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### Article

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1 **Article type:** Special Article

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

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13 Abstract

#### 14 **Context**

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

#### 17 **Objective**

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

#### 21 **Data Sources**

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

#### 24 **Data Extraction**

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

#### 27 **Data Analysis**

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

#### 32 **Results**

33 Carbohydrate restricted diets showed a none significant difference in low density lipoprotein-  
34 cholesterol after 6, 12, and 24 months. While an overall pooled analysis statistically favoured  
35 low-fat diets [0.07 mmol/L; 95% CI 0.02, 0.13; p = 0.009] this was clinically insignificant.  
36 High density lipoprotein-cholesterol and plasma triglycerides at 6 and 12 months, favoured  
37 carbohydrate restricted diets [0.08 mmol/L, 95% CI 0.06, 0.11; p < 1x10<sup>-5</sup> and -0.13 mmol/L,  
38 95% CI -0.19, -0.08; p < 1x10<sup>-5</sup>] respectively. These favourable changes were more marked in  
39 the subgroup with very-low carbohydrate content (< 50 g/day) [0.12 mmol/L, 95% CI 0.10,  
40 0.14; p < 1x10<sup>-5</sup> and -0.19 mmol/L, 95% CI -0.26, -0.12, p = 0.02] respectively.

## 41 **Conclusions**

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

46

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

49

50

## 51 **Introduction**

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

56

Austin Bradford Hill

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

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

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

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

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

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

## 116 **Methods**

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

### 123 **Search methods**

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

### 132 **Inclusion criteria and data abstraction**

133 RCTs included in this research were required to compare the effects of carbohydrate restricted  
134 diets (CRD) (defined as  $\leq 45\%$  total energy intake (TEI) from CHO, including MLCDD  $\leq 45\%$  -  
135  $>26\%$  TEI or 130 – 225 g, LCD as 10 -  $< 26\%$  TEI or 50 – 130 g, and VLCD as  $< 10\%$  TEI or  
136  $< 50$  g, and  $> 35\%$  TEI from fat, fed ad libitum) versus a LFD (defined as  $\leq 35\%$  TEI from fat  
137 and  $\geq 50\%$  TEI from CHO, and restriction on total energy intake)<sup>40,41</sup> with outcomes on  
138 serum/plasma LDL-C and other lipid profile markers, namely total cholesterol (TC), high  
139 density lipoprotein-cholesterol (HDL-C) and triglycerides (TG), published between 1970 and  
140 June, 2017. Large randomised controlled trials with duration of at least six months and with at

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

#### 146 **Exclusion criteria**

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

#### 153 **Data extraction and quality assessment**

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

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

## 170 **Data synthesis and data analysis**

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



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

## 194 **Results**

### 195 **Literature search**

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

### 208 **Study and participant characteristics**

209 The main characteristics of the eight published articles eligible for meta-analysis are  
210 summarised in Table 3<sup>84-91</sup>. All eight RCTs were open and parallel group trials with no  
211 possibility for blinding of participants due to the polarity of diets. Intervention duration ranged  
212 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.*<sup>88</sup> 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<sup>2</sup> respectively. All 8 trials<sup>84-91</sup>  
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<sup>84,86,87,89,90</sup> and 2 studies with a total of 715 (n = 357 on CRD, n =  
221 358 on LFD) reported data for 24 months.<sup>86,91</sup> 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<sup>86,88,90</sup> followed the Atkins diet (Dr. Atkins New  
224 Diet Revolution, 1998)<sup>92</sup>, 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<sup>84</sup> the CHO intake  
226 was restricted to < 40 g of CHO daily. The other 4 trials<sup>85,87,89,91</sup> 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.<sup>87,88,90</sup> 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.*<sup>88</sup> with a very low fat (< 10%) high CHO (70%) intervention (Ornish) diet.<sup>93</sup>

232 Diet compliance was measured via three 24 h dietary recalls<sup>84,87,88,91</sup> or 7-day food  
233 diaries.<sup>86,89,90</sup> In the study of Due *et al.*<sup>85</sup> 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

238 intervention, but were well balanced in both the CRD and LFD arm of intervention in each  
239 study (Table 4<sup>84-91</sup>).

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

#### 247 **Quality assessment and risk of bias**

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

#### 257 **Meta-analyses**

##### 258 *Effects of CRD and LFD on LDL-Cholesterol levels*

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

261 presented in Figure 4<sup>84-91</sup> & Table S1. Although participants on the CRD intervention  
262 experienced a greater increase in LDL-C compared to the LFD, these changes are statistically  
263 non-significant regardless of intervention duration [6 months: 0.08 mmol/L; 95% CI -0.01,  
264 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  
265 mmol/L; 95% CI -0.01, 0.21; P = 0.06]. However, analysis of the global pooled effect between  
266 CRD and LFD interventions on LDL-C levels shows a significant weighted mean difference in  
267 favour of the LFD [0.07 mmol/L; 95% CI 0.02, 0.13; P = 0.009]. Significant (moderate)  
268 heterogeneity ( $I^2 = 58\%$ ; P = 0.009) for the estimated difference of LDL-C between both diets  
269 was observed only at 6 months. Sensitivity analysis (exclusion of studies one by one) was  
270 carried out to identify the possible studies that could explain this heterogeneity. After  
271 exclusion of the study of Foster *et al.*,<sup>86</sup> which had the highest weight effect, the heterogeneity  
272 considerably decreased ( $I^2 = 28\%$ , P = 0.22), but did not significantly change the weighted  
273 mean difference of LDL-C (P = 0.25). However, exclusion of the study of Due *et al.*,<sup>85</sup> did not  
274 change the heterogeneity, but resulted with a statistically significant mean difference of LDL-C  
275 at 6 months in favour of the LFD ( $I^2 = 58\%$ , P = 0.04). This is possibly because it is the  
276 smallest study and/or has the lowest mean age of participants of 29.8 (Table 3).

