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**

5   Teuta Gjuladin-Hellon[1,2], Ian G. Davies[1*], Peter Penson[3], Raziyeh Amiri Baghbadorani[1]

6   [1]School of Sports Studies and Nutrition, Faculty of Education, Health and Community,
7   Liverpool John Moores University, Merseyside, UK. [2]Faculty of Food Technology and
8   Nutrition, University of Tetovo, Macedonia. [3] School of Pharmacy and Biomolecular Sciences,
9   Faculty of Science, Liverpool John Moores University, Merseyside, UK.

10   ***Corresponding author:** i.g.davies@ljmu.ac.uk, School of Sports Studies and Nutrition,
11   Faculty of Education, Health and Community, Liverpool John Moores University. IM Marsh
12   Campus, Barkhill Road, Liverpool UK, L17 6BD.

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^{-5} and -0.13 mmol/L,
38   95% CI -0.19, -0.08; p < 1x10^{-5}] 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^{-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

69   to scarcity of dietary carbohydrates, leading to a reduction in lipogenesis and fat

70   accumulation.[15-17] 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.[15-18] 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.[12,19]

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[6,20,21] 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.[22-26] 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.[27] 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,[28-30] others report non-significant changes[31] or decreased levels[32]

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[2] 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,[14] 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[32] and many report only the pooled net effect of large and small trials without

98   stratification by duration of intervention or follow up.[28-30] Small studies may overestimate

99   intervention effects, introduce higher heterogeneity and increase risk of selection bias[33-36]

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[37]. Based on these

102 limitations, Santos *et al.*[38] 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[39] (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 MLCD $\leq$ 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)[40,41] 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 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.[38]

Exclusion criteria

147   To increase power, reduce heterogeneity, and selection bias, [33-35,37], 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.

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[42] 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.[39]

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).[43]

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.[44]   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.[42] 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[45-83]. Five trials[45-49] did not include LDL-C as an outcome;

204   ten trials[50-59] were performed on participants with Diabetes mellitus and/or CVD; eleven

205   trials[60-70] had less than 100 randomised participants; three[71-73] had duration < 6 months; two

206   trials[74,75] did not report on SD or 95% CI; seven trials[76-82] were irrelevant with inappropriate

207   intervention; and one trial[83] 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[84-91]. 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.[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

238   intervention, but were well balanced in both the CRD and LFD arm of intervention in each

239   study (Table 4[84-91]).

240   LDL-C concentrations were directly measured except in the trials of Bazzano *et al.*[84] and Due

241   et al.[85] where it was calculated using the Friedewald formula.[94] In the study of Klemsdal *et*

242   *al.*[89] 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.*[90], apolipoprotein-B concentration in the trial of Klemsdal *et al.*,[89]

245   and concentration of the very low density lipoprotein cholesterol (VLDL-C) fraction in the

246   study of Foster *et al.*[86]

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[84-91]. Three studies did not

250   clearly report on the sequence generation[89-91] and allocation concealment[86,89,90] 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[84-88] showed low risk of attrition bias. Four studies[86,89-91] 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[84-91] & 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.,[86] 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.,[85] 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[84,86,88,90] & Table S2) and the

280   moderate carbohydrate subgroup (MLCD) with 35–45% CHO TEI (Figure 6[85,87,89,91] & 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[84-91] & Table S1) and TG [-0.13 mmol/L, 95% CI -0.19, -0.08; P $< 1 \times 10^{-5}$]

289 (Figure 8[84-91] & 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.*[87] without affecting the

297 significance of the weighted mean difference ($I^2 = 45\%$; P $< 1 \times 10^{-4}$).

298 The VLCD (Figure 9[84,86,88,90] & 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 = 1×10^{-5}; for 12 months: 0.13 mmol/L, 95% CI 0.09, 0.17; P = 1×10^{-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 = 1×10^{-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[84,86,88,90] & 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[85,87,89,91], 12[85,87,89,91], & 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[84-87,89,91], 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)[84-87,89,91] &

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*.[90] 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*.[89] Decreases in VLDL-C

331   levels reported by Foster *et al*.[86] 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,[28,32,95] 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.*[29] and Lu *et al.*[30] investigating the effects of a CRD vs LFD on cardiovascular

367   risk markers. While the Lu *et al.*[30] 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.*[29] 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.[96] 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).[97] 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.[29,30]

382   Targeting LDL-C has been a conventional strategy in prevention and treatment of CVD and

383   reduction of mortality rate[98,99] 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.[100] However, the reduction of CVD risk accomplished with

386   this strategy, as it has been reported in several clinical trials,[101,102] 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[103] 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.[104,105] 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[106]; the Framingham Offspring Study[107]; the 11 year follow up of the EPIC

399   (European Prospective Investigation Into Cancer and Nutrition) Norfolk prospective

400   population study.[108] 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.[108] 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.[109] 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.[110,111] 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.[109,112]

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 atherogenecity, 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).[24,25,113,114] 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.[26,113] 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.[25] 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.[114,115]

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,[116] particularly among subjects with metabolic

428   syndrome and insulin resistance, as found in the Framingham Heart Study[117] and in the cohort

429   of the Quebec Cardiovascular Study.[118] 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.[119] 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.*[90] 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.[86] 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.*[120] 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.[120] Similar findings, namely, increase in peak

443 LDL-P size, a shift towards lbLDL 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[121] and after 12 weeks in subjects with

446 atherogenic dyslipidaemia[11] 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,[4,7,14] although the magnitude of the effect shows variations in constellation to

450 the specific diet quality and individual susceptibility.[5,122,123] 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.[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]

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[131] and 11 cohort studies[132]

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.*[133]   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.[14,122,130] 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[134,135] and subsequent

513   discrepancies in effect estimates in the meta-analysis[136] 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 extend 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.[86-88] This has also been confirmed in the three-year follow-up of

520   a RCT[51], 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[94]; 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.[137]

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

551 **Acknowledgments**

552 I.G.D. and T.G-H conceptualised the original idea and constructed the literature search
553 strategy. T.GH, and R.A.B assessed identified studies in duplicate with final review by I.G.D.
554 T.G-H and PP performed the meta-analysis and assessment of bias respectively. T.G-H wrote
555 the manuscript with critical feedback by I.G.D. All authors contributed to editing the
556 manuscript. The above work received no funding and the authors declare no conflict of
557 interest. We would like to acknowledge Ms. Jackie Fealey, Academic Liaison Librarian at
558 Liverpool John Moores University, and Dr Nicola Harman, Research Associate, Clinical Trials
559 Research Centre, University of Liverpool for their assistance with the database search,
560 accessing electronic resources, and referencing.

