Low-carbohydrate diets differing in carbohydrate restriction improve cardiometabolic and anthropometric markers in healthy adults: A randomised clinical trial

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Background. Low-carbohydrate, high-fat (LCHF) diets are useful for treating a range of health conditions, but there is little research evaluating the degree of carbohydrate restriction on outcome measures. This study compares anthropometric and cardiometabolic outcomes between differing carbohydrate-restricted diets.

Objective. Our hypothesis was that moderate carbohydrate restriction is easier to maintain and more effective for improving cardiometabolic health markers than greater restriction.

Design. Seventy-seven healthy participants were randomised to a very low carbohydrate ketogenic diet (VLCKD), low-carbohydrate diet (LCD), or moderate-low carbohydrate diet (MCD), containing 5%, 15% and 25% total energy from carbohydrate respectively, for 12-weeks. Anthropometric and metabolic health measures were taken at baseline and at 12 weeks. Using ANOVA, both within and between-group outcomes were analysed.

Results. Of 77 participants, 39 (51%) completed the study. In these completers overall, significant reductions in weight and body mass index occurred ([mean change] 3.7 kg/m^2; 95% confidence limits [CL]: 3.8, 1.8), along with increases in high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, (0.49 mmol/L; 95% CL; 0.06, 0.92; $p = 0.03$), and total cholesterol concentrations (0.11 mmol/L; 95% CL; 0.00, 0.23; $p = 0.05$). Triglyceride (TG) levels were reduced by 0.12 mmol/L (95% CL; -0.20, 0.02; $p = 0.02$). No significant changes occurred between groups. The largest improvements in HDL-c and TG and anthropometric changes occurred for the VLCKD group.

Conclusions. LCHF diets have a positive effect on markers of health. Adherence to the allocation of carbohydrate was more easily achieved in MCD, and LCD groups compared to VLCKD and there were comparable improvements in weight loss and waist circumference and greater improvements in HDL-c and TG with greater carbohydrate restriction.

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1   **Abstract**

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3   conditions, but there is little research evaluating the degree of carbohydrate restriction on

4   outcome measures. This study compares anthropometric and cardiometabolic outcomes between

5   differing carbohydrate-restricted diets.

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9   ketogenic diet (VLCKD), low-carbohydrate diet (LCD), or moderate-low carbohydrate diet

10   (MCD), containing 5%, 15% and 25% total energy from carbohydrate respectively, for 12-

11   weeks. Anthropometric and metabolic health measures were taken at baseline and at 12 weeks.

12   Using ANOVA, both within and between-group outcomes were analysed.

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14   significant reductions in weight and body mass index occurred ([mean change] 3.7 kg/m^2; 95%

15   confidence limits [CL]: 3.8, 1.8), along with increases in high-density lipoprotein cholesterol,

16   low-density lipoprotein cholesterol, (0.49 mmol/L; 95% CL; 0.06, 0.92; $p = 0.03$), and total

17   cholesterol concentrations (0.11 mmol/L; 95% CL; 0.00, 0.23; $p = 0.05$). Triglyceride (TG)

18   levels were reduced by 0.12 mmol/L (95% CL; -0.20, 0.02; $p = 0.02$). No significant changes

19   occurred between groups. The largest improvements in HDL-c and TG and anthropometric

20   changes occurred for the VLCKD group.

21   **Conclusions.** LCHF diets have a positive effect on markers of health. Adherence to the

22   allocation of carbohydrate was more easily achieved in MCD, and LCD groups compared to

23   VLCKD and there were comparable improvements in weight loss and waist circumference and

24   greater improvements in HDL-c and TG with greater carbohydrate restriction.