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

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

287 The pooled global mean differences for HDL-C [HDL-C: 0.08 mmol/L, 95% CI 0.06, 0.11; P  
288  $< 1 \times 10^{-5}$ ] (Figure 7<sup>84-91</sup> & Table S1) and TG [-0.13 mmol/L, 95% CI -0.19, -0.08; P  $< 1 \times 10^{-5}$ ]  
289 (Figure 8<sup>84-91</sup> & Table S1) showed an overall more favourable total effect of the CRD  
290 intervention. However, the mean differences for both parameters were significant at 6 months  
291 [HDL-C: 0.09 mmol/L, 95% CI 0.06, 0.12; P  $< 1 \times 10^{-5}$  and TG: -0.18 mmol/L, 95% CI -0.25, -  
292 0.11; P  $< 1 \times 10^{-5}$ ] and 12 months [HDL-C: 0.09 mmol/L, 95% CI 0.02, 0.15; P = 0.008 and  
293 TG: -0.11 mmol/L, 95% CI -0.18, -0.03; P = 0.005], but non-significant at 24 months [HDL-C:  
294 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;  
295 P=0.93]. High heterogeneity of 74% was observed for HDL-C at 12 months, which was  
296 considerably decreased after removal of the trial of Frisch *et al.*<sup>87</sup> without affecting the  
297 significance of the weighted mean difference ( $I^2 = 45\%$ ; P  $< 1 \times 10^{-4}$ ).

298 The VLCD (Figure 9<sup>84,86,88,90</sup> & Table S2) showed a greater increase of HDL-C compared to  
299 the LFD throughout the entire observed period [for 6 months: 0.13 mmol/L, 95% CI 0.09,  
300 0.16; P =  $1 \times 10^{-5}$ ; for 12 months: 0.13 mmol/L, 95% CI 0.09, 0.17; P =  $1 \times 10^{-5}$  and for 24  
301 months: 0.08 mmol/L, 95% CI 0.02, 0.14; P = 0.01]. Regarding TG concentration, the VLCD  
302 was more favourable at 6 months [-0.24 mmol/L, 95% CI -0.32, -0.16; P =  $1 \times 10^{-5}$ ] and 12  
303 months [-0.16 mmol/L, 95% CI -0.25, -0.06; P = 0.002] of the diet intervention, levelling its  
304 effect with the LFD group at 24 months [0.02 mmol/L, 95% CI -0.16, 0.02; P = 0.82] (Figure  
305 10<sup>84,86,88,90</sup> & Table S2). Compared to the LFD, the MLCD showed more favourable effects  
306 regarding HDL-C and TG only for the initial period of 6 months of intervention duration  
307 respectively [HDL-C: 0.06 mmol/L, 95% CI 0.02, 0.10; P = 0.002] and [TG: -0.09 mmol/L,  
308 95% CI -0.18, 0.0; P = 0.05] (Figures 11<sup>85,87,89,91</sup>, 12<sup>85,87,89,91</sup>, & Table S3). Based on the  
309 overall total effect, the subgroup analyses showed that the VLCD was more effective than the

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

### 312 *Effects of CRD and LFD on Total Cholesterol levels*

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

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

325 Results of the LDL-peak density in the trial of Morgan *et al.*<sup>90</sup> showed that after six months of  
326 intervention, this variable decreased within both dietary groups included in this RCT.  
327 However, the decrease of the LDL-peak density indicating an increase in LDL particle size  
328 was significantly greater than the control (no intervention group) only among participants on  
329 the VLCD diet. No significant changes of apolipoprotein-B after 12 months were found within  
330 and between dietary intervention groups in the trial of Klemsdal *et al.*<sup>89</sup> Decreases in VLDL-C  
331 levels reported by Foster *et al.*<sup>86</sup> were significantly greater in the CRD than in the LFD group  
332 at 6 months [LFD: -0.12 mmol/L; 95% CI -0.17, -0.08 vs CRD: -0.23 mmol/L; 95%CI -0.27, -  
333 0.19; P < 0.001] and 12 months [LFD: -0.09 mmol/L; 95% CI -0.16, -0.02 vs CRD: -0.21

334 mmol/L; 95% CI -0.27, -0.19; P = 0.009], but non-significant differences were found at 24  
335 months [LFD: -0.05 mmol/L; 95% CI -0.12, -0.004 vs CRD: -0.05 mmol/L; 95%CI -0.12, -  
336 0.0007; P = 0.99]

### 337 *Funnel Plots and Publication Bias*

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

### 342 **Discussion**

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

358 The more favourable changes in several lipid parameters (HDL-C and TG) and non-significant  
359 changes of LDL-C in both the VLCD and MLCD subgroup analysis, despite the slight global  
360 increase in LDL-C, support the view that carbohydrate restriction, especially the VLCD, is  
361 more effective in improving investigated CVD risk markers. The presented findings with  
362 regard to LDL-C, HDL-C and TG weighted mean changes are relatively consistent with the  
363 findings of several other meta-analyses,<sup>28,32,95</sup> all concluding that CRDs are at least as  
364 beneficial as the LFD and thus proposing CRDs as an alternative tool for treatment of  
365 metabolic risk and obesity. These findings are also in line with the most recent meta-analyses  
366 by Mansoor *et al.*<sup>29</sup> and Lu *et al.*<sup>30</sup> investigating the effects of a CRD vs LFD on cardiovascular  
367 risk markers. While the Lu *et al.*<sup>30</sup> study showed an increase in LDL-C of 0.11 mmol/L (95%  
368 CI 0.205, 0.026) with the CRD, the authors emphasised the beneficial HDL-C raising effect of  
369 the CRD of 0.066 mmol/L (95% CI, 0.10, 0.033) equating to a 7.45% reduction in relative risk  
370 of CVD. However, Mansoor *et al.*<sup>29</sup> found an overall increase in LDL-C level of 0.16 mmol/L  
371 (95% CI 0.003, 0.33) with the CRD and highlighted its possible detrimental effect on CVD,  
372 stating this may outweigh the benefits of the increased HDL-C and decreased TG levels  
373 observed. The results of the present study show the inverse; the overall increase in LDL-C of  
374 0.07 mmol/L (95% CI 0.02, 0.13) with the CRD in the primary meta-analysis equates to a  
375 1.54% relative risk reduction in cardiovascular events.<sup>96</sup> With HDL-C the pooled increase of  
376 0.08 mmol/L (95% CI 0.06, 0.11) reduces relative risk by 4.6% (using the latest evidence from  
377 the European Atherosclerosis Society).<sup>97</sup> Furthermore, the lack of significant difference for  
378 LDL-C at 6, 12 and 24 months and in the VLCD and the MLCD-subgroup analysis supports a  
379 negated risk of CVD from LDL-C. These differences are presumably due to the different  
380 inclusion/exclusion criteria during the selection process between the current and the two  
381 previous meta-analyses.<sup>29,30</sup>