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

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

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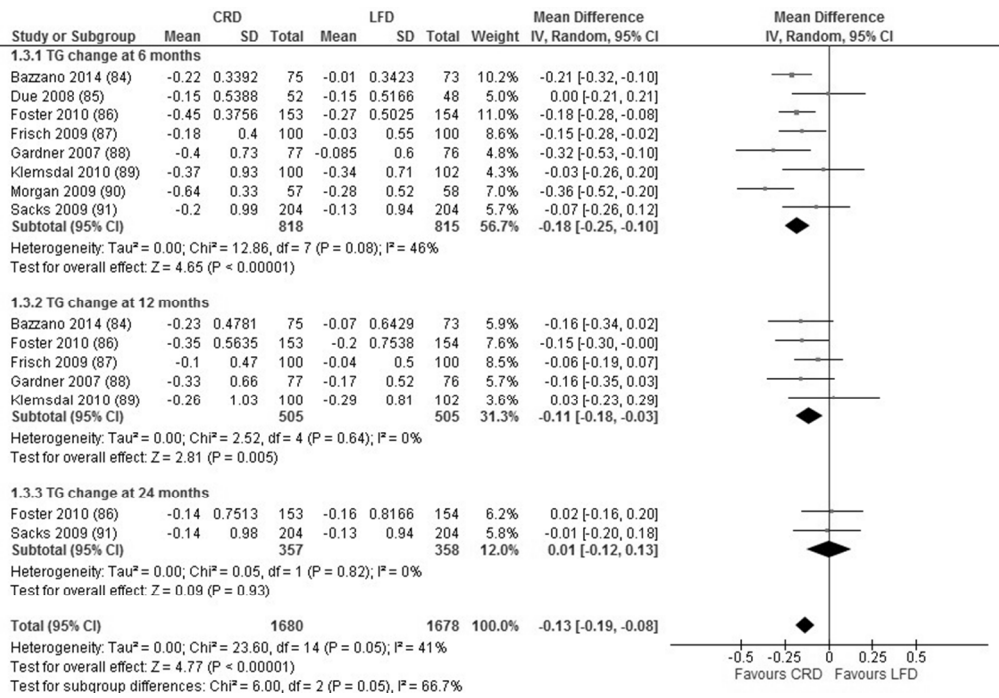
Figure 8. Forest plot for TG changes between CRD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). *Abbreviations*: CRD, carbohydrate restricted diet; LFD, low fat diet; HDL, high density lipoprotein.

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

190x166mm (96 x 96 DPI)

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)

Study or Subgroup	CRD Mean	SD	Total	LFD Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 LDL-C change at 6 months								
Bazzano 2014 (84)	-0.04	0.4781	75	0.02	0.4286	73	8.2%	-0.06 [-0.21, 0.09]
Due 2008 (85)	-0.08	0.431	52	0.01	0.6543	48	4.9%	-0.09 [-0.31, 0.13]
Foster 2010 (86)	0.014	0.5885	153	-0.24	0.5653	154	9.4%	0.25 [0.12, 0.38]
Frisch 2009 (87)	-0.03	0.5	100	-0.03	0.51	100	8.6%	0.00 [-0.14, 0.14]
Gardner 2007 (88)	0.04	0.58	77	-0.08	0.5	76	6.8%	0.12 [-0.05, 0.29]
Klemsdal 2010 (89)	-0.01	0.89	100	-0.12	0.92	102	4.0%	0.11 [-0.14, 0.36]
Morgan 2009 (90)	-0.16	0.76	57	-0.44	0.57	58	4.1%	0.28 [0.03, 0.53]
Sacks 2009 (91)	-0.13	0.85	204	-0.21	0.75	204	7.7%	0.08 [-0.08, 0.24]
Subtotal (95% CI)			818			815	53.7%	0.08 [-0.01, 0.18]
Heterogeneity: Tau² = 0.01; Chi² = 16.85, df = 7 (P = 0.02); I² = 58%								
Test for overall effect: Z = 1.72 (P = 0.08)								
1.1.2 LDL-C change after 12 months								
Bazzano 2014 (84)	-0.08	0.6954	75	-0.05	0.6429	73	5.0%	-0.03 [-0.25, 0.19]
Foster 2010 (86)	-0.222	0.6762	153	-0.224	0.6658	154	8.0%	0.00 [-0.15, 0.15]
Frisch 2009 (87)	0.02	0.65	100	0.06	0.59	100	6.8%	-0.04 [-0.21, 0.13]
Gardner 2007 (88)	0.02	0.58	77	-0.1	0.49	76	6.9%	0.12 [-0.05, 0.29]
Klemsdal 2010 (89)	0.06	0.83	100	-0.14	0.92	102	4.2%	0.20 [-0.04, 0.44]
Subtotal (95% CI)			505			505	30.8%	0.04 [-0.04, 0.12]
Heterogeneity: Tau² = 0.00; Chi² = 4.01, df = 4 (P = 0.40); I² = 0%								
Test for overall effect: Z = 0.90 (P = 0.37)								
1.1.3 LDL-C change after 24 months								
Foster 2010 (86)	-0.12	0.7519	153	-0.2	0.5653	154	8.1%	0.08 [-0.07, 0.23]
Sacks 2009 (91)	-0.05	0.85	204	-0.18	0.8	204	7.4%	0.13 [-0.03, 0.29]
Subtotal (95% CI)			357			358	15.5%	0.10 [-0.01, 0.21]
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%								
Test for overall effect: Z = 1.85 (P = 0.06)								
Total (95% CI)			1680			1678	100.0%	0.07 [0.02, 0.13]
Heterogeneity: Tau² = 0.00; Chi² = 22.25, df = 14 (P = 0.07); I² = 37%								
Test for overall effect: Z = 2.55 (P = 0.01)								
Test for subgroup differences: Chi² = 1.04, df = 2 (P = 0.59), I² = 0%								

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.

Study or Subgroup	VLCD Mean	SD	Total	LFD Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 LDL-C change VLCD vs LFD at 6 months								
Bazzano 2014 (84)	-0.04	0.4781	75	0.02	0.4286	73	13.5%	-0.06 [-0.21, 0.09]
Foster 2010 (86)	0.014	0.5885	153	-0.24	0.5653	154	14.2%	0.25 [0.12, 0.38]
Gardner 2007 (88)	0.04	0.58	77	-0.08	0.5	76	12.5%	0.12 [-0.05, 0.29]
Morgan 2009 (90)	-0.16	0.76	57	-0.44	0.57	58	9.7%	0.28 [0.03, 0.53]
Subtotal (95% CI)			362			361	49.9%	0.14 [-0.02, 0.30]

Heterogeneity: Tau² = 0.02; Chi² = 11.46, df = 3 (P = 0.009); I² = 74%
Test for overall effect: Z = 1.69 (P = 0.09)

1.4.2 LDL-C change VLCD vs LFD at 12 months								
Bazzano 2014 (84)	-0.08	0.6954	75	-0.05	0.6429	73	10.8%	-0.03 [-0.25, 0.19]
Foster 2010 (86)	-0.222	0.6762	153	-0.0224	0.6658	154	13.4%	-0.20 [-0.35, -0.05]
Gardner 2007 (88)	0.02	0.58	77	-0.1	0.49	76	12.6%	0.12 [-0.05, 0.29]
Subtotal (95% CI)			305			303	36.7%	-0.04 [-0.24, 0.16]

Heterogeneity: Tau² = 0.02; Chi² = 7.68, df = 2 (P = 0.02); I² = 74%
Test for overall effect: Z = 0.39 (P = 0.70)

1.4.3 LDL-C change VLCD vs LFD at 24 months								
Foster 2010 (86)	-0.12	0.7519	153	-0.2	0.5653	154	13.4%	0.08 [-0.07, 0.23]
Subtotal (95% CI)			153			154	13.4%	0.08 [-0.07, 0.23]

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)

Total (95% CI)			820			818	100.0%	0.07 [-0.05, 0.18]

Heterogeneity: Tau² = 0.02; Chi² = 27.49, df = 7 (P = 0.0003); I² = 75%
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Chi² = 1.89, df = 2 (P = 0.39), I² = 0%

Favours VLCD   Favours LFD
-0.5 -0.25 0 0.25 0.5

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.