25 **Introduction**

26 Low-carbohydrate, high-fat (LCHF) and very low-carbohydrate ketogenic diets (VLCKD) are

27 increasingly used for the management of a range of health conditions, including neurological

28 disorders, obesity, diabetes, metabolic syndrome, and various cancers. (Castro et al. 2015;

29 Henderson et al. 2006; Keene 2006; Kulak & Polotsky 2013; Lefevre & Aronson 2000; Levy et

30 al. 2012; Maalouf et al. 2009; Neal et al. 2008; Paoli et al. 2013; Sumithran & Proietto 2008;

31 Varshneya et al. 2015) They are also used widely in the general population for weight-loss and

32 maintenance, (Bueno et al. 2013) with improved satiety and control of hunger frequently

33 reported by those who adhere to these diets. (Johnstone et al. 2008; McClernon et al. 2007; Paoli

34 et al. 2015) Despite the potential offered by LCHF and low-carbohydrate, high-protein (LCHP)

35 diets, there is little evidence for the superiority of greater carbohydrate restriction compared to

36 moderate. Systematic reviews show that despite greater weight- and fat-loss initially, over longer

37 timeframes, when energy intake is restricted, there is little difference in outcomes for weight-

38 loss, total and low density liproprotein cholesterol (LDL-c) concentrations between diets that are

39 higher or lower in carbohydrate. (Hernández Alcantara et al. 2015; Huntriss et al. 2017; Naude et

40 al. 2014; Snorgaard et al. 2017; van Wyk et al. 2016) However, there are greater reductions in

41 fasted glucose concentrations, (Snorgaard et al. 2017) and greater improvements in high density

42 lipoprotein cholesterol (HDL-c) and glycated haemoglobin (HbA1c) with greater degrees of

43 carbohydrate restriction. (Huntriss et al. 2017) Controversy exists about the nature of low-

44 carbohydrate diets (LCD) and VLCKDs, (Wood & Fernandez 2009) and definitions for LCDs

45 range from 20-200 g of carbohydrate per day, (Last & Wilson 2006; Westman et al. 2007) or up

46 to 40-45% of daily energy from carbohydrate. (2012; Wheeler et al. 2012) Definitions for

47 VLCKDs are similarly vague. The accepted definition for nutritional ketosis (NK) in the clinical

48 nutrition field has become the achievement of ≥ 0.5 mmol/L ß- hydroxybutyrate (BOHB), as the

49 majority of people following a VLCKD achieve this level of blood ketones (Gibson et al. 2015),

50 and this threshold has been used by several studies as an indicator of entry into NK. (Guerci et al.

51 2003; Harvey et al. 2018) Ketonaemia consistent with NK typically results from diets containing

52 a 3:1 to 4:1 ratio of lipids to non-lipid macronutrients, or at least 75% of calories coming from

53 lipids, very low carbohydrates (often less than 50 g) and low-to-moderate amounts of protein,

54 (Livingston et al. 1977; Livingstone 1972) or diets containing 60%-75% of calories from lipids

55 that include a high proportion of medium chain triglycerides (MCTs). (Huttenlocher et al. 1971;

56 Huttenlocher 1976) Studies report that adherence is difficult with extreme carbohydrate

57 restriction, i.e. < 50 g of carbohydrate per day, (Huntriss et al. 2017) but insulin-resistant (IR)

58 people may be less likely to adhere to a low-fat, high-carbohydrate diet, compared to those who

59 are more insulin-sensitive (IS). Adherence and weight-loss are similar between both IR and IS

60 participants allocated to a less restrictive low-carbohydrate diet. (McClain et al. 2013)

61 Few studies directly compare very low-carbohydrate diets with less extreme carbohydrate-

62 restricted diets. Johnstone and colleagues compared the effects of a non-ketogenic low-

63 carbohydrate diet (fat 30% of total energy (TE); carbohydrate 40% of TE) to a ketogenic, low-

64 carbohydrate diet (fat 60% TE; carbohydrate 5%TE) in twenty adults over six weeks, finding

65 that the diets were equally effective in reducing body weight and insulin resistance. (Johnston et

66 al. 2006)

67 Our hypothesis was that moderate carbohydrate restriction may be easier to maintain, and thus

68 more effective than greater degrees of carbohydrate restriction. The aim of the present study

69 therefore, is to compare anthropometric and cardiometabolic outcomes between a VLCKD, LCD

70 and moderate-low carbohydrate diet (MCD), containing 5%, 15% and 25% TE from

71 carbohydrate respectively, in healthy adults.