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

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

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

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

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

432 inflammation.<sup>119</sup> Evidence regarding the effect of CRDs on LDL-P size and apo-B in the  
433 published literature is scarce, which was also revealed during this study. In the presented  
434 systematic review, decreased LDL-peak density were reported by Morgan *et al.*<sup>90</sup> only among  
435 participants following the Atkins diet when compared to the control, while decreased VLDL-C  
436 concentrations were found by Foster *et al.*<sup>86</sup> These findings, though in favour of the VLCD, are  
437 not yet sufficient to make a meaningful judgement, as more large RCTs with longer duration  
438 are necessary in order to compare and critically discuss these variables. However, the results of  
439 the RCT conducted by Sharman *et al.*<sup>120</sup> show that a short-term (6 week) hypoenergetic VLCD  
440 (< 10% CHO TEI) led to improvement of cardiometabolic risk factors: increased mean and  
441 peak LDL-P size along with fasting serum TG, TG/HDL-C ratio, postprandial lipaemia, serum  
442 glucose and insulin resistance in overweight men.<sup>120</sup> Similar findings, namely, increase in peak  
443 LDL-P size, a shift towards lLDL in participants who started with a predominance of sdLDL-  
444 P, and overall improvement of CVD and diabetic risk markers after a 6 week KD-intervention  
445 in normolipidaemic men with normal body weight<sup>121</sup> and after 12 weeks in subjects with  
446 atherogenic dyslipidaemia<sup>11</sup> were found.

447 The main argument against low-carbohydrate high-fat diets is the potential adverse effect on  
448 the TC and LDL-C levels as a result of a relative or absolute increase in dietary SFA due to  
449 CHO restriction,<sup>4,7,14</sup> although the magnitude of the effect shows variations in constellation to  
450 the specific diet quality and individual susceptibility.<sup>5,122,123</sup> Macronutrient dietary content  
451 with SFA intake is almost unavoidable, because these fatty acids are present in all fat-  
452 containing foods (dairy products, meats, egg yolk, and in some vegetable fats and oils). SFA  
453 are non-uniform compounds and their metabolic effects and potency to alter plasma lipids and  
454 lipoproteins depend on the composition of SFA in their structure. As an illustration, evidence  
455 suggests that palmitate increases LDL-C and the LDL-C/HDL-C ratio and may enhance  
456 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.<sup>124,125</sup> 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.<sup>6,20,21</sup> Though associated with increased LDL-C concentration, higher SFA  
461 intake mainly increases the less atherogenic lbLDL,<sup>126,127</sup> 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.<sup>128</sup> 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<sup>14,122,129,130</sup>. 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.*<sup>71</sup> 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.<sup>27</sup>  
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.<sup>7,9,14</sup>

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

498

#### 499 **Strengths and Limitations of the study**

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

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

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

## 527 **Conclusions and Implications for future research**

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

550

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## 561 **Supporting Information**

562 Appendix S1 PRISMA checklist

563 Appendix S2 Search strategy

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

566 Table S2 Weighted mean difference of LDL-C, HDL-C and TG between VLCD and LFD at 6,  
567 12 and 24 months compared to baseline (mmol/L)

568 Table S3 Weighted mean difference of LDL-C, HDL-C and TG between MLCD and LFD at 6,  
569 12 and 24 months compared to baseline (mmol/L)

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

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

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

576

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**Table 1:** PICOS criteria for inclusion of studies

<b>Parameter</b>	<b>Inclusion criteria</b>
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)

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

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	Intervention	Completed % CRD/LFD	Missing data
					CRD	LFD		
Bazzano <i>et al</i> (2014) <sup>84*</sup> 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 <i>et al</i> (2008) <sup>85**</sup> 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 <i>et al</i> (2010) <sup>86*</sup> 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 <i>et al</i> (2009) <sup>87**</sup> 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 <i>et al</i> (2007) <sup>88*</sup> 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 <i>et al</i> (2010) <sup>89**</sup> 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 <i>et al</i> (2009) <sup>90*</sup> 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 <i>et al</i> (2009) <sup>91**</sup> 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			
	LDL-C (SD)	HDL-C (SD)	TG (SD)	TC (SD)	LDL-C (SD)	HDL-C (SD)	TG (SD)	TC (SD)
Bazzano <i>et al</i> (2014) <sup>84</sup>	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 <i>et al</i> (2008) <sup>85</sup>	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 <i>et al</i> (2010) <sup>86</sup>	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 <i>et al</i> (2009) <sup>87</sup>	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 <i>et al</i> (2007) <sup>88</sup>	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 <i>et al</i> (2010) <sup>89</sup>	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 <i>et al</i> (2009) <sup>90</sup>	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 <i>et al</i> (2009) <sup>91</sup>	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.