Study or Subgroup	CRD Mean	CRD SD	CRD Total	LFD Mean	LFD SD	LFD Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 HDL-C change at 6 months								
Bazzano 2014 (84)	0.1	0.1884	75	0	0.1902	73	7.8%	0.10 [0.04, 0.16]
Due 2008 (85)	0.09	0.32	52	0.05	0.17	48	4.7%	0.04 [-0.06, 0.14]
Foster 2010 (86)	0.16	0.2504	153	0.02	0.1633	154	9.3%	0.14 [0.09, 0.19]
Frisch 2009 (87)	-0.02	0.2	100	-0.09	0.19	100	8.5%	0.07 [0.02, 0.12]
Gardner 2007 (88)	0.13	0.25	77	0	0.24	76	6.2%	0.13 [0.05, 0.21]
Klemsdal 2010 (89)	0.08	0.35	100	0.08	0.39	102	4.5%	0.00 [-0.10, 0.10]
Morgan 2009 (90)	-0.08	0.32	57	-0.2	0.25	58	4.3%	0.12 [0.01, 0.23]
Sacks 2009 (91)	0.07	0.33	204	-0.01	0.39	204	6.9%	0.08 [0.01, 0.15]
Subtotal (95% CI)			818			815	52.1%	0.09 [0.06, 0.12]
Heterogeneity: Tau² = 0.00; Chi² = 9.97, df = 7 (P = 0.19); I² = 30%								
Test for overall effect: Z = 6.10 (P < 0.00001)								
1.2.2 HDL-C change at 12 months								
Bazzano 2014 (84)	0.24	0.2638	75	0.06	0.2662	73	5.6%	0.18 [0.09, 0.27]
Foster 2010 (86)	0.21	0.313	153	0.1	0.2513	154	7.5%	0.11 [0.05, 0.17]
Frisch 2009 (87)	-0.02	0.21	100	-0.03	0.17	100	8.6%	0.01 [-0.04, 0.06]
Gardner 2007 (88)	0.127	0.23	77	0	0.16	76	7.6%	0.13 [0.06, 0.19]
Klemsdal 2010 (89)	0.12	0.35	100	0.11	0.44	102	4.1%	0.01 [-0.10, 0.12]
Subtotal (95% CI)			505			505	33.5%	0.09 [0.02, 0.15]
Heterogeneity: Tau² = 0.00; Chi² = 16.54, df = 4 (P = 0.002); I² = 76%								
Test for overall effect: Z = 2.68 (P = 0.007)								
1.2.3 HDL-C change at 24 months								
Foster 2010 (86)	0.2	0.313	153	0.12	0.2513	154	7.5%	0.08 [0.02, 0.14]
Sacks 2009 (91)	0.163	0.33	204	0.14	0.39	204	6.9%	0.02 [-0.05, 0.09]
Subtotal (95% CI)			357			358	14.4%	0.05 [-0.00, 0.11]
Heterogeneity: Tau² = 0.00; Chi² = 1.39, df = 1 (P = 0.24); I² = 28%								
Test for overall effect: Z = 1.88 (P = 0.06)								
Total (95% CI)			1680			1678	100.0%	0.08 [0.06, 0.11]
Heterogeneity: Tau² = 0.00; Chi² = 30.49, df = 14 (P = 0.007); I² = 54%								
Test for overall effect: Z = 6.15 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.53, df = 2 (P = 0.46), I² = 0%								

Favours CRD   Favours LCD
-0.5   -0.25   0   0.25   0.5

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.

Study or Subgroup	CRD Mean	SD	Total	LFD Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 TG change at 6 months								
Bazzano 2014 (84)	-0.22	0.3392	75	-0.01	0.3423	73	10.2%	-0.21 [-0.32, -0.10]
Due 2008 (85)	-0.15	0.5388	52	-0.15	0.5166	48	5.0%	0.00 [-0.21, 0.21]
Foster 2010 (86)	-0.45	0.3756	153	-0.27	0.5025	154	11.0%	-0.18 [-0.28, -0.08]
Frisch 2009 (87)	-0.18	0.4	100	-0.03	0.55	100	8.6%	-0.15 [-0.28, -0.02]
Gardner 2007 (88)	-0.4	0.73	77	-0.085	0.6	76	4.8%	-0.32 [-0.53, -0.10]
Klemsdal 2010 (89)	-0.37	0.93	100	-0.34	0.71	102	4.3%	-0.03 [-0.26, 0.20]
Morgan 2009 (90)	-0.64	0.33	57	-0.28	0.52	58	7.0%	-0.36 [-0.52, -0.20]
Sacks 2009 (91)	-0.2	0.99	204	-0.13	0.94	204	5.7%	-0.07 [-0.26, 0.12]
Subtotal (95% CI)			818			815	56.7%	-0.18 [-0.25, -0.10]
Heterogeneity: Tau² = 0.00; Chi² = 12.86, df = 7 (P = 0.08); I² = 46%								
Test for overall effect: Z = 4.65 (P < 0.00001)								
1.3.2 TG change at 12 months								
Bazzano 2014 (84)	-0.23	0.4781	75	-0.07	0.6429	73	5.9%	-0.16 [-0.34, 0.02]
Foster 2010 (86)	-0.35	0.5635	153	-0.2	0.7538	154	7.6%	-0.15 [-0.30, -0.00]
Frisch 2009 (87)	-0.1	0.47	100	-0.04	0.5	100	8.5%	-0.06 [-0.19, 0.07]
Gardner 2007 (88)	-0.33	0.66	77	-0.17	0.52	76	5.7%	-0.16 [-0.35, 0.03]
Klemsdal 2010 (89)	-0.26	1.03	100	-0.29	0.81	102	3.6%	0.03 [-0.23, 0.29]
Subtotal (95% CI)			505			505	31.3%	-0.11 [-0.18, -0.03]
Heterogeneity: Tau² = 0.00; Chi² = 2.52, df = 4 (P = 0.64); I² = 0%								
Test for overall effect: Z = 2.81 (P = 0.005)								
1.3.3 TG change at 24 months								
Foster 2010 (86)	-0.14	0.7513	153	-0.16	0.8166	154	6.2%	0.02 [-0.16, 0.20]
Sacks 2009 (91)	-0.14	0.98	204	-0.13	0.94	204	5.8%	-0.01 [-0.20, 0.18]
Subtotal (95% CI)			357			358	12.0%	0.01 [-0.12, 0.13]
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%								
Test for overall effect: Z = 0.09 (P = 0.93)								
Total (95% CI)			1680			1678	100.0%	-0.13 [-0.19, -0.08]
Heterogeneity: Tau² = 0.00; Chi² = 23.60, df = 14 (P = 0.05); I² = 41%								
Test for overall effect: Z = 4.77 (P < 0.00001)								
Test for subgroup differences: Chi² = 6.00, df = 2 (P = 0.05), I² = 66.7%								