72   **Materials and Methods**

73   *Population*

74   Seventy-seven participants, 25 males, 52 females (mean age: 39 years, range: 25 to 49; mean

75   BMI 27 kg/m^2, range: 20-39) were recruited between the 7th and 19th of August 2017 and gave

76   written, informed consent to participate in this 12-week, randomised, clinical intervention study.

77   The study took place between 11th September and 10th December 2017. Collection of data and

78   analysis was performed at AUT's Human Potential Centre, Auckland, New Zealand.

79   *Inclusion and exclusion criteria*

80   Participants were required to be healthy and between the ages of 25 and 49 years. Exclusion

81   criteria were; underweight (< 18.5 BMI kg/m^2), diagnosed with diabetes, diagnosed with any

82   serious medical condition, having previously following a ketogenic diet, or being a current or

83   former client of any of the researchers in clinical practice.

84   *Ethical approval*

85   The trial was registered by the Australia New Zealand Clinical Trial Registry.

86   (ACTRN12617000421336p). Ethics approval for this study was granted by the Southern

87   Committee of the Health and Disability Ethics Committee of New Zealand. 17/STH/60

88   *Dietary interventions and allocation*

89   Participants completed baseline testing of blood and basic anthropometric measures and a lead-in

90   dietary recording week to identify habitual calorie intake. Participants were randomised by the

91   study statistician to one of three low-carbohydrate diet plans which advised intakes of either 5%,

92   15%, or 25% of TE from carbohydrate. The randomisation was stratified by gender, using a pre-

93   prepared sequence, with investigators blinded to treatment allocation at baseline and follow-up.

94   Participants were assigned to the next treatment group according to their order of recruitment.

95   The primary researcher responsible for initial statistical analysis was blinded to the treatment

96   group allocation until this analysis had been completed.

97   Diet plans, which included macronutrient and calorie allocation and a sample menu plan, were

98   individualised to the participant, with energy intake determined by the mean reported energy

99   consumed per day in the lead-in dietary recording week. Advice was given to limit protein intake

100   to 1.4 g/kg/d (weight at baseline testing), consistent with International Society of Sports

101   Nutrition guidelines for optimal protein intake for performance. (Campbell et al. 2007) This was

102   chosen as an appropriate protein intake that was not likely to unduly influence the study results,

103   because the study participants were healthy people, who may also be engaged in physical activity

104   and sports. Participants were advised to adhere as strictly as possible to the energy and

105   macronutrient prescription for the first three weeks of the intervention. For the final nine weeks

106   of the intervention, they were advised to eat *ad libitum* but to adhere as closely as possible to the

107   carbohydrate energy limit for their treatment group as a percentage of their total energy intake.

108   Usual exercise patterns were continued. Dietary intake was recorded by participants in a mobile

109   application (Fat Secret) with the researchers able to obtain real time entry on a partner mobile

110   application (Fat Secret Pro). Results were monitored for safety and compliance by the primary

111   researcher and research assistants tasked with data-monitoring. Compliance to the dietary

112   allocation was monitored daily by a data monitoring team. Where non-compliance to the dietary

113   allocation, especially for carbohydrate, was noticed, the participant was notified and offered

114   support and advice.

115   Figure 1 profiles the instructions for the dietary allocations over the 13-week study course.

116   [Figure 1.]

117   Figure 1. Flow-chart showing instructions for the dietary allocations

118   Participants were instructed to contact either the clinical nutritionist or the registered dietitian in

119   the research team for any assistance during the study duration.

120   *Anthropometry*

121   The following measures were taken: height, weight, waist circumference at the narrowest point

122   between the lowest rib and the iliac crest, and hip circumference at the widest point of the hips

123   and buttocks. These measures were then used to derive body mass index (BMI), waist-hip ratio,

124   and the waist-height ratio at baseline and during follow-up.