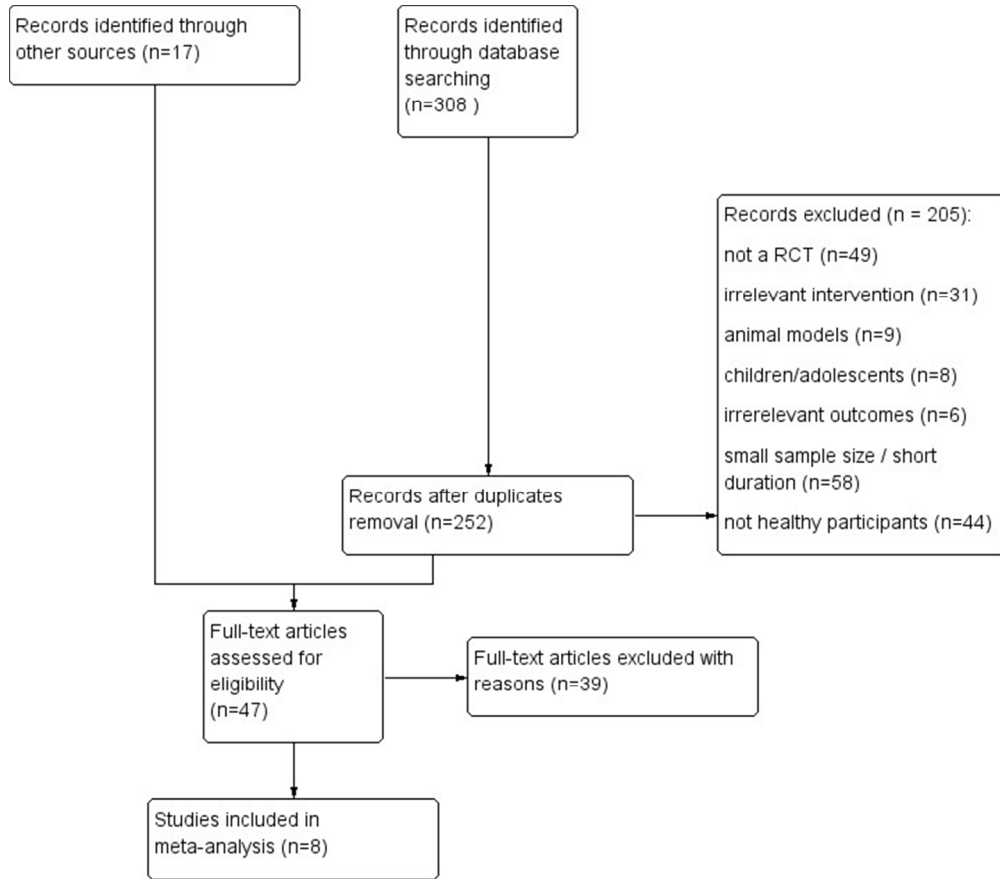


Figure 1. Flow diagram of literature search

190x166mm (96 x 96 DPI)

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bazzano 2014 (84)	+	+	+	+	+	+	+
Due 2008 (85)	+	+	+	+	+	+	+
Foster 2010 (86)	+	?	+	+	+	+	?
Frisch 2009 (87)	+	+	+	+	+	+	+
Gardner 2007 (88)	+	+	+	+	+	+	+
Klemsdal 2010 (89)	?	?	+	+	?	+	?
Morgan 2009 (90)	?	?	+	+	?	+	?
Sacks 2009 (91)	?	+	+	+	?	+	+

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

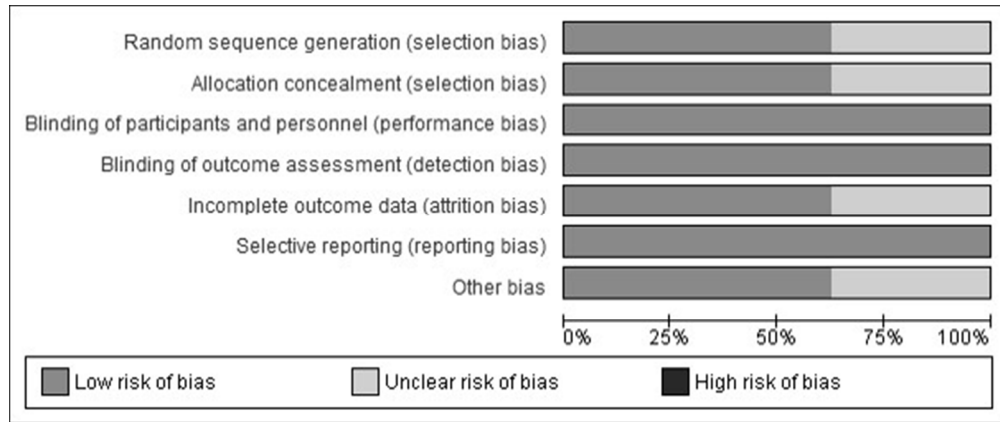


Figure 3. Risk of bias (%) across included studies (n = 8) using the Cochrane Risk of Bias Tool: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.

176x102mm (87 x 63 DPI)

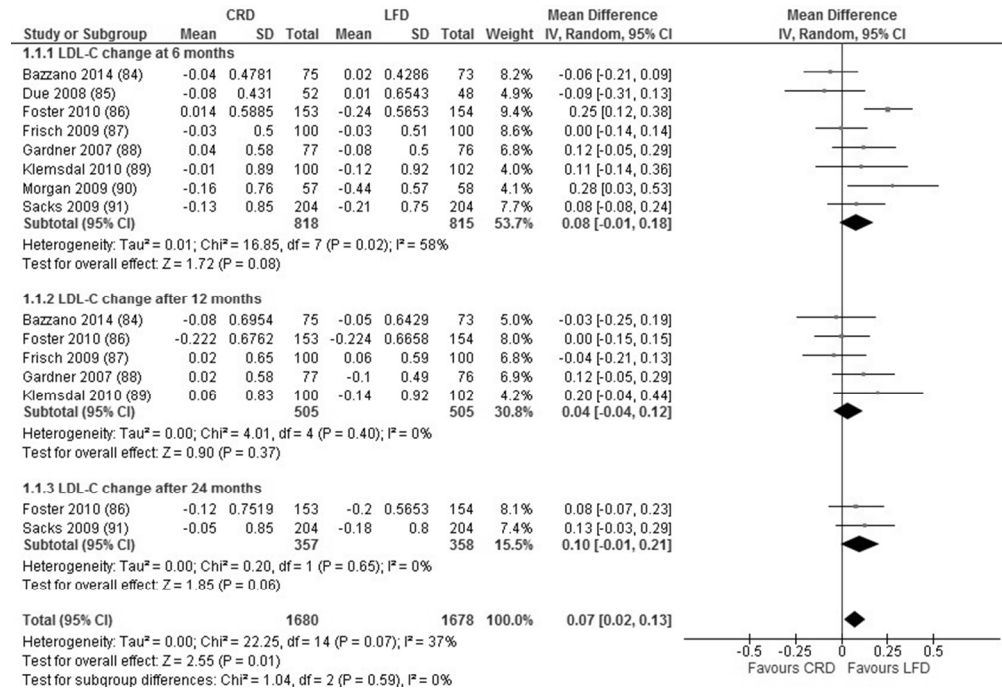


Figure 4. Forest plot for LDL-C changes between CRD and LFD at 6, 12, and 24 months compared to baseline (mmol/L). Abbreviations: CRD, carbohydrate restricted diet; LFD, low fat diet; LDL, low density lipoprotein.