-0.5 -0.25 0 0.25 0.5
Favours CRD   Favours LFD

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.
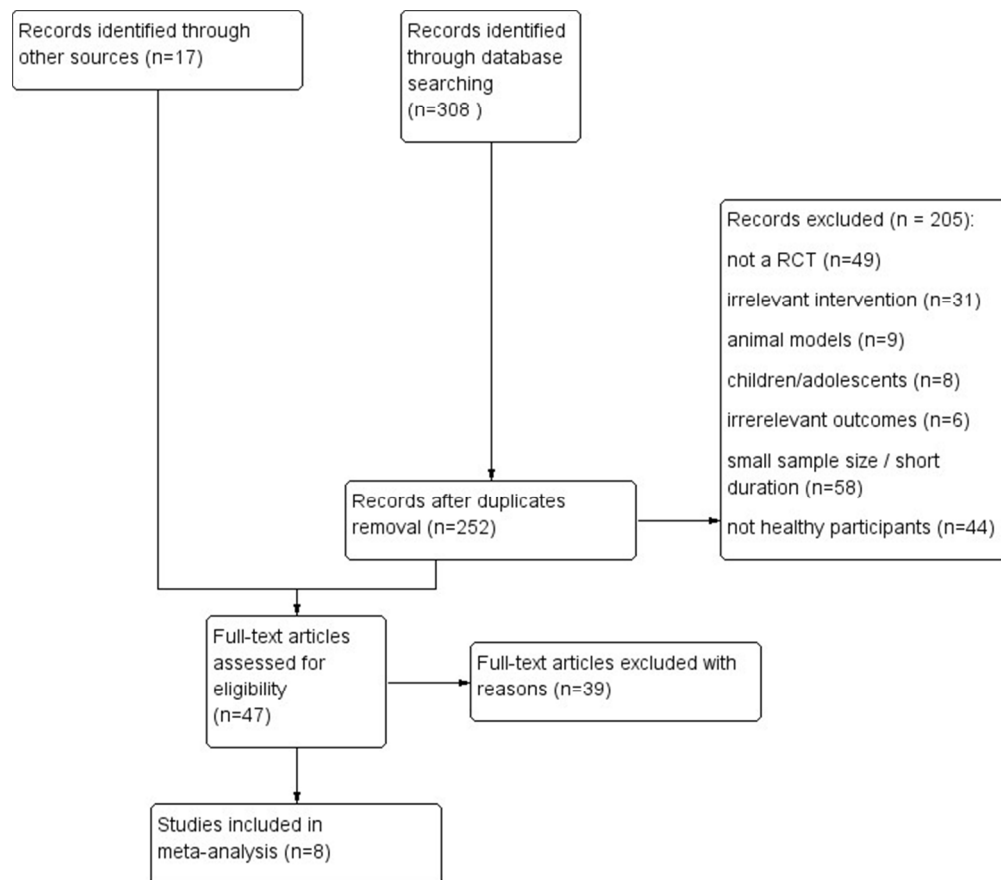
Study or Subgroup	VLCD Mean	SD	Total	LFD Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.2.1 HDL-C change VLCD vs LFD at 6 months								
Bazzano 2014 (84)	0.1	0.1884	75	0	0.1902	73	14.5%	0.10 [0.04, 0.16]
Foster 2010 (86)	0.16	0.2504	153	0.02	0.1633	154	24.0%	0.14 [0.09, 0.19]
Gardner 2007 (88)	0.13	0.25	77	0	0.24	76	8.9%	0.13 [0.05, 0.21]
Morgan 2009 (90)	-0.08	0.32	57	-0.2	0.25	58	4.9%	0.12 [0.01, 0.23]
Subtotal (95% CI)			362			361	52.3%	0.13 [0.09, 0.16]
Heterogeneity: Tau² = 0.00; Chi² = 1.06, df = 3 (P = 0.79); I² = 0%								
Test for overall effect: Z = 7.66 (P < 0.00001)								
3.2.2 HDL-C change VLCD vs LFD at 12 months								
Bazzano 2014 (84)	0.24	0.2638	75	0.06	0.2662	73	7.4%	0.18 [0.09, 0.27]
Foster 2010 (86)	0.21	0.313	153	0.1	0.2513	154	13.3%	0.11 [0.05, 0.17]
Gardner 2007 (88)	0.127	0.23	77	0	0.16	76	13.7%	0.13 [0.06, 0.19]
Subtotal (95% CI)			305			303	34.4%	0.13 [0.09, 0.17]
Heterogeneity: Tau² = 0.00; Chi² = 1.70, df = 2 (P = 0.43); I² = 0%								
Test for overall effect: Z = 6.53 (P < 0.00001)								
3.2.3 HDL-C change VLCD vs LFD at 24 months								
Foster 2010 (86)	0.2	0.313	153	0.12	0.2513	154	13.3%	0.08 [0.02, 0.14]
Subtotal (95% CI)			153			154	13.3%	0.08 [0.02, 0.14]
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.47 (P = 0.01)								
Total (95% CI)			820			818	100.0%	0.12 [0.10, 0.14]
Heterogeneity: Tau² = 0.00; Chi² = 4.71, df = 7 (P = 0.70); I² = 0%								
Test for overall effect: Z = 10.27 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.95, df = 2 (P = 0.38), I² = 0%								

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.

Study or Subgroup	VLCD Mean	SD	Total	LFD Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.4.1 TG change VLCD vs LFD at 6 months								
Bazzano 2014 (84)	-0.22	0.3392	75	-0.01	0.3423	73	17.7%	-0.21 [-0.32, -0.10]
Foster 2010 (86)	-0.45	0.3756	153	-0.27	0.5025	154	19.3%	-0.18 [-0.28, -0.08]
Gardner 2007 (88)	-0.4	0.73	77	-0.085	0.6	76	8.1%	-0.32 [-0.53, -0.10]
Morgan 2009 (90)	-0.64	0.33	57	-0.28	0.52	58	12.0%	-0.36 [-0.52, -0.20]
Subtotal (95% CI)			362			361	57.0%	-0.24 [-0.32, -0.16]

Heterogeneity: Tau² = 0.00; Chi² = 4.29, df = 3 (P = 0.23); I² = 30%
Test for overall effect: Z = 5.92 (P < 0.00001)

3.4.2 TG change VLCD vs LFD at 12 months								
Bazzano 2014 (84)	-0.23	0.4781	75	-0.07	0.6429	73	9.9%	-0.16 [-0.34, 0.02]
Foster 2010 (86)	-0.35	0.5635	153	-0.2	0.7538	154	12.9%	-0.15 [-0.30, -0.00]
Gardner 2007 (88)	-0.33	0.66	77	-0.17	0.52	76	9.6%	-0.16 [-0.35, 0.03]
Subtotal (95% CI)			305			303	32.5%	-0.16 [-0.25, -0.06]

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 2 (P = 1.00); I² = 0%
Test for overall effect: Z = 3.10 (P = 0.002)

3.4.3 TG change VLCD vs LFD at 24 months								
Foster 2010 (86)	-0.14	0.7513	153	-0.16	0.8166	154	10.5%	0.02 [-0.16, 0.20]
Subtotal (95% CI)			153			154	10.5%	0.02 [-0.16, 0.20]

Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.82)

| Total (95% CI) | | | 820 | | | 818 | 100.0% | -0.19 [-0.26, -0.12] |

Heterogeneity: Tau² = 0.00; Chi² = 11.88, df = 7 (P = 0.10); I² = 41%
Test for overall effect: Z = 5.32 (P < 0.00001)
Test for subgroup differences: Chi² = 7.45, df = 2 (P = 0.02), I² = 73.2%