125   *Blood measures*

126   Following an overnight fast, blood samples were obtained from participants, before the first

127   meal, via venipuncture by a certified phlebotomist from an antecubital vein and collected into

128   PST Vacutainer tubes using lithium-heparin as the anticoagulant (Becton Dickinson). Within 15

129   minutes of collection, tubes were centrifuged at 1500 revolutions per minute for 10 min at +4°C,

130   and plasma samples were transferred into clean polypropylene tubes and frozen at −80°C until

131   analyses were conducted using specific diagnostics assays on a Roche Modular analyser (P800

132   and E170). Blood samples were analysed for total cholesterol (Total-c), LDL-c, HDL-c,

133   triglycerides (TG), C-reactive protein (CRP), gamma-glutamyl transferase (GGT), alanine

134   aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glucose

135   and uric acid on the P800 module. Insulin, and C-peptide concentrations were measured on the

136   E170 module. All analytical biomarkers were measured at baseline and immediately following

137   the 12-week intervention. The total duration of the assay for each analyte was less than 20 min

138 based on the electrochemiluminescence principle (ruthenium-conjugated monoclonal antibodies)

139 for the E170 module and specific enzyme assay methods for the P800 module. Quantitative

140 results were determined via instrument-specific full point calibration curves and validated with

141 specific controls. Additional information for analytes, lower limits of measurement, measuring

142 range, and test principle can be found in appendix 1.

143 *Statistical analyses*

144 Effects of the dietary interventions on outcomes were determined for each participant by

145 calculating the change in the various measures from baseline. The significance of these within-

146 group changes from baseline was determined by a paired t-test. All between-group variations

147 were compared using ANOVA. A 5% two-sided alpha level was used to determine significance.

148 Further comparisons were made by undertaking multiple linear regression with adjustment made

149 for variables recorded at baseline. A sensitivity analysis of the results was carried out using

150 stabilised inverse-probability of completing weights for the BMI change outcome to check

151 whether these results were likely to have been different had the whole group returned for

152 followed-up.

153 **Results**

154 A total of 283 people were assessed for eligibility with 206 excluded and 77 included for

155 randomisation to the trial groups (Figure 2). Ten participants withdrew after they were

156 randomised. Two failed to comply with guidelines to submit baseline data and withdrew from

157 the study (one male, one female), and three females withdrew due to changes in personal

158 circumstances, including two who became pregnant. A further five withdrew due to challenges

159 arising from following the diets. The reasons for withdrawals were as follows: two female

160   participants found the dietary allocation of carbohydrate too difficult to sustain (one each in the

161   5% and 15% allocation groups); one did not want to continue tracking with the food app; one felt

162   that she could not maintain her sports performance on 15% total energy from carbohydrate; and

163   one female in the 5% allocation group reported amenorrhea and reductions in strength and

164   power, despite improved mental clarity. A further 28 did not book for or failed to present for

165   post-intervention measurements. This left 39 participants with follow-up results available for

166   analysis.

167   There were no significant differences in baseline characteristics between completers and

168   non-completers and no meaningful difference in the number of non-completers by group with

169   50%, 50%, and 48% of participants not completing post-intervention measures in the MCD,

170   LCD, and VLCKD groups respectively. Mean baseline levels of TG were, however, 36% higher

171   at baseline in those lost to follow-up compared to those who were not, even though the

172   difference between the two distributions was not significant ($p = 0.08$). There was also no

173   significant variation for age, gender, or ethnicity between the groups, in the participants

174   analysed. At baseline, blood measures were all within reference ranges except for Total-c which

175   had an overall mean of 5.31 mmol/L (SD = 1.29) for completers, and a significant between-

176   group difference ($p = 0.005$).

177   Baseline characteristics of those included for analysis are presented in Table 1, by randomised

178   treatment group.

179   [Table 1. Baseline characteristics of study participants]

180   [Figure 2.]