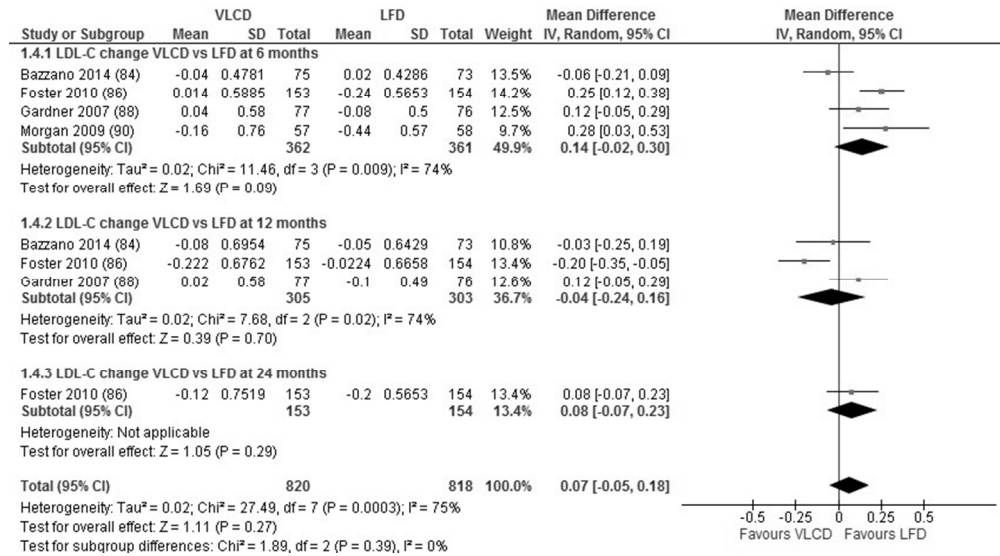


Figure 5. Forest plot for LDL-C changes between VLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: VLCD, very low carbohydrate diet; LFD, low fat diet; LDL, low density lipoprotein.

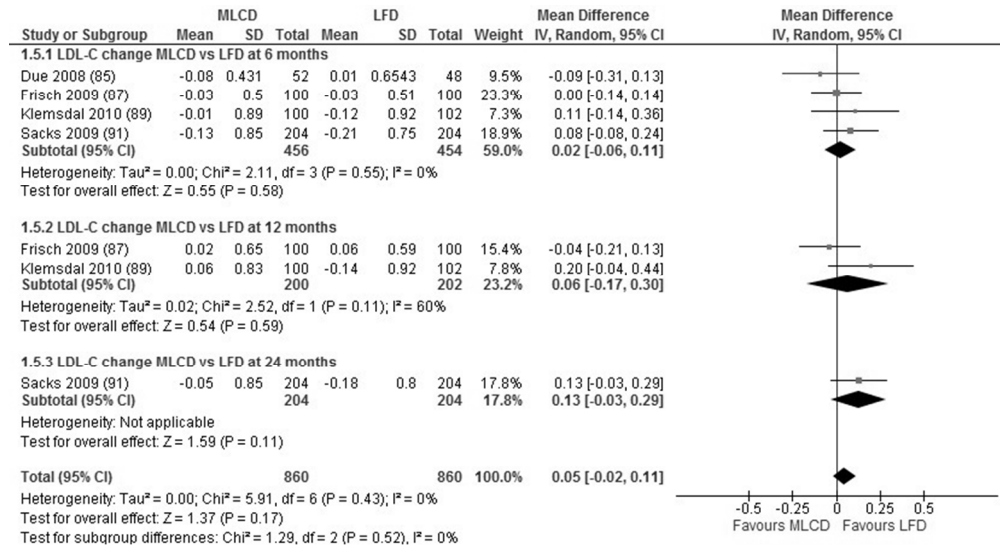


Figure 6. Forest plot for LDL-C changes between MLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: MLCD, moderate low carbohydrate diet; LFD, low fat diet; LDL, low density lipoprotein.

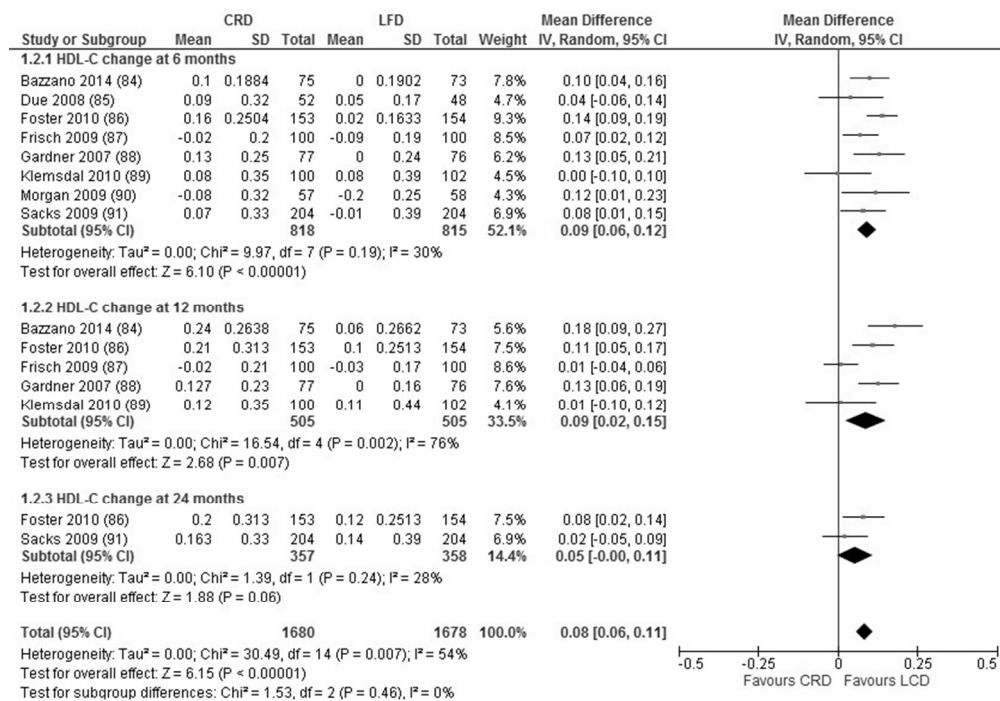


Figure 7. Forest plot for HDL-C changes between CRD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: CRD, carbohydrate restricted diet; LFD, low fat diet; HDL, high density lipoprotein.