-0.5 -0.25   0   0.25   0.5
Favours VLCD   Favours LFD

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.
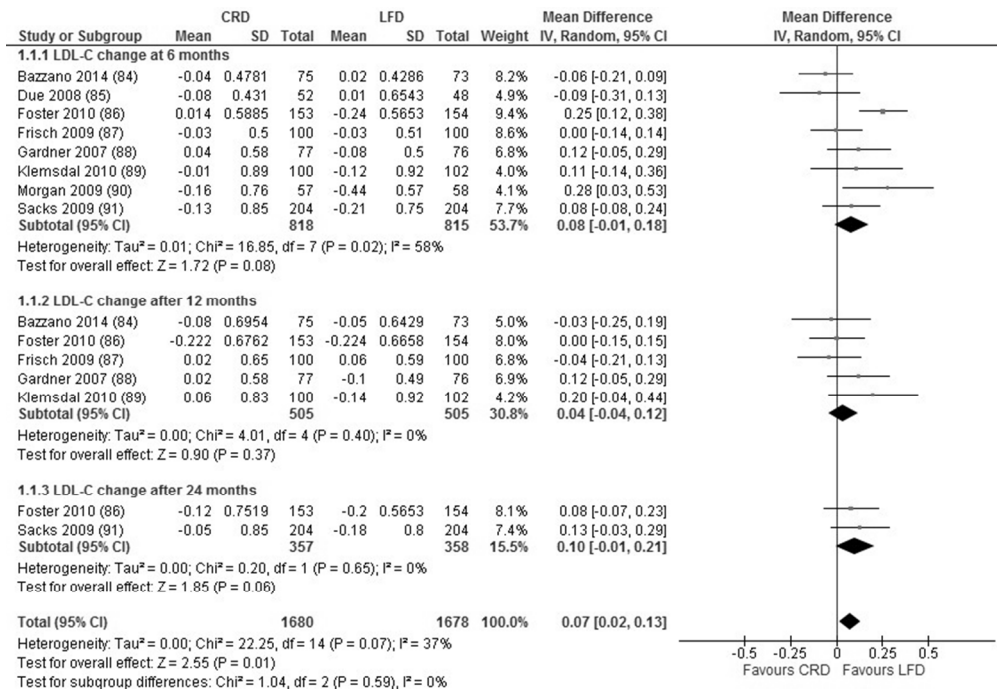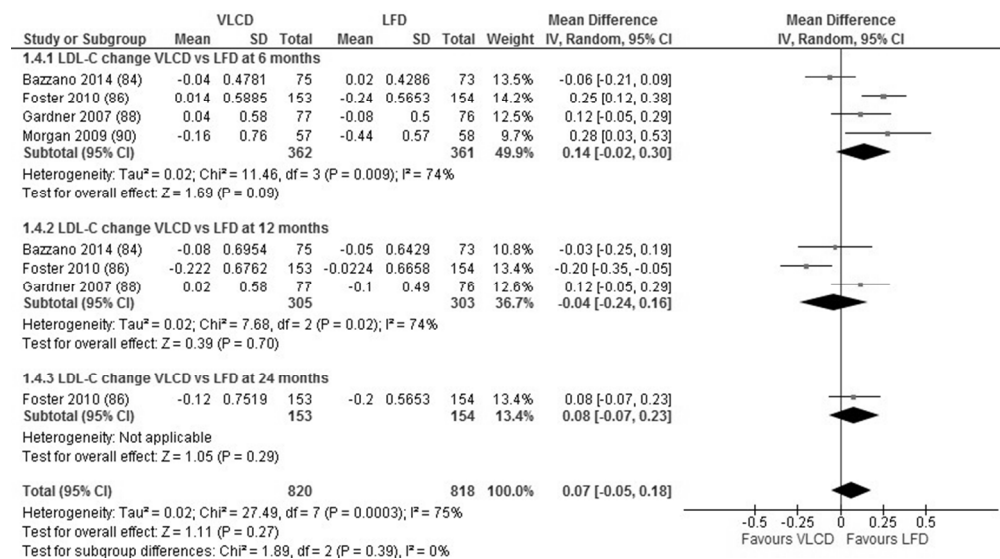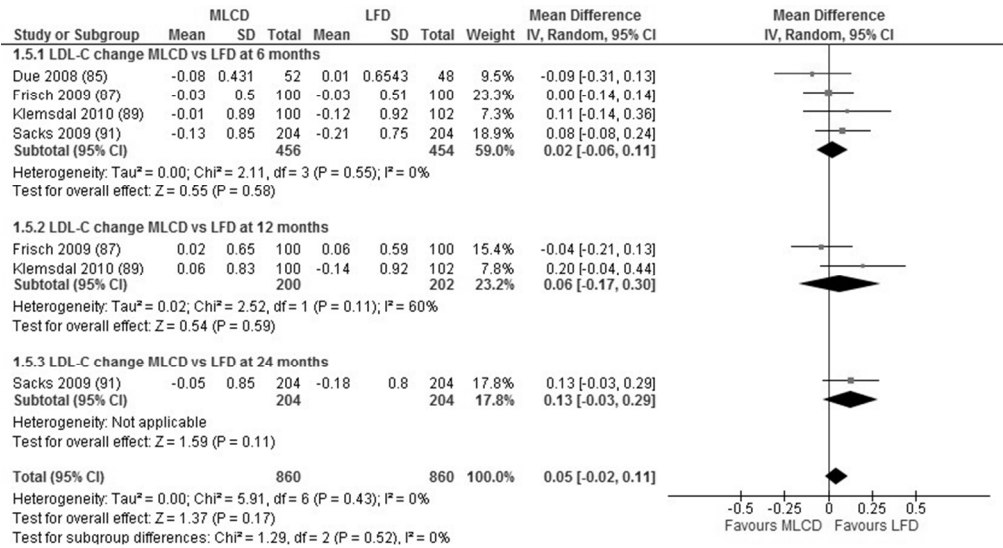
Figure 11. Forest plot for HDL-C changes between MLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: MLCD, moderate low carbohydrate diet; LFD, low fat diet; HDL, high density lipoprotein.
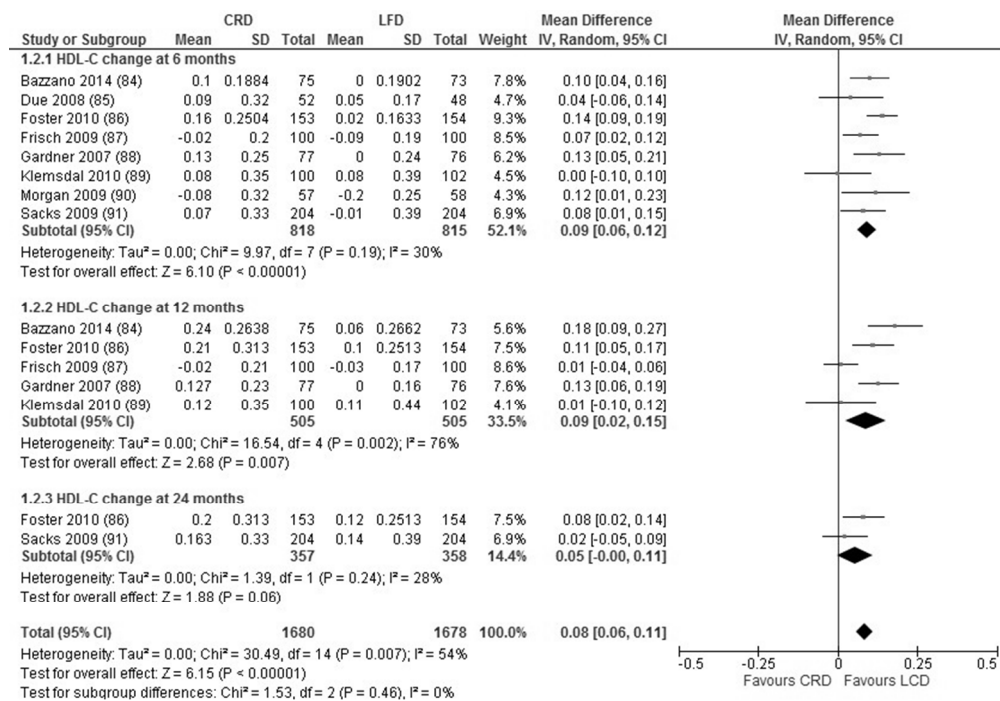
	MLCD			LFD				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
3.5.1 TG change MLCD vs LFD at 6 months									
Due 2008 (85)	-0.15	0.5388	52	-0.15	0.5166	48	10.3%	0.00 [-0.21, 0.21]	
Frisch 2009 (87)	-0.18	0.4	100	-0.03	0.55	100	24.8%	-0.15 [-0.28, -0.02]	
Klemsdal 2010 (89)	-0.37	0.93	100	-0.34	0.71	102	8.5%	-0.03 [-0.26, 0.20]	
Sacks 2009 (91)	-0.2	0.99	204	-0.13	0.94	204	12.6%	-0.07 [-0.26, 0.12]	
Subtotal (95% CI)			456			454	56.2%	-0.09 [-0.18, 0.00]	