181   Figure 2. Flow-chart showing participant recruitment, randomisation, allocation and lost-to-

182   follow-up

183 *Anthropometry*

184 Mean weight and BMI at baseline differed between groups ($p = 0.046$ and 0.050 respectively).

185 The LCD group had the highest starting BMI at baseline of 29.1 kg/m^2 (SD = 4.9), followed by

186 MCD (BMI = 26.4 kg/m^2, SD = 3.2). The lowest starting BMI was in the VLCKD group with a

187 mean BMI of 25.5 kg/m^2 (SD = 2.8). Overall, there was a significant reduction in weight across

188 all groups ($p < 0.001$). Mean weight loss increased with the magnitude of carbohydrate

189 restriction, with 4.12 kg (SD = 2.54), 3.93 kg (SD = 3.71), and 2.97 kg (SD = 3.25) lost by the

190 VLCKD, LCD, and MCD groups respectively. However, the differences in weight loss between

191 these groups were not statistically significant ($p = 0.626$). Similarly, a highly significant change

192 in BMI of -1.22 kg/m^2 (SD = 1.03, $p < 0.001$) was recorded overall. While the reduction in BMI

193 was greater per magnitude of carbohydrate restriction, this difference was not significant ($p =$

194 0.686).

195 All dietary interventions led to reductions in both waist and hip girth. There was an overall

196 reduction in waist measurement of 2.85 cm (SD = 2.99) and hip girth reduced by 3.43 cm (SD =

197 4.67, $p < 0.001$ for both measures). The reduction in waist measurement girth did not differ

198 significantly by group ($p = 0.99$) but the change in hip girth approached the threshold for

199 significance ($p = 0.06$). There was a significant change overall to the waist-height ratio (-0.02, p

200 < 0.001) but no significant difference between groups and no significant overall change in the

201 waist-hip ratio. All changes in measures, both overall and by group, with 95% confidence

202 intervals are reported in Table 2.

203 *Blood measures*

204   This paper focuses on the key cardiometabolic outcome measures of Total-c, LDL-c, HDL-c,

205   TG, CRP, glucose, and insulin. Liver enzymes and uric acid were included in the initial analysis

206   as they are emerging markers of interest for metabolic syndrome and insulin resistance. (Babio et

207   al. 2015; Ballestri et al. 2016) One participant had GGT levels above the reference range upper

208   limit of 60 U/L. This was reduced from baseline to completion; 143 U/L to 106 U/L. Another

209   participant had baseline levels of ALT of 79 U/L which normalised to 30 U/L at completion

210   (reference range upper limit, 45 U/L). Overall, there was no meaningful change in liver enzymes

211   or uric acid and the differences between groups were not significant.

212   The most meaningful changes observed were for CRP and insulin. CRP was reduced in the MCD

213   and LCD treatment groups overall by -3.90 mg/L (SD = 12.60), and -3.04 mg/L (SD = 3.90),

214   respectively. There was a marginal increase in CRP in the VLCKD group of 0.14 mg/L (SD =

215   1.10) which we would not consider to be meaningful. While the overall change from baseline

216   CRP approached the threshold for significance ($p = 0.074$), there was no difference between the

217   groups ($p = 0.339$). While at baseline, no significant difference for CRP was present between

218   groups ($p = 0.346$), there were several readings for CRP that were above the reference range

219   upper limit of 5 mg/L. The highest reading of 46.9 mg/L was recorded in the MCD group and

220   there were also three readings > 5 mg/L in the LCD group, with the highest maximal reading of

221   13 mg/L. Conversely, the maximal recorded value for CRP in the VLCKD group at baseline was

222   2.6 mg/L. On follow-up, all results were < 5 mg/L.

223   Insulin concentration was reduced overall by 13.6 pmol/L (SD = 24.8, $p < 0.001$). The greatest

224   change occurred in the LCD group, followed by the VLCKD group, with the smallest change in

225   the MLC group. The difference between groups, however, was not statistically significant ($p =$

226   0.185).