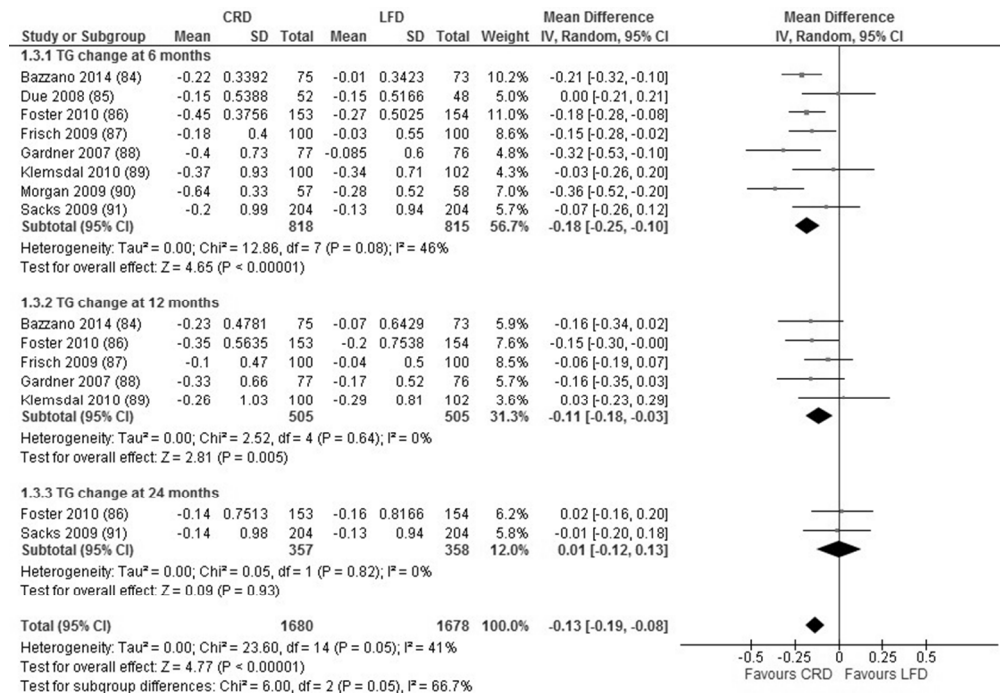


Figure 8. Forest plot for TG changes between CRD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: CRD, carbohydrate restricted diet; LFD, low fat diet; HDL, high density lipoprotein.

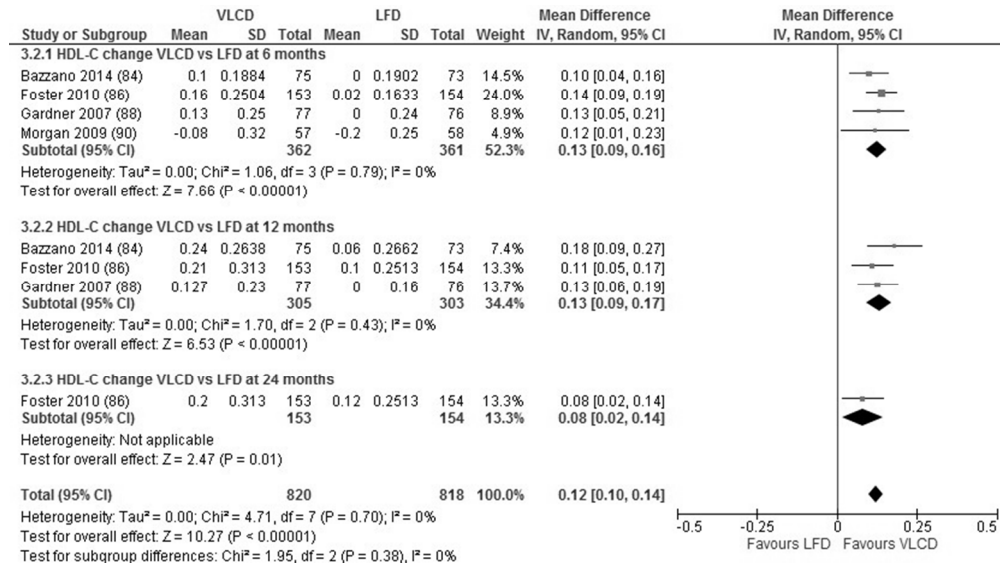


Figure 9. Forest plot for HDL-C changes between VLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: VLCD, very low carbohydrate diet; LFD, low fat diet; HDL, high density lipoprotein.

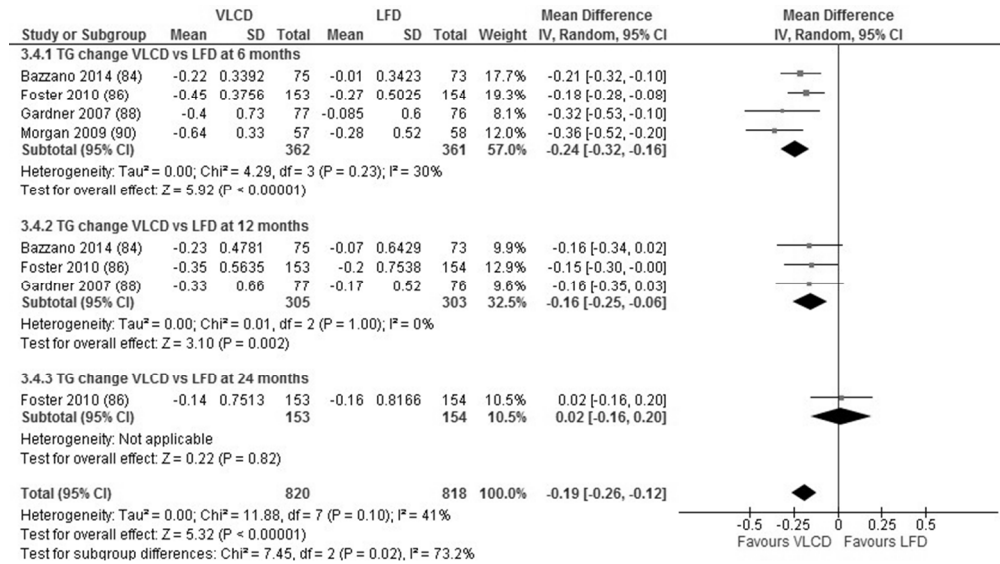


Figure 10. Forest plot for TG changes between VLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: VLCD, very low carbohydrate diet; LFD, low fat diet; TG, triglycerides.