Heterogeneity: Tau² = 0.00; Chi² = 1.81, df = 3 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.91 (P = 0.06)

3.5.2 TG change MLCD vs LFD at 12 months									
Frisch 2009 (87)	-0.1	0.47	100	-0.04	0.5	100	24.4%	-0.06 [-0.19, 0.07]	
Klemsdal 2010 (89)	-0.26	1.03	100	-0.29	0.81	102	6.7%	0.03 [-0.23, 0.29]	
Subtotal (95% CI)			200			202	31.1%	-0.04 [-0.16, 0.08]	

Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.67 (P = 0.50)

3.5.3 TG change MLCD vs LFD at 24 months									
Sacks 2009 (91)	-0.14	0.98	204	-0.13	0.94	204	12.7%	-0.01 [-0.20, 0.18]	
Subtotal (95% CI)			204			204	12.7%	-0.01 [-0.20, 0.18]	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.92)

Total (95% CI)			860			860	100.0%	-0.06 [-0.13, 0.00]	

Heterogeneity: Tau² = 0.00; Chi² = 2.90, df = 6 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.84 (P = 0.07)
Test for subgroup differences: Chi² = 0.72, df = 2 (P = 0.70), I² = 0%

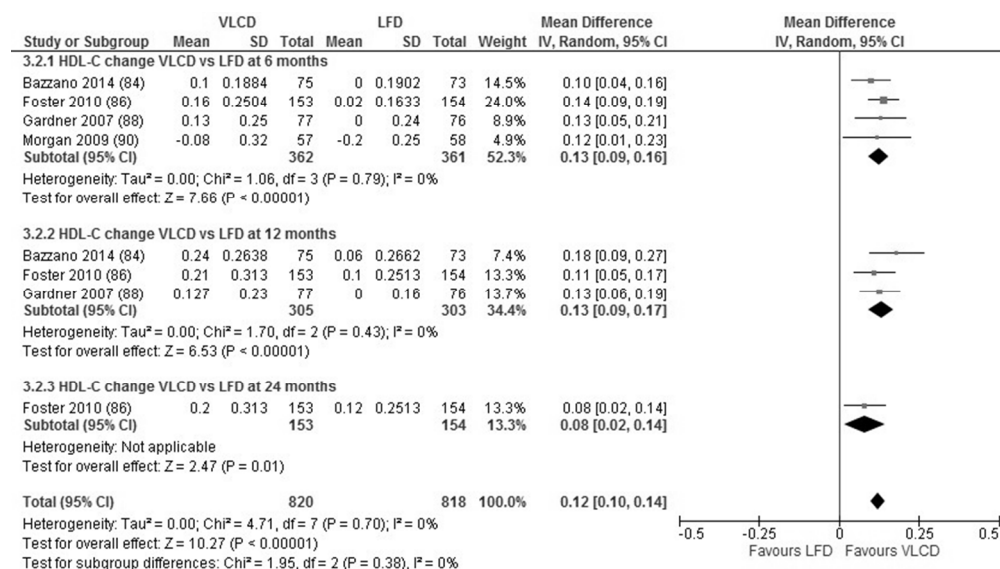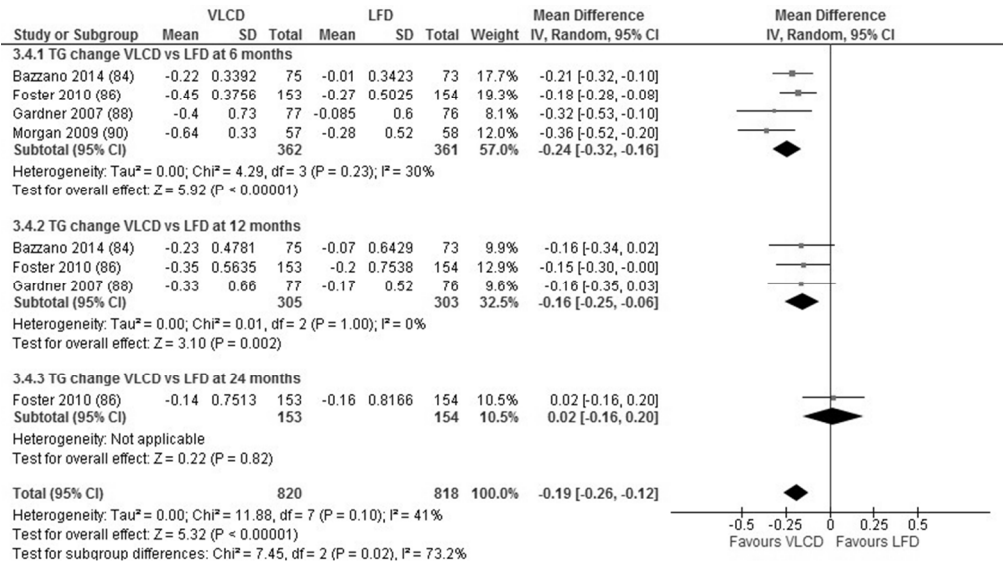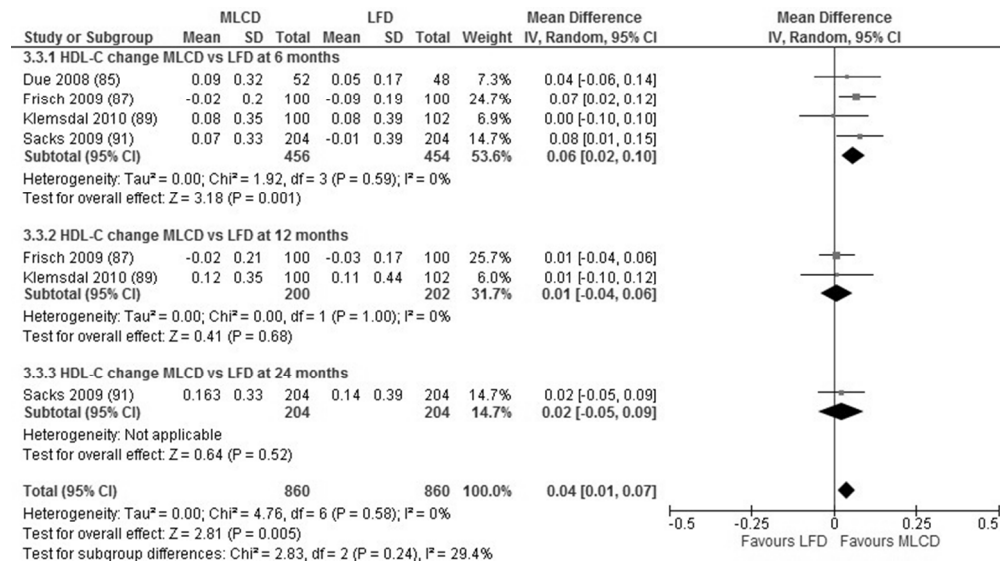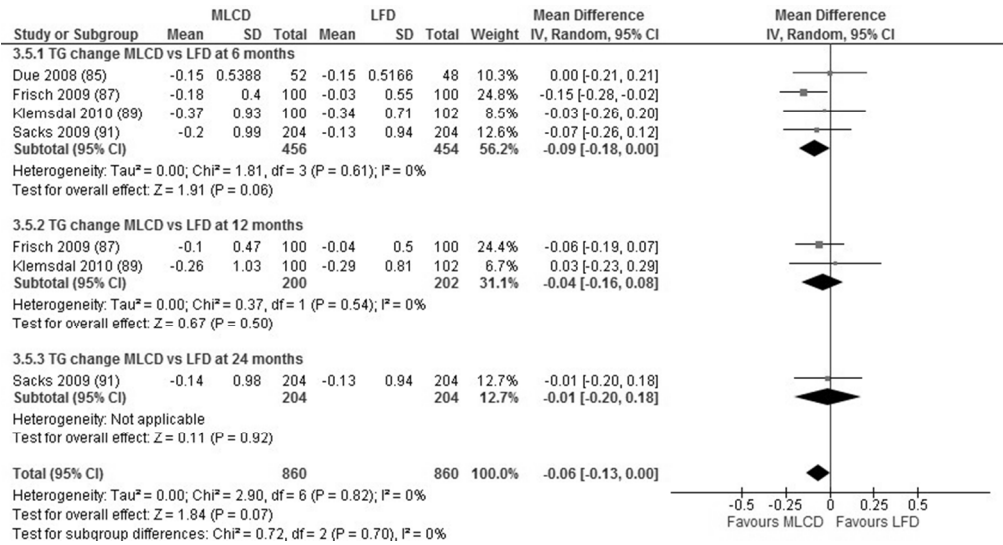-0.5 -0.25 0 0.25 0.5
Favours MLCD   Favours LFD