227   Statistically significant changes, albeit of a relatively small magnitude, occurred for Total-c,

228   LDL-c and HDL-c, which were all increased at completion vs baseline, and for TG which were

229   reduced, with no significant variation between groups. No meaningful change from baseline was

230   observed for fasted glucose. There was however, a significant improvement in the TG-HDL ratio

231   of -0.102 (SD = 0.220, p = 0.006). This improvement was increased with greater carbohydrate

232   restriction with changes of -0.023 (SD = 0.158), -0.118 (SD = 0.291) and -0.154 (SD = 0.182),

233   for MCD, LCD, and VLCKD respectively (p = 0.308).

234   Large proportional changes from baseline occurred for insulin, TG, Total-c, LDL-c and HDL-c.

235   Proportional increases from baseline for Total-c and LDL-c were greatest for LCD, followed by

236   VLCKD, and MCD. There was no relative change from baseline for both TG and HDL-c in the

237   MCD group. Improvements in HDL-c and TG occurred for the LCD group, with the greatest

238   proportional change in the VLCKD group. There were relatively minor proportional changes for

239   the remaining measures. (Figure 3.) All changes in reported measures, overall and by group, with

240   95% confidence intervals, are reported in Table 2.

241   [Figure 3.]

242   Figure 3. Percent change in outcome measures from baseline. MCD, moderately-low

243   carbohydrate diet; LCD, low-carbohydrate diet; VLCKD, very-low-carbohydrate ketogenic diet;

244   BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG,

245   triglyceride; CRP, c-reactive protein

246   ***Adherence to diet***

247   The individual mean daily energy intake per group, by week, is shown in Figure 4. A marginal

248   increase in reported energy intake occurred during the first three weeks, during which time

249   participants had been advised to maintain usual energy intake. After the first three weeks,

250   participants had been advised to eat *ad libitum* but preserve the carbohydrate allocation as a

251   percentage of total energy intake. In this phase, the pattern of increased energy over baseline was

252   maintained over most weeks but eventually declined. By week 12 there was an overall reduction

253   in mean energy compared to baseline of 66 Kcal, 95 Kcal, and 192 Kcal for MCD, LCD, and

254   VLCKD respectively. So, overall there was a greater magnitude of energy increase initially with

255   greater carbohydrate restriction, but over time this resulted in a greater reduction in total energy

256   consumed commensurate with the magnitude of carbohydrate restriction. These changes from

257   baseline were relatively small with the greatest magnitude of change from baseline, 12%, 10%,

258   and 18% for MCD, LCD, and VLCKD respectively.

259   [Figure 4.]

260   Figure 4. Mean reported daily energy intake (Kcal) per week by group over twelve weeks. The

261   continuous line represents the 50th percentile, whereas the straight (linear) line is a linear

262   regression. MCD, moderately-low-carbohydrate diet; LCD, low-carbohydrate diet; VLCKD,

263   very-low-carbohydrate ketogenic diet

264   Over 12 weeks carbohydrate intake by group was less than allocation for both MCD (22.5%, SD

265   = 4.5%) and LCD (14.1%, SD = 3.2%) and higher than allocation for VLCKD (7.9%, SD =

266   4.9%). A linear trend was observed for reduction in carbohydrate intake as a proportion of TE for

267   MCD relative to week (Beta = -0.137, p = 0.24). Conversely increased intake by week was

268   observed for LCD (Beta = 0.096, p = 0.24), and VLCKD (Beta = 0.174, p = 0.15) but these

269   trends were not significant within groups, or between group allocations (p = 0.108). Figure 5

270   shows the reported energy per participant, derived from carbohydrate per group, by week.

271 [Figure 5.]

272 Figure 5. Reported carbohydrate intake as a percentage of TE. The continuous line represents the

273 50th percentile. MCD, moderately-low-carbohydrate diet; LCD, low-carbohydrate diet; VLCKD,

274 very-low-carbohydrate ketogenic diet

275 Protein intake did not differ between the groups at baseline (p = 0.299). There was no

276 significant variation between groups for average protein intake per day over the course of the

277 study. Fat intake varied by group but was consistent with their total energy intake, and protein

278 and carbohydrate allocations.