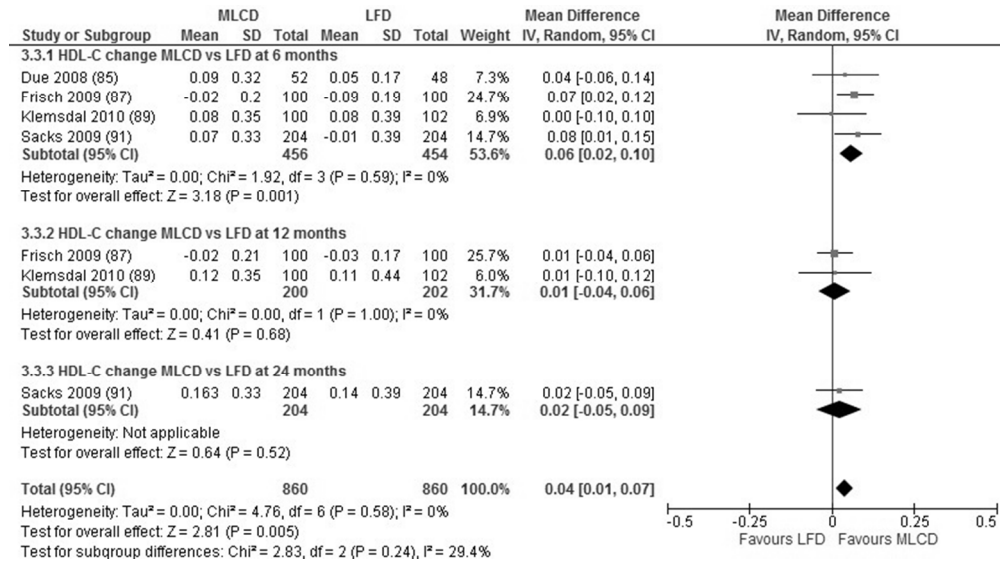


Figure 11. Forest plot for HDL-C changes between MLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: MLCD, moderate low carbohydrate diet; LFD, low fat diet; HDL, high density lipoprotein.

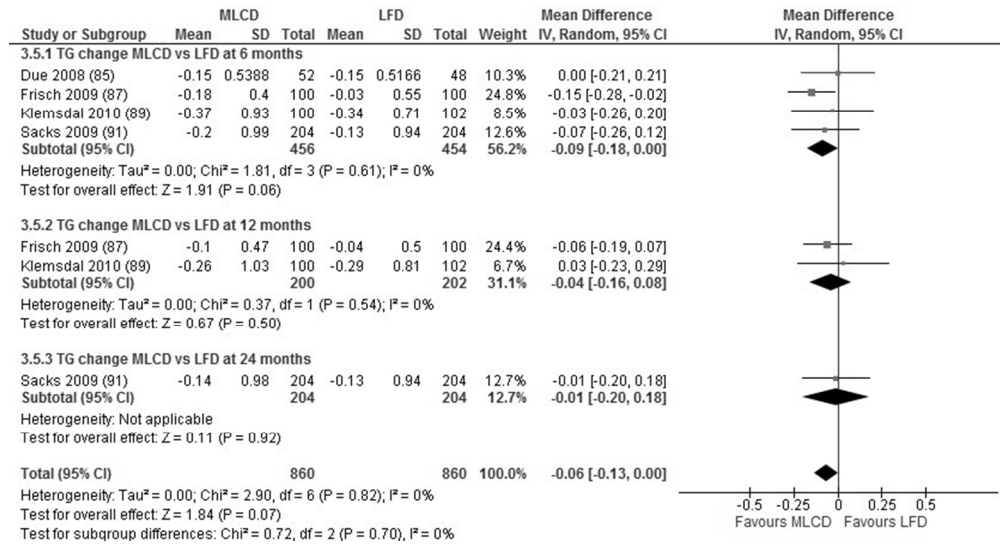


Figure 12. Forest plot for TG changes between MLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: MLCD, moderate low carbohydrate diet; LFD, low fat diet; TG, triglycerides.



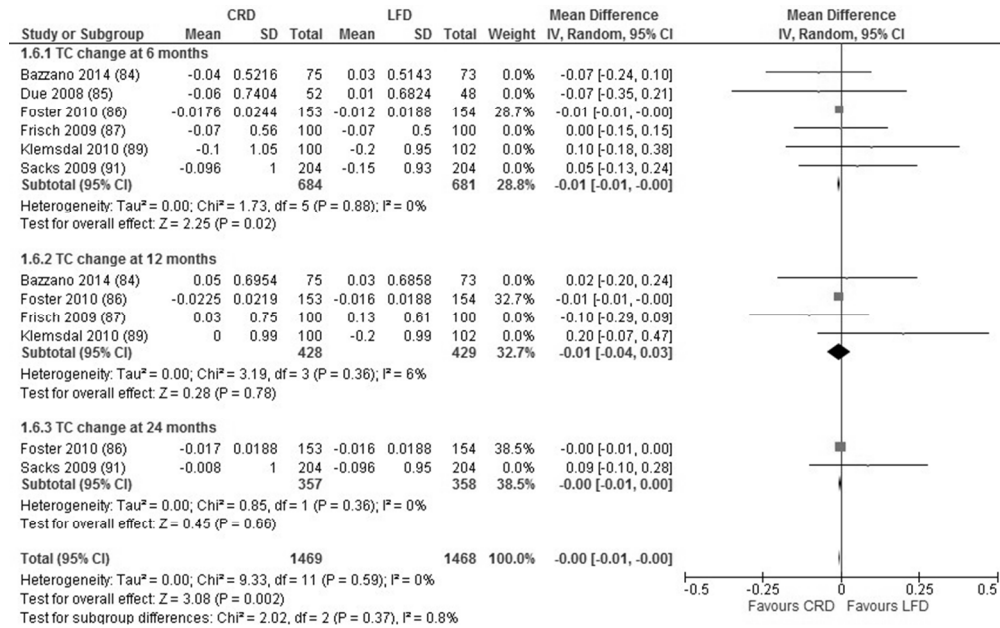


Figure 13. Forest plot for Total Cholesterol changes between CRD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: CRD, carbohydrate restricted diet; LFD, low fat diet.



## PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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

Page 1 of 2

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
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			
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
<b>FUNDING</b>			
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](http://www.prisma-statement.org).