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.

Study or Subgroup	CRD Mean	SD	Total	LFD Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.6.1 TC change at 6 months								
Bazzano 2014 (84)	-0.04	0.5216	75	0.03	0.5143	73	0.0%	-0.07 [-0.24, 0.10]
Due 2008 (85)	-0.06	0.7404	52	0.01	0.6824	48	0.0%	-0.07 [-0.35, 0.21]
Foster 2010 (86)	-0.0176	0.0244	153	-0.012	0.0188	154	28.7%	-0.01 [-0.01, -0.00]
Frisch 2009 (87)	-0.07	0.56	100	-0.07	0.5	100	0.0%	0.00 [-0.15, 0.15]
Klemsdal 2010 (89)	-0.1	1.05	100	-0.2	0.95	102	0.0%	0.10 [-0.18, 0.38]
Sacks 2009 (91)	-0.096	1	204	-0.15	0.93	204	0.0%	0.05 [-0.13, 0.24]
Subtotal (95% CI)			684			681	28.8%	-0.01 [-0.01, -0.00]

Heterogeneity: Tau² = 0.00; Chi² = 1.73, df = 5 (P = 0.88); I² = 0%
Test for overall effect: Z = 2.25 (P = 0.02)

1.6.2 TC change at 12 months								
Bazzano 2014 (84)	0.05	0.6954	75	0.03	0.6858	73	0.0%	0.02 [-0.20, 0.24]
Foster 2010 (86)	-0.0225	0.0219	153	-0.016	0.0188	154	32.7%	-0.01 [-0.01, -0.00]
Frisch 2009 (87)	0.03	0.75	100	0.13	0.61	100	0.0%	-0.10 [-0.29, 0.09]
Klemsdal 2010 (89)	0	0.99	100	-0.2	0.99	102	0.0%	0.20 [-0.07, 0.47]
Subtotal (95% CI)			428			429	32.7%	-0.01 [-0.04, 0.03]

Heterogeneity: Tau² = 0.00; Chi² = 3.19, df = 3 (P = 0.36); I² = 6%
Test for overall effect: Z = 0.28 (P = 0.78)

1.6.3 TC change at 24 months								
Foster 2010 (86)	-0.017	0.0188	153	-0.016	0.0188	154	38.5%	-0.00 [-0.01, 0.00]
Sacks 2009 (91)	-0.008	1	204	-0.096	0.95	204	0.0%	0.09 [-0.10, 0.28]
Subtotal (95% CI)			357			358	38.5%	-0.00 [-0.01, 0.00]

Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.66)

Total (95% CI)			1469			1468	100.0%	-0.00 [-0.01, -0.00]

Heterogeneity: Tau² = 0.00; Chi² = 9.33, df = 11 (P = 0.59); I² = 0%
Test for overall effect: Z = 3.08 (P = 0.002)
Test for subgroup differences: Chi² = 2.02, df = 2 (P = 0.37), I² = 0.8%

(Mean Difference IV, Random, 95% CI; axis: -0.5 -0.25 0 0.25 0.5; Favours CRD Favours LFD)
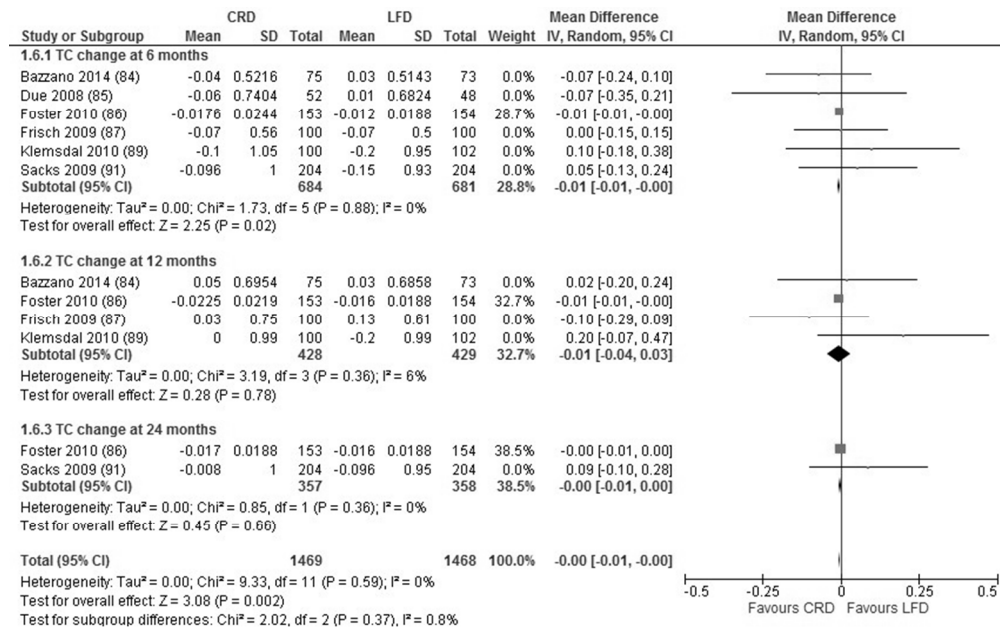
Figure 13. Forest plot for Total Cholesterol changes between CRD and LFD at 6, 12 and 24 months compared to baseline (mmol/L). Abbreviations: CRD, carbohydrate restricted diet; LFD, low fat diet.