279 **Discussion**

280 *Principal findings*

281 Overall, the results demonstrated that reduced carbohydrate diets have a positive effect on select

282 markers of health. Despite a high number of participants who did not present for follow-up

283 testing, in those included for analysis, low-carbohydrate diets were easily adhered to over a 12-

284 week period. While there was little difference in the consistency of adherence between the

285 differing dietary interventions for calorie and macronutrient allocations overall, carbohydrate

286 intake was more easily maintained in the MCD and LCD groups, as demonstrated by mean

287 intakes lower than allocation, whereas mean intake of carbohydrate as a percentage of TE was

288 higher than allocation in the VLCKD group. There was a marginal increase in energy intake

289 from baseline, but this declined over the course of the study in all groups. Of interest was the

290 relatively low-calorie intake recorded at baseline which might indicate a cohort focussed on

291 weight loss or under-reporting of actual food intake.

292   Almost all participants began the study with anthropometric and blood measurements within the

293   normal range. We would, therefore, not expect large changes for markers of health in a generally

294   'healthy' cohort. This was also a eucaloric intervention, designed to match habitual energy intake

295   and was not designed as a 'weight loss' trial. Despite this, there were significant and clinically

296   meaningful, albeit relatively small, improvements in weight, waist-height ratio, HDL-c and TG.

297   Of the changes in outcome measures that reached the threshold for significance, seven of nine

298   were improved from baseline favourably (HDL, TG, insulin, weight, waist, hip, and BMI) while

299   only Total-c and LDL-c increased by a small magnitude. Of particular interest, was the

300   improvement in waist-height ratio, as this is a strong predictor of all-cause mortality. (Ashwell et

301   al. 2014) We would also consider the significant improvements in HDL-c and TG to be clinically

302   meaningful measures of interest when compared to relatively minor changes in Total-c or LDL-

303   c. Of all the commonly measured biomarkers of cardiovascular risk, TG concentrations are most

304   convincingly linked to incident cardiovascular disease. (Harcombe et al. 2015; Liu et al. 2013;

305   Ravnskov et al. 2016) Reductions in relative risk are seen at TG < 1.02 mmol/L, with every 1

306   mmol/L increase associated with a > 12% increase in risk, for both cardiovascular disease

307   mortality and all-cause mortality. (Liu et al. 2013) Interestingly, in the current study, while mean

308   TG levels were reduced in all groups at 12-weeks, only the VLCKD group showed an

309   improvement in TG levels, with a reduction of 0.04 mmol/L at the upper limit of the 95%

310   confidence intervals, compared to an increase of 0.16 mmol/Land 0.09 mmol/L for the MCD and

311   LCD groups, respectively. This suggests that the higher the baseline TG, the greater the benefit

312   of carbohydrate restriction. Our weighted regression re-analysis also showed that baseline TG

313   affected the change in BMI relative to treatment group, suggesting the hypothesis that baseline

314   lipids may predict outcomes from diets differing in carbohydrate allocation. This hypothesis will

315   be investigated and reported in a separate paper.

316   There is debate around the respective roles that Total-c, LDL-c, HDL-c, TG, and their

317   interactions play with respect to mortality and morbidity outcomes. This warrants further

318   investigation, especially in the context of reduced carbohydrate diets.

319   An additional sensitivity analysis was subsequently carried out which modelled the probability of

320   completing the study, given baseline values of age, gender, weight, TG and glucose

321   concentration using a logistic regression model. These values were then used in a re-analysis of

322   the change in BMI at the end of the study with observations re-weighted by stabilised-inverse

323   probability of treatment from the logistic model. This model showed a larger decrease in mean

324   BMI, comparing the VLCKD to the MCD group (mean change from baseline: -0.59 kg/m^2; 95%

325   CI: 0.21 to -1.39). This difference from the unweighted analysis is likely to be due to different

326   effects of the diets by baseline triglyceride concentration. These changes will be explored further

327   in a future analysis.

328   Several CRP readings were above the reference range of < 5 mg/L. The highest