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## 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)

<b>Outcome or Subgroup (mmol/L)</b>	<b>Studies</b>	<b>Participants</b>	<b>Mean Difference (Random, 95% CI)</b>	<b>P</b>	<b>I<sup>2</sup></b>
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 <sup>-5</sup>	52
HDL-C change at 6 months	8	1633	0.09 [0.06, 0.12]	1x10 <sup>-5</sup>	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 <sup>-5</sup>	40
TG change at 6 months	8	1633	-0.18 [-0.25, -0.10]	1x10 <sup>-5</sup>	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)

<b>Outcome or Subgroup (mmol/L)</b>	<b>Studies</b>	<b>Participants</b>	<b>Mean Difference (Random, 95% CI)</b>	<b>P</b>	<b>I<sup>2</sup> %</b>
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 <sup>-5</sup>	0
HDL-C change at 6 months	4	723	0.13 [0.09, 0.16]	1x10 <sup>-5</sup>	0
HDL-C change at 12 months	3	608	0.13 [0.09, 0.17]	1x10 <sup>-5</sup>	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 <sup>-5</sup>	41
TG change at 6 months	4	723	-0.24 [-0.32, -0.16]	1x10 <sup>-5</sup>	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

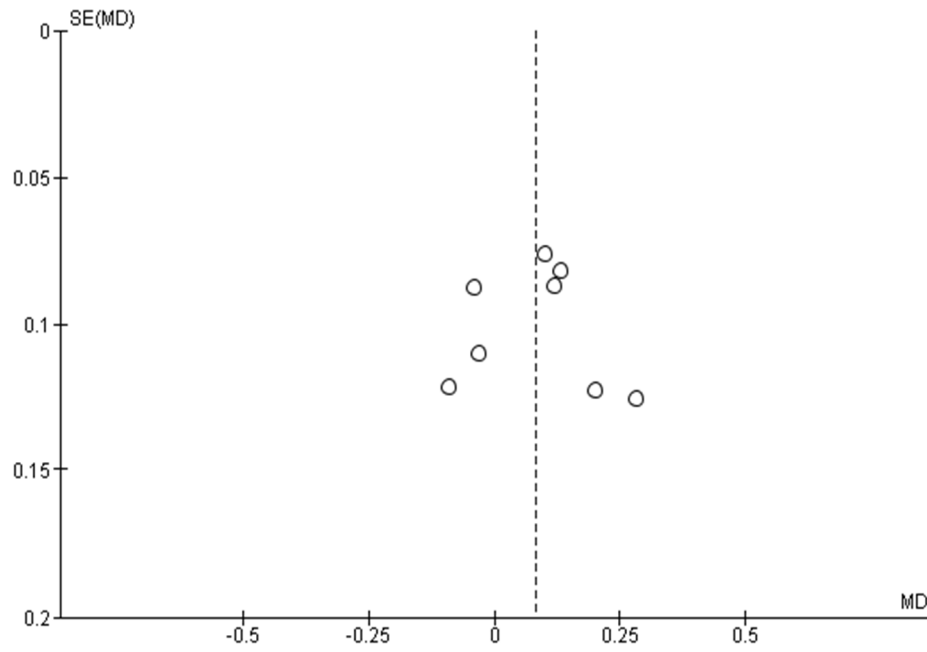


**Table S3.** Weighted mean difference of LDL-C, HDL-C and TG between MLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L)

<b>Outcome or Subgroup (mmol/L)</b>	<b>Studies</b>	<b>Participants</b>	<b>Mean Difference (Random, 95% CI)</b>	<b>P</b>	<b>I<sup>2</sup> %</b>
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

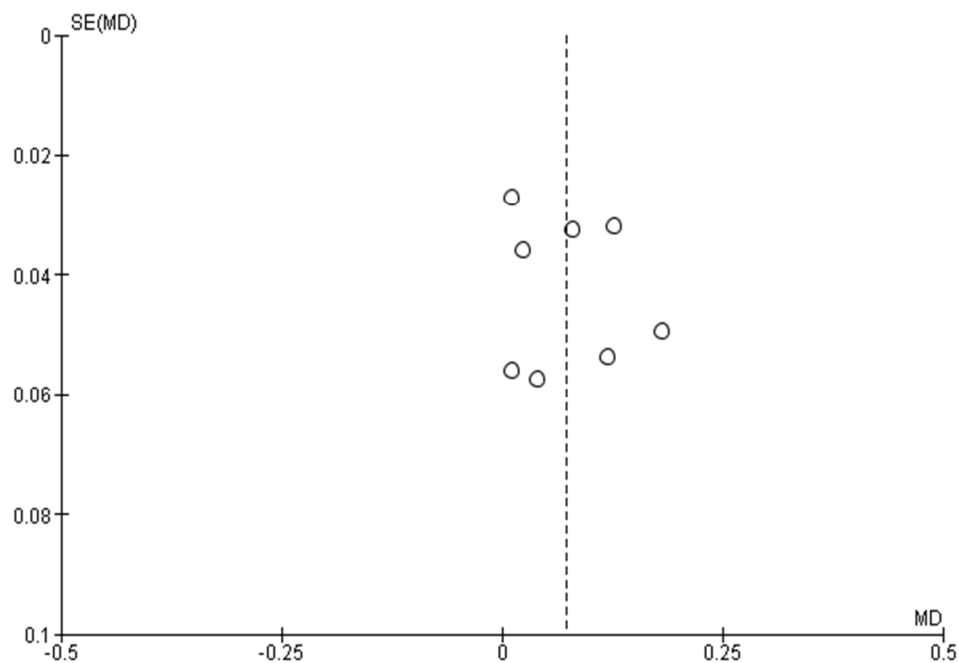
**Figure S1:** Funnel plot of the mean LDL-C differences (mmol/L) between CRD and LFD across trials (n=8)



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

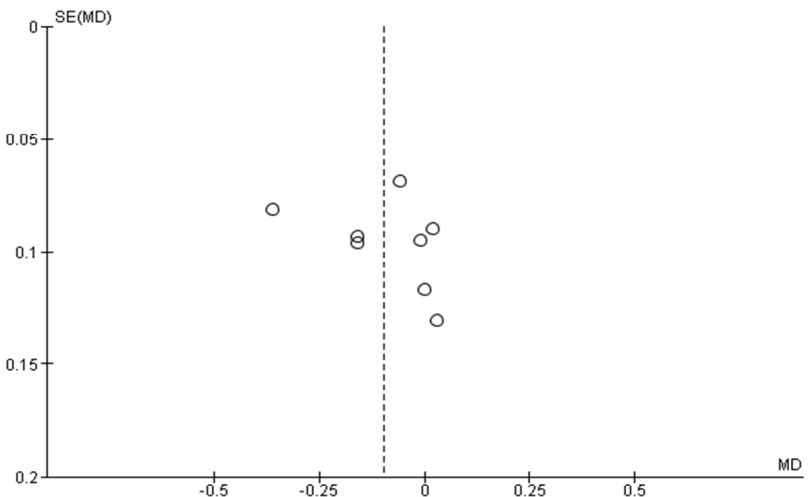
**Figure S2:** Funnel plot of the mean HDL-C differences (mmol/L) between CRD and LFD across trials (n=8)



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