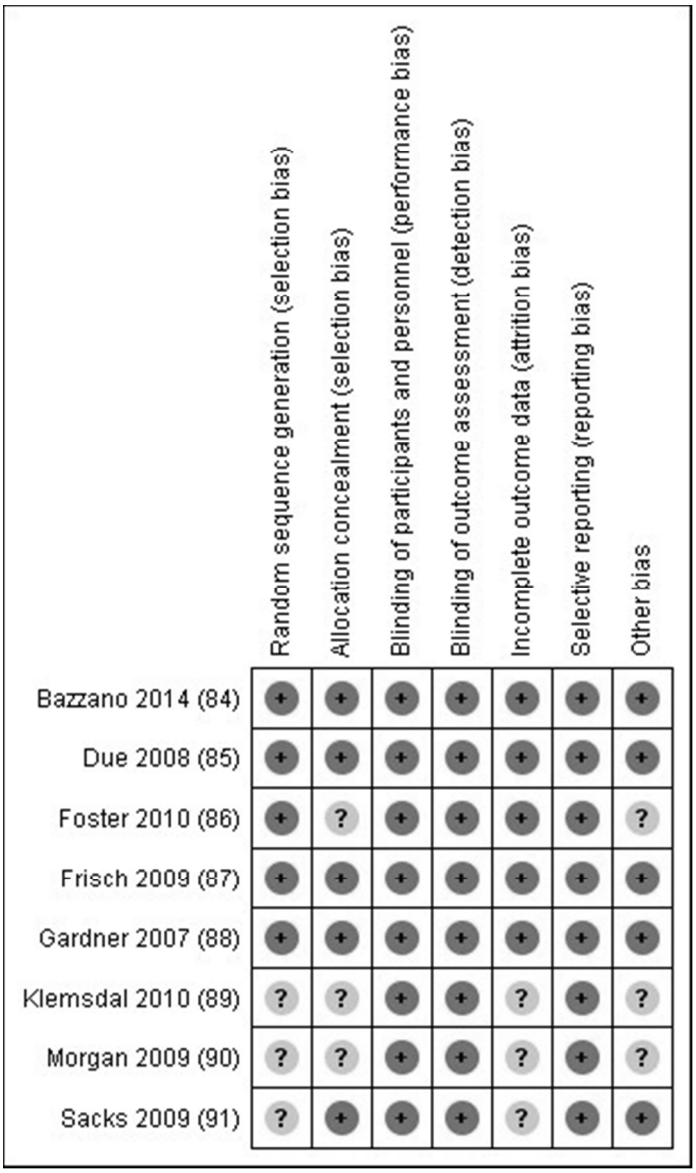

Figure 2. Quality assessment of each included study (n = 8) using the Cochrane Risk of Bias Tool

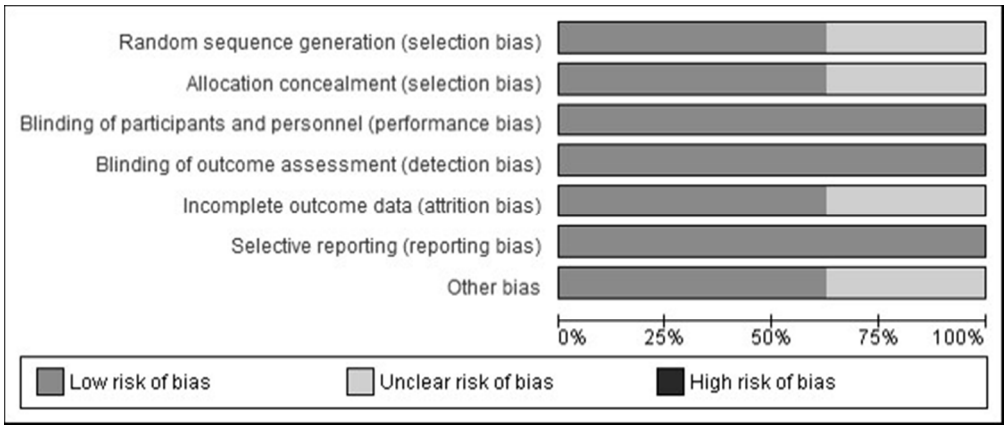

Figure 3. Risk of bias (%) across included studies (n = 8) using the Cochrane Risk of Bias Tool: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.