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

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
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

For more information, visit: **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)

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]	1×10^{-5}	52
HDL-C change at 6 months	8	1633	0.09 [0.06, 0.12]	1×10^{-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]	1×10^{-5}	40
TG change at 6 months	8	1633	-0.18 [-0.25, -0.10]	1×10^{-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]	1×10^{-5}	0
HDL-C change at 6 months	4	723	0.13 [0.09, 0.16]	1×10^{-5}	0
HDL-C change at 12 months	3	608	0.13 [0.09, 0.17]	1×10^{-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]	1×10^{-5}	41
TG change at 6 months	4	723	-0.24 [-0.32, -0.16]	1×10^{-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
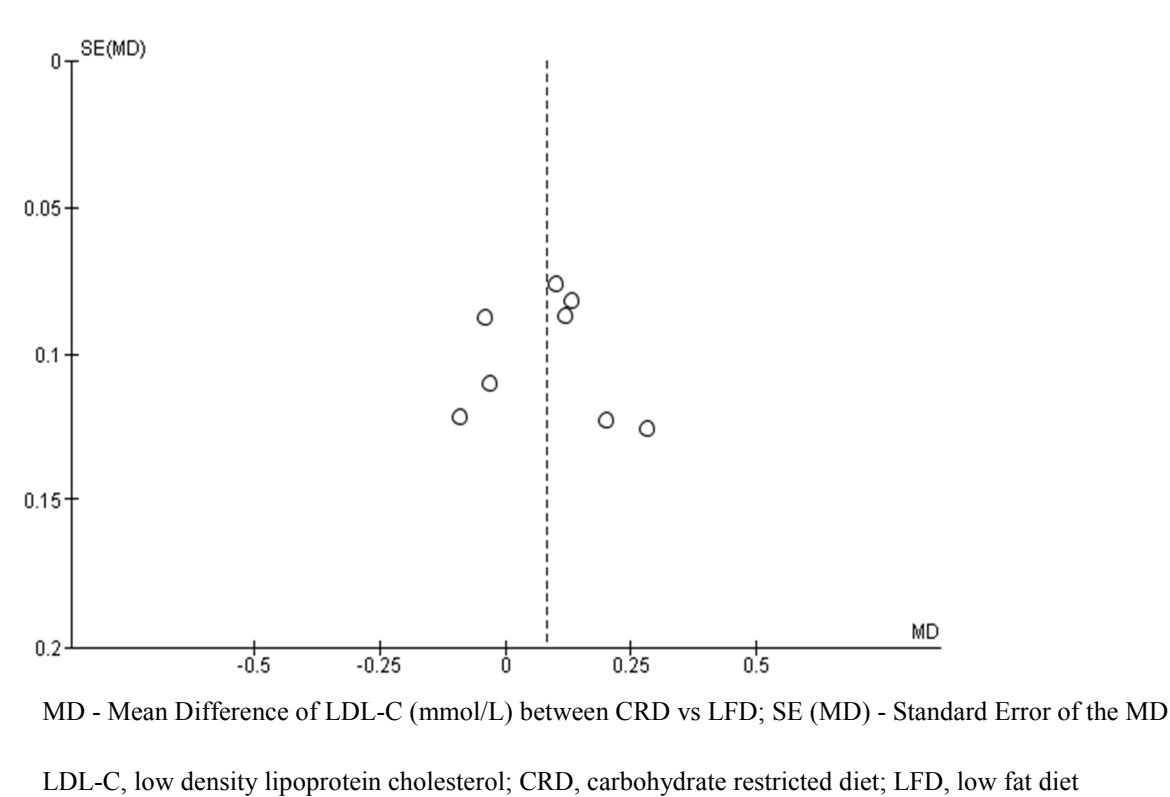
Table S3. Weighted mean difference of LDL-C, HDL-C and TG between MLCD and LFD at 6, 12 and 24 months compared to baseline (mmol/L)

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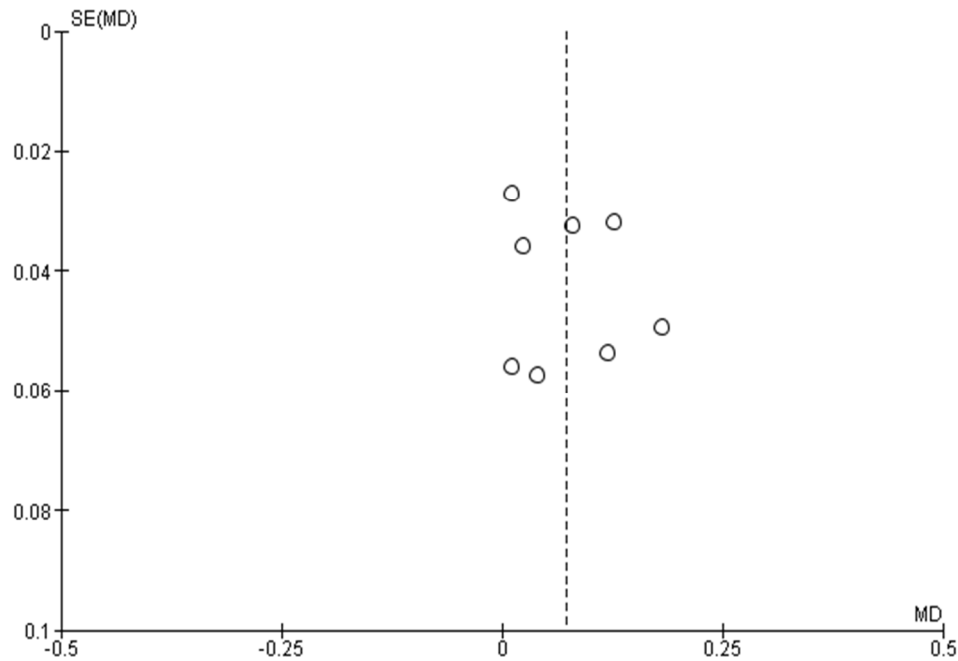
MD - Mean Difference of HDL-C (mmol/L) between CRD vs LFD; SE (MD) - Standard Error of the MD

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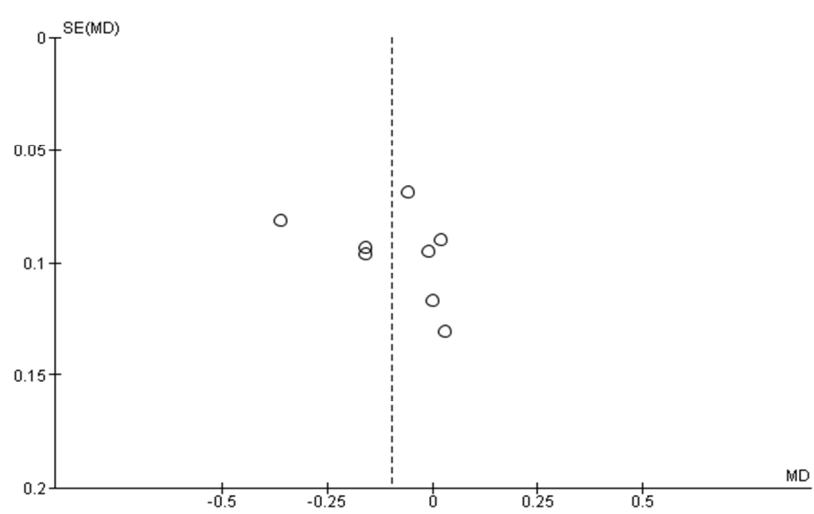
MD - Mean Difference of TG (mmol/L) between CRD vs LFD; SE (MD) - Standard Error of the MD
TG, plasma triglycerides; CRD, carbohydrate restricted diet; LFD, low fat diet