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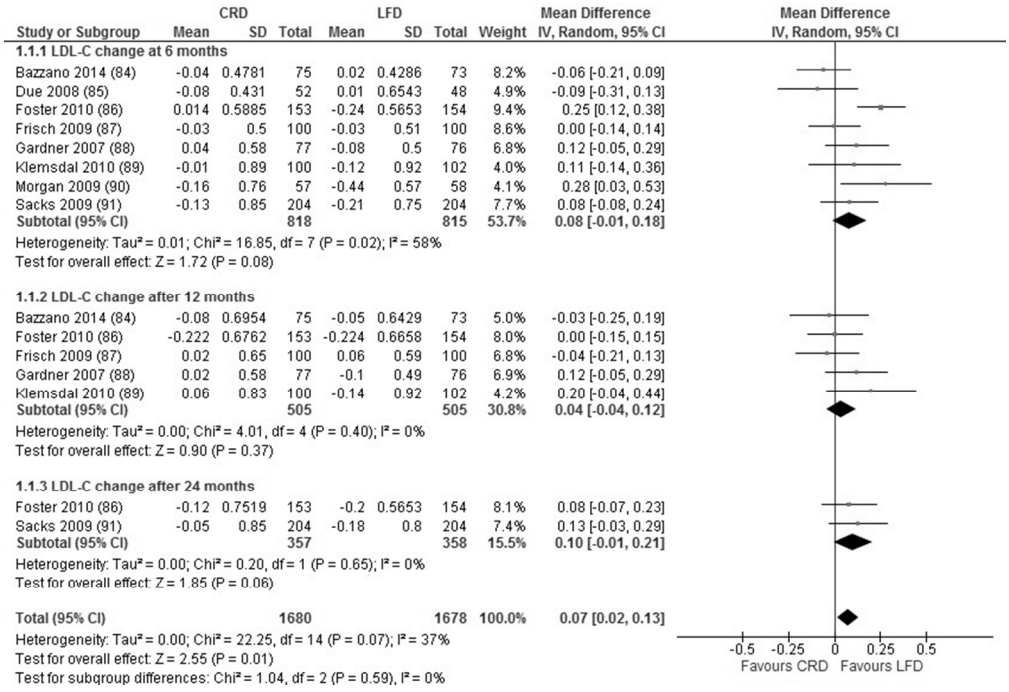


Figure 4. Forest plot for LDL-C changes between CRD and LFD at 6, 12, and 24 months compared to baseline (mmol/L). Abbreviations: CRD, carbohydrate restricted diet; LFD, low fat diet; LDL, low density lipoprotein.

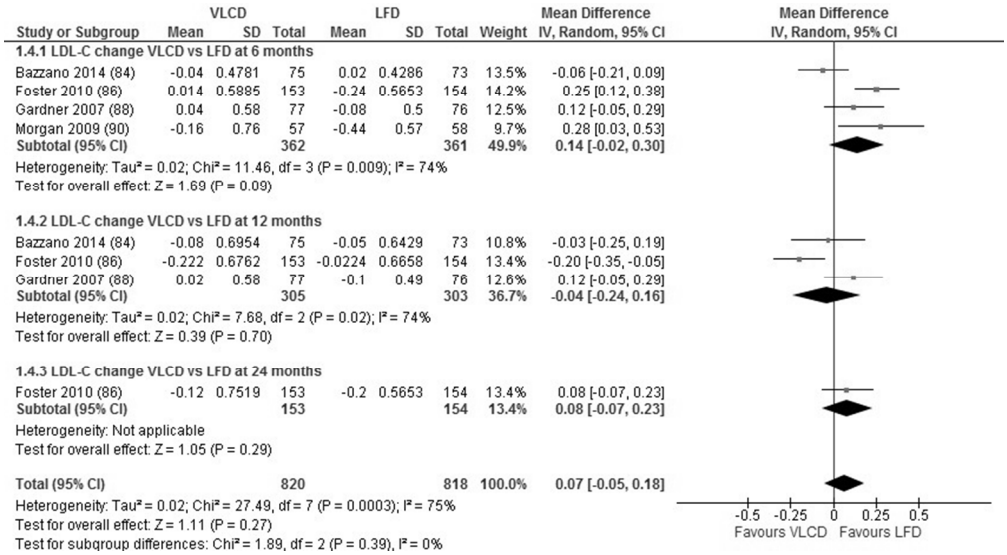


Figure 5. Forest plot for LDL-C changes between VLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: VLCD, very low carbohydrate diet; LFD, low fat diet; LDL, low density lipoprotein.

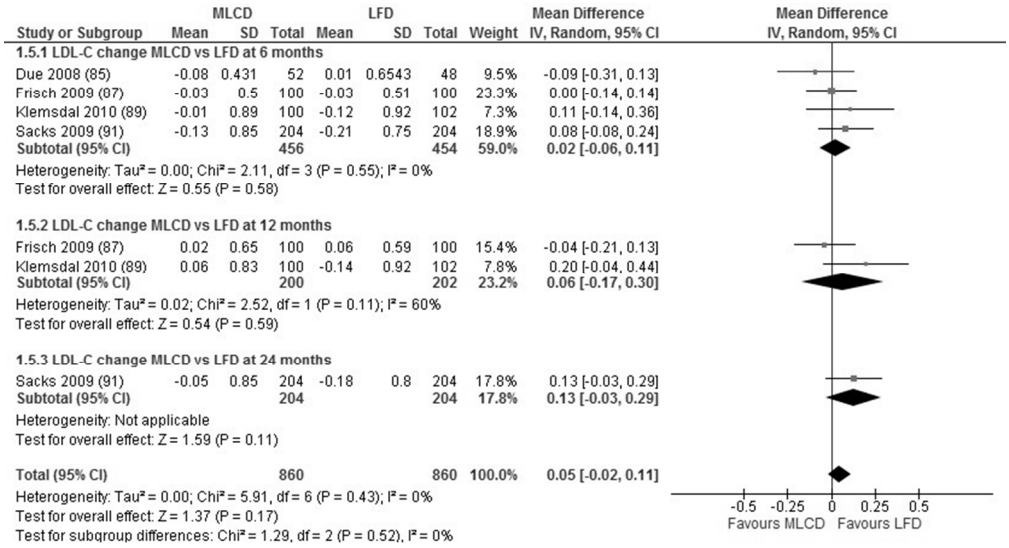


Figure 6. Forest plot for LDL-C changes between MLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: MLCD, moderate low carbohydrate diet; LFD, low fat diet; LDL, low density lipoprotein.

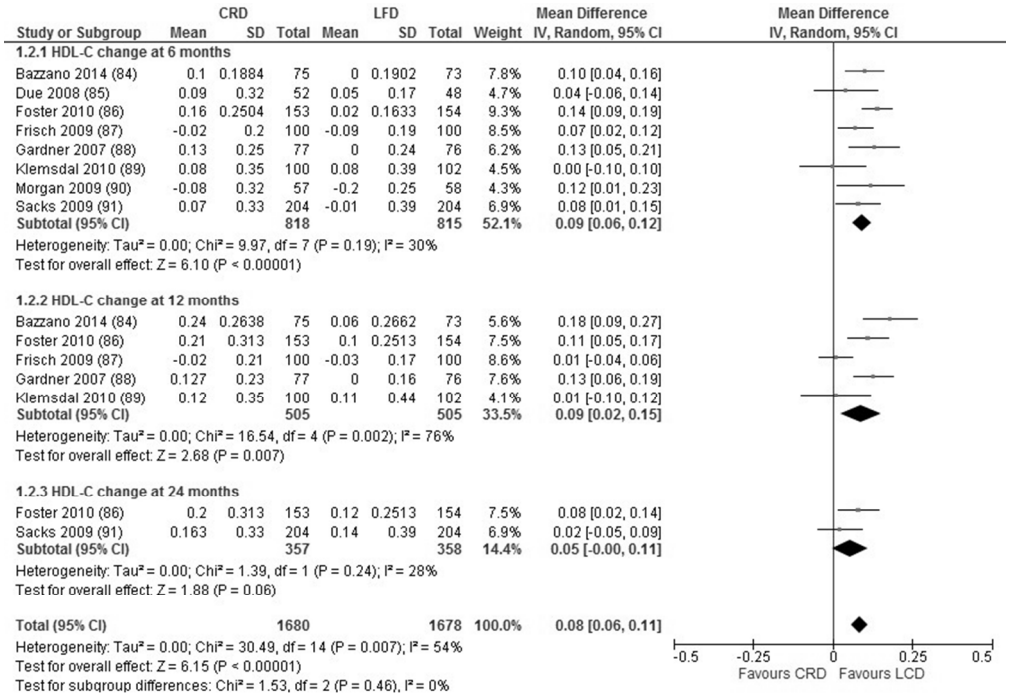


Figure 7. Forest plot for HDL-C changes between CRD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: CRD, carbohydrate restricted diet; LFD, low fat diet; HDL, high density lipoprotein.

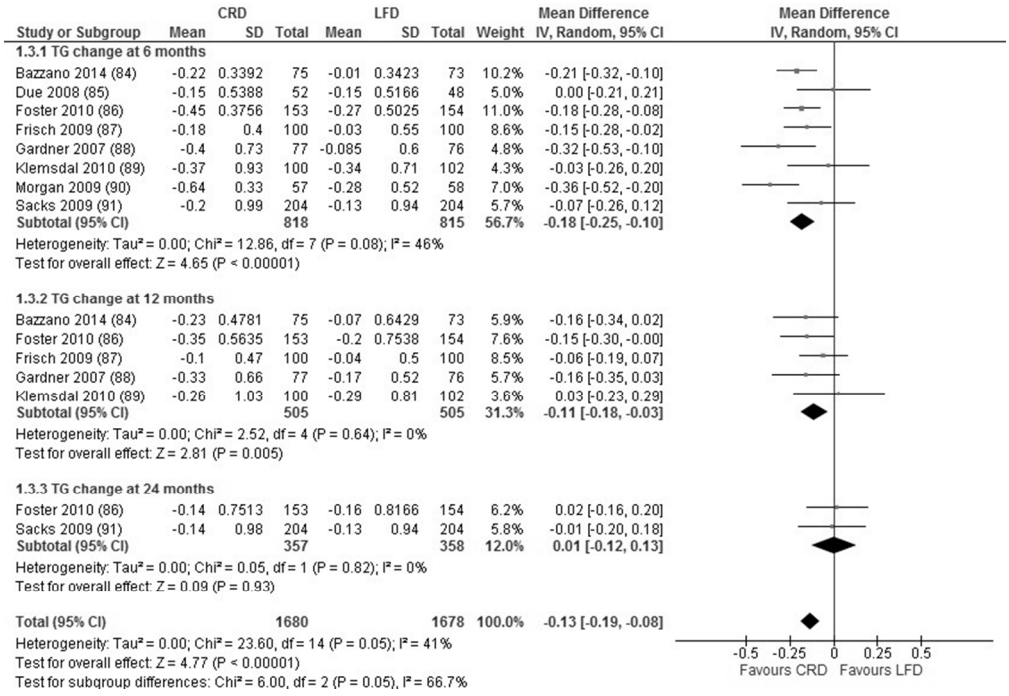


Figure 8. Forest plot for TG changes between CRD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: CRD, carbohydrate restricted diet; LFD, low fat diet; HDL, high density lipoprotein.

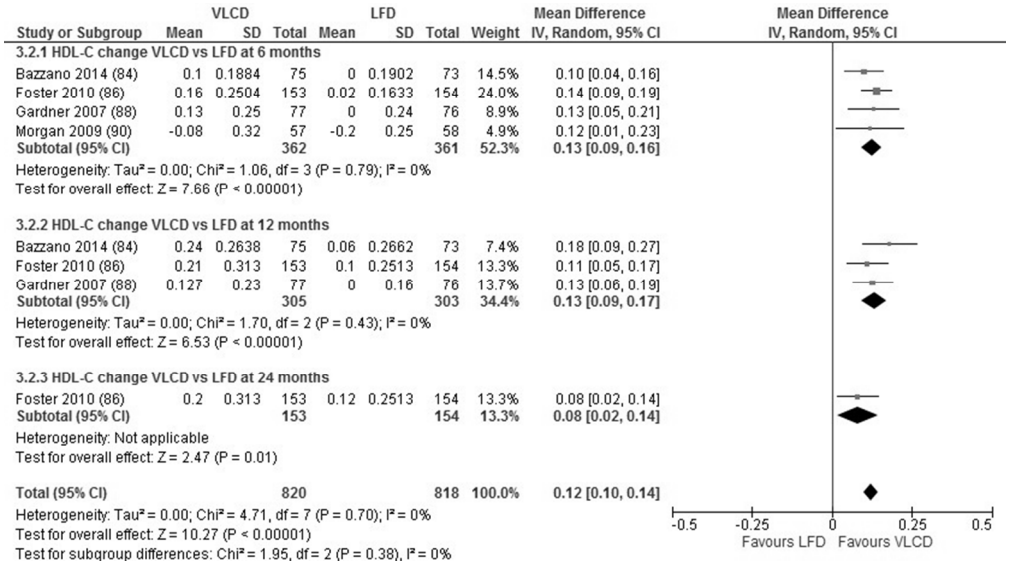


Figure 9. Forest plot for HDL-C changes between VLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: VLCD, very low carbohydrate diet; LFD, low fat diet; HDL, high density lipoprotein.

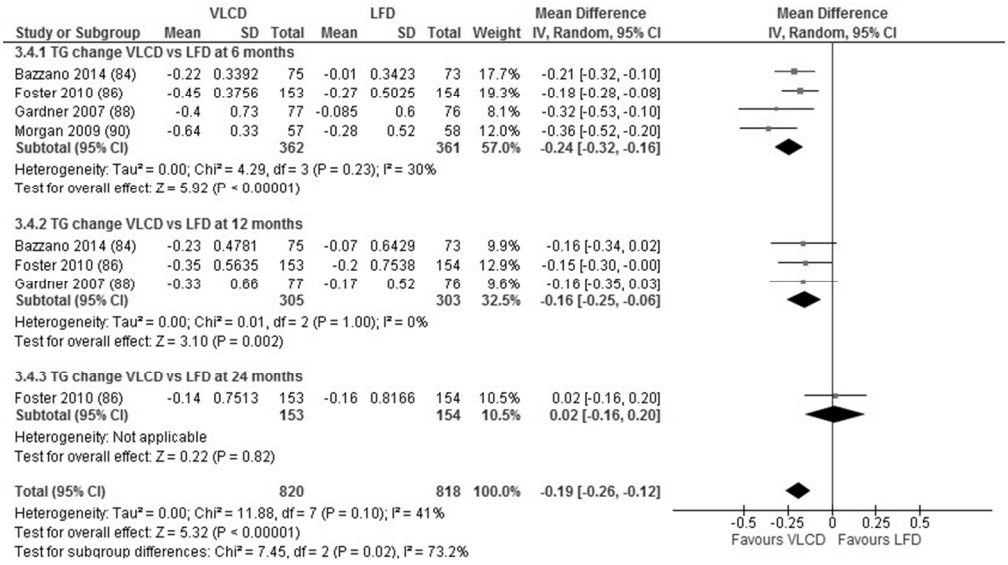


Figure 10. Forest plot for TG changes between VLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: VLCD, very low carbohydrate diet; LFD, low fat diet; TG, triglycerides.

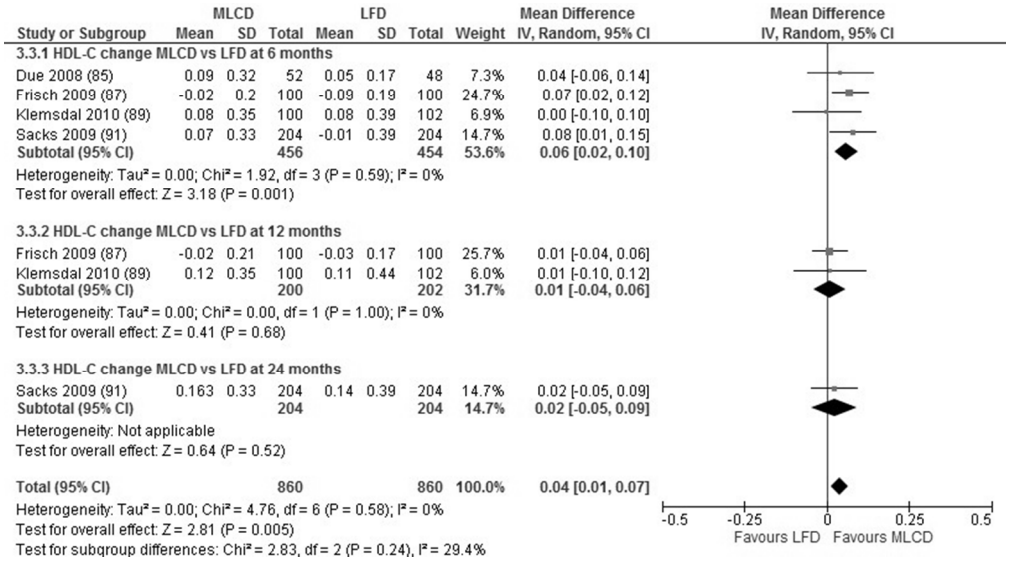


Figure 11. Forest plot for HDL-C changes between MLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: MLCD, moderate low carbohydrate diet; LFD, low fat diet; HDL, high density lipoprotein.

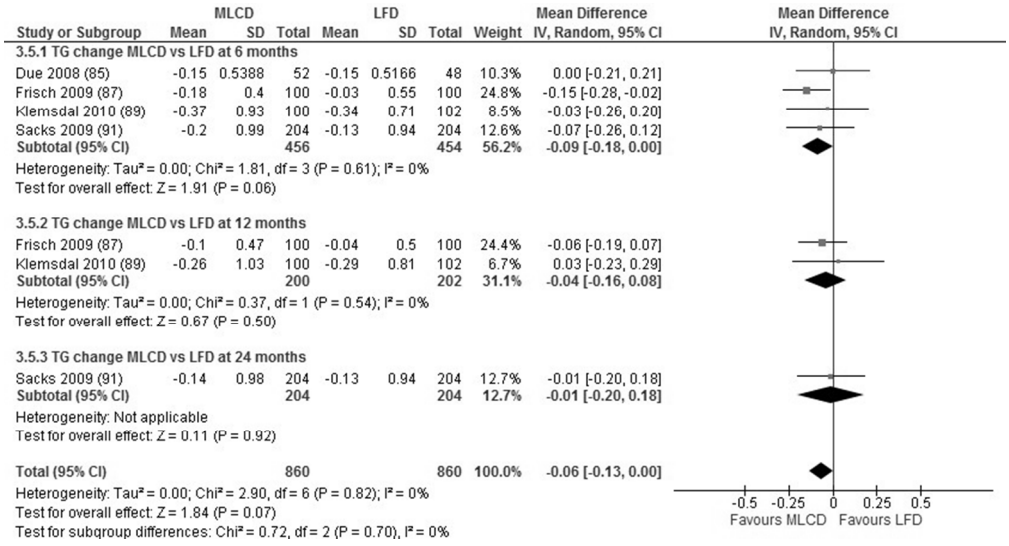


Figure 12. Forest plot for TG changes between MLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: MLCD, moderate low carbohydrate diet; LFD, low fat diet; TG, triglycerides.

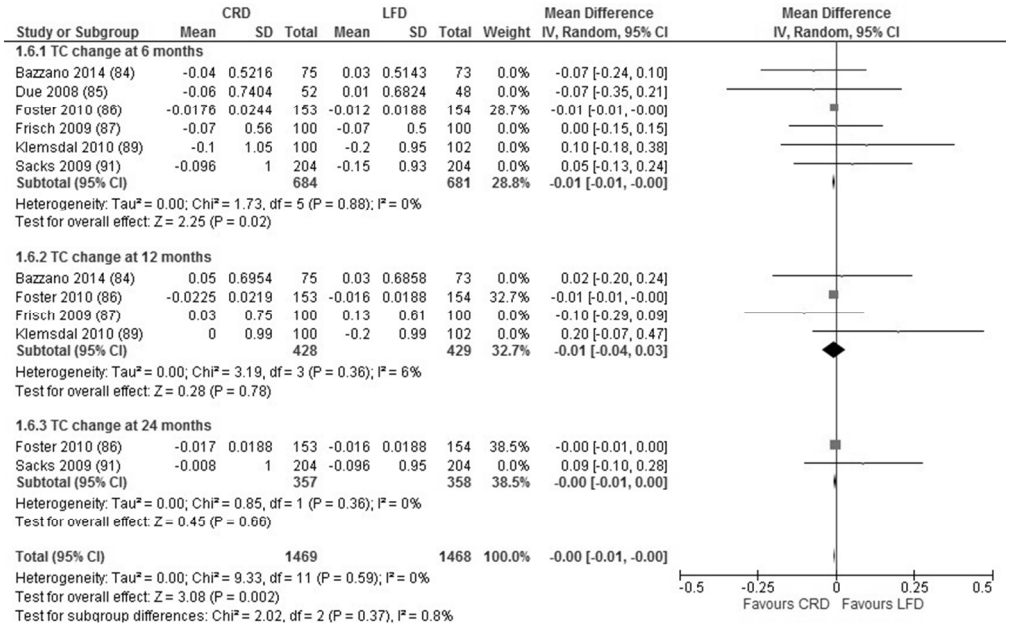


Figure 13. Forest plot for Total Cholesterol changes between CRD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: CRD, carbohydrate restricted diet; LFD, low fat diet.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not registered
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8 (Figure 1)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13-14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21-22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Search strategy

Medline and CINAHL (EBSCO)

#1 Diet, Carbohydrate-Restricted. mm
#2 (low carbohydrate). ti, kw.
#3 (carbohydrate N2 restrict*).ti, kw.
#4 Ketogenic Diet. mm
#5 (ketogenic and diet*).ti, kw.
#6 (atkins and diet*).ti, kw.
#7 1 or 2 or 3 or 4 or 5 or 6
#8 Diet, Fat-Restricted. mm
#9 (fat N2 restrict*).ti, kw.
#10 low fat. ti, kw.
#11 (conventional and diet*). ti, kw.
#12 8 or 9 or 10 or 11
#13 7 and 12
#14 Dyslipidemias. mm
#15 Lipoproteins. mm
16 (low density lipoprotein). ti, ab
17 (cholesterol). ti, ab
18 (LDL*). ti, ab
19 (lipid profil*). kw, ab
20 (Dyslipid*). kw, ab
21 (high density lipoprotein). ti, ab
22 (HDL*). ti, ab
23 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
#24 13 and 23
25 (Random* controlled trial). Pt
26 (Controlled clinical trial). Pt
27 Random*. ab
28 Trial*. ab
29 Placebo*. ab
30 Group*. ab
31 25 or 26 or 27 or 28 or 29 or 30
32 Animals. mm not humans. mw
33 31 not 32
34 24 and 33

Pubmed central

#1 Diet, Carbohydrate-Restricted. mh
#2 low carbohydrate. ti, kw.
#3 “carbohydrate N2 restrict*”.ti, kywd.
#4 Ketogenic Diet. mh
#5 “ketogenic and diet*”.ti, kywd.
#6 “atkins and diet*”.ti, kywd.
#7 1 or 2 or 3 or 4 or 5 or 6
#8 Diet, Fat-Restricted. mh

#9 "fat N2 restrict*".ti, kywd.
#10 low fat. ti, kywd.
#11 "conventional and diet*". ti, kywd.
#12 8 or 9 or 10 or 11
#13 7 and 12
#14 Dyslipidemias. mh
#15 Lipoproteins. mh
16 "low density lipoprotein". ti, ab
17 "cholesterol". ti, ab
18 "LDL*". ti, ab
19 "lipid profil*". kywd, ab
20 "Dyslipid*". kywd, ab
21 "high density lipoprotein". ti, ab
22 "HDL*". ti, ab
23 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
#24 13 and 23
25 "Random* controlled trial". Pt
26 "Controlled clinical trial". Pt
27 Random*. ab
28 Trial*. ab
29 Placebo*. ab
30 Group*. ab
31 25 or 26 or 27 or 28 or 29 or 30
32 Animals. mh not humans. mh
33 31 not 32
34 24 and 33

Cochrane Library Trials

#1 MeSH descriptor: [Diet, Carbohydrate-Restricted]
#2 "low carbohydrate". ti, ab, kw.
#3 carbohydrate near/2 restrict*.ti, ab, kw.
#4 MeSH descriptor: [Ketogenic Diet]
#5 (ketogenic and diet*).ti, ab, kw.
#6 (atkins and diet*).ti, ab, kw.
#7 1 or 2 or 3 or 4 or 5 or 6
#8 MeSH descriptor: [Diet, Fat-Restricted]
#9 (fat near/2 restrict*).ti, ab, kw.
#10 "low fat". ti, ab, kw.
#11 "conventional and diet*". ti, ab, kw.
#12 8 or 9 or 10 or 11
#13 7 and 12
#14 MeSH descriptor: [Dyslipidemias]
#15 MeSH descriptor: [Lipoproteins]
16 "low density lipoprotein". ti, ab, kw
17 "cholesterol". ti, ab, kw
18 "LDL*". ti, ab, kw
19 "lipid profil*". kw, ab

20 "Dyslipid*". kw, ab
21 "high density lipoprotein". ti, ab, kw
22 "HDL*". ti, ab, kw
23 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
#24 13 and 23
25 MeSH descriptor [Randomized controlled trial]
26 MeSH descriptor [Controlled clinical trial]
27 25 or 26
28 MeSH descriptor [Animals] not MeSH descriptor [humans]
29 27 not 28
30 24 and 29

Table S1. Weighted mean difference of LDL-C, HDL-C, TG, and TC between CRD and LFD at 6, 12 and 24 months compared to baseline (mmol/L)

Outcome or Subgroup (mmol/L)	Studies	Participants	Mean Difference (Random, 95% CI)	P	I^2
Mean LDL-C change	8	3358	0.07 [0.02, 0.13]	0.009	36
LDL- C change at 6 months	8	1633	0.08 [-0.01, 0.18]	0.08	58
LDL-C change after 12 months	5	1010	0.04 [-0.04, 0.12]	0.37	1
LDL-C change after 24 months	2	715	0.10 [-0.01, 0.21]	0.06	0
Mean HDL-C change	8	3358	0.08 [0.06, 0.11]	$1x10^{-5}$	52
HDL-C change at 6 months	8	1633	0.09 [0.06, 0.12]	$1x10^{-5}$	28
HDL-C change at 12 months	5	1010	0.09 [0.02, 0.15]	0.004	74
HDL-C change at 24 months	2	715	0.05 [-0.00, 0.11]	0.06	28
Mean TG change	8	3358	-0.13 [-0.19, -0.08]	$1x10^{-5}$	40
TG change at 6 months	8	1633	-0.18 [-0.25, -0.10]	$1x10^{-5}$	43
TG change at 12 months	5	1010	-0.11 [-0.18, -0.03]	0.005	0
TG change at 24 months	2	715	0.01 [-0.12, 0.13]	0.93	0
Mean TC change	6	2937	0.00 [-0.01, -0.00]	0.002	0
TC change at 6 months	6	1365	-0.01 [-0.01, -0.00]	0.02	0
TC change at 12 months	4	857	-0.01 [-0.04, 0.03]	0.78	6
TC change at 24 months	2	715	-0.00 [-0.01, 0.00]	0.66	0

LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; TG, plasma triglycerides; TC, total cholesterol; CRD, carbohydrate restricted diet; LFD-low fat diet

Table S2. Weighted mean difference of LDL-C, HDL-C and TG between VLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L)

Outcome or Subgroup (mmol/L)	Studies	Participants	Mean Difference (Random, 95% CI)	P	I^2 %
Mean LDL-C change	4	1638	0.07 [-0.05, 0.18]	0.27	75
LDL- C change at 6 months	4	723	0.14 [-0.02, 0.30]	0.09	74
LDL-C change after 12 months	3	608	-0.04 [-0.24, 0.16]	0.70	74
LDL-C change after 24 months	1	307	0.08 [-0.07, 0.23]	0.29	N/A
Mean HDL-C change	4	1638	0.12 [0.10, 0.14]	$1x10^{-5}$	0
HDL-C change at 6 months	4	723	0.13 [0.09, 0.16]	$1x10^{-5}$	0
HDL-C change at 12 months	3	608	0.13 [0.09, 0.17]	$1x10^{-5}$	0
HDL-C change at 24 months	1	307	0.08 [0.02, 0.14]	0.01	N/A
Mean TG change	4	1638	-0.19 [-0.26, -0.12]	$1x10^{-5}$	41
TG change at 6 months	4	723	-0.24 [-0.32, -0.16]	$1x10^{-5}$	30
TG change at 12 months	3	608	-0.16 [-0.25, -0.06]	0.002	0
TG change at 24 months	1	307	0.02 [-0.16, 0.20]	0.82	N/A

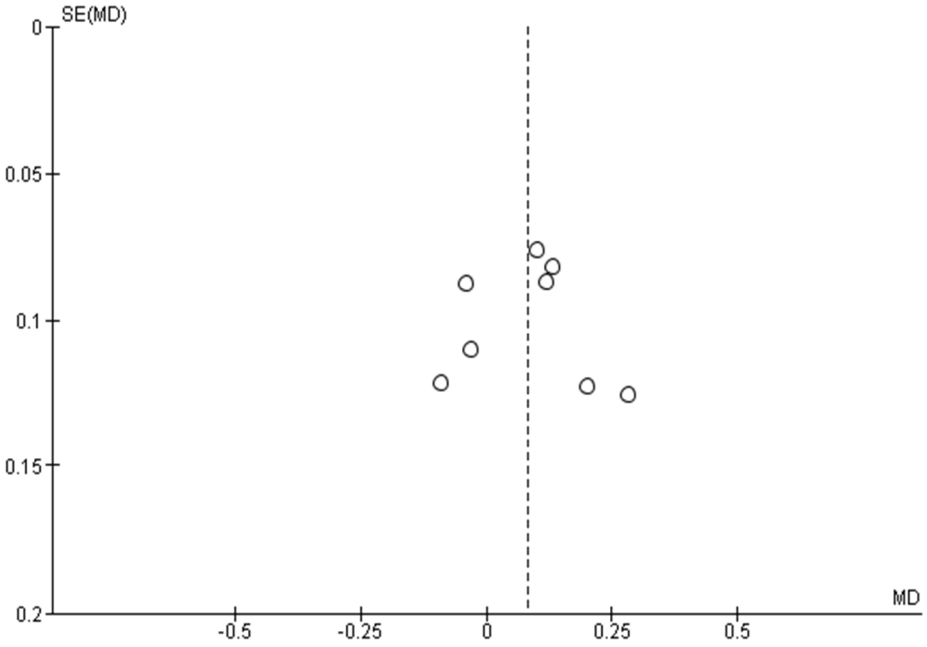
LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; TG, plasma triglycerides; N/A, not applicable; VLCD, very low carbohydrate diet; LFD, low fat diet

Table S3. Weighted mean difference of LDL-C, HDL-C and TG between MLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L)

Outcome or Subgroup (mmol/L)	Studies	Participants	Mean Difference (Random, 95% CI)	P	I^2 %
Mean LDL-C change	4	1720	0.05 [-0.02, 0.11]	0.16	0
LDL- C change at 6 months	4	910	0.02 [-0.06, 0.11]	0.54	0
LDL-C change after 12 months	2	402	0.06 [-0.17, 0.30]	0.59	60
LDL-C change after 24 months	1	408	0.13 [-0.03, 0.29]	0.11	N/A
Mean HDL-C change	4	1720	0.04 [0.01, 0.07]	0.005	0
HDL-C change at 6 months	4	910	0.06 [0.02, 0.10]	0.02	0
HDL-C change at 12 months	2	402	0.01 [-0.04, 0.06]	0.68	0
HDL-C change at 24 months	1	408	0.02 [-0.05, 0.09]	0.52	N/A
Mean TG change	4	1720	-0.06 [-0.13, 0.00]	0.06	0
TG change at 6 months	4	910	-0.09 [-0.18, 0.00]	0.05	0
TG change at 12 months	2	402	-0.04 [-0.16, 0.08]	0.5	0
TG change at 24 months	1	408	-0.01 [-0.20, 0.18]	0.92	N/A

LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; TG, plasma triglycerides; N/A, not applicable; MLCD, moderate low carbohydrate diet; LFD, low fat diet

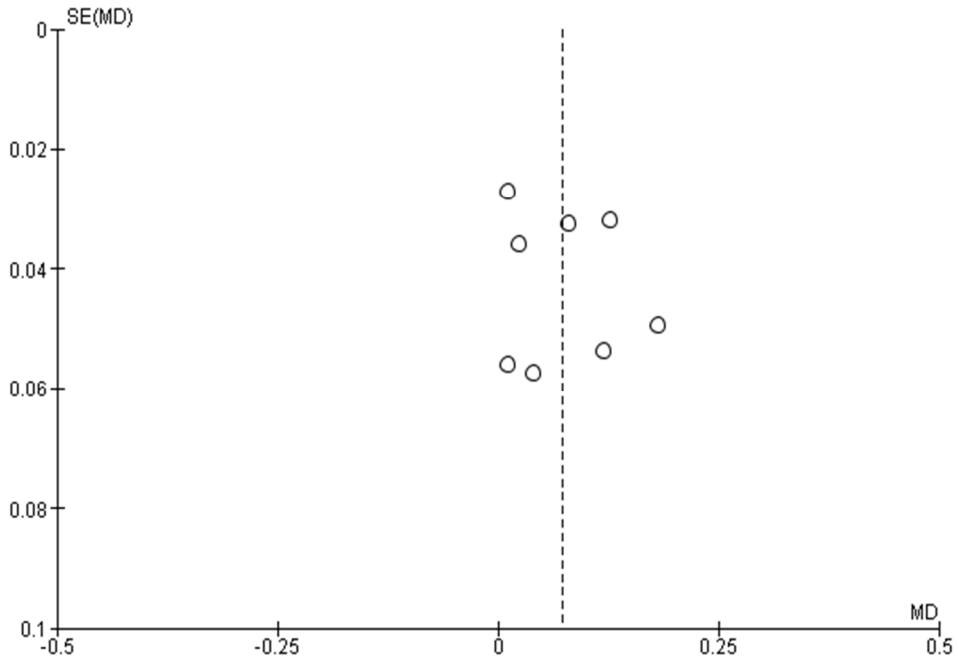
Figure S1: Funnel plot of the mean LDL-C differences (mmol/L) between CRD and LFD across trials (n=8)



MD - Mean Difference of LDL-C (mmol/L) between CRD vs LFD; SE (MD) - Standard Error of the MD

LDL-C, low density lipoprotein cholesterol; CRD, carbohydrate restricted diet; LFD, low fat diet

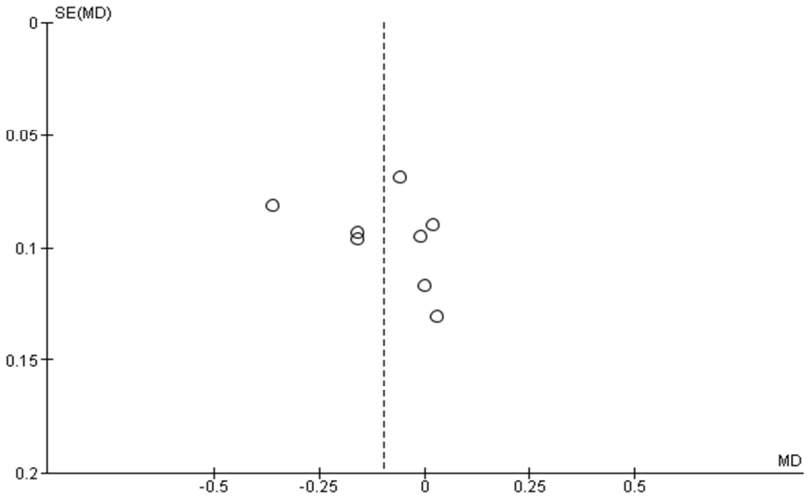
Figure S2: Funnel plot of the mean HDL-C differences (mmol/L) between CRD and LFD across trials (n=8)



MD - Mean Difference of HDL-C (mmol/L) between CRD vs LFD; SE (MD) - Standard Error of the MD

HDL-C, high density lipoprotein cholesterol; CRD, carbohydrate restricted diet; LFD, low fat diet

Figure S3: Funnel plot of the mean TG differences (mmol/L) between CRD and LFD across trials (n=8)



MD - Mean Difference of TG (mmol/L) between CRD vs LFD; SE (MD) - Standard Error of the MD
TG, plasma triglycerides; CRD, carbohydrate restricted diet; LFD, low fat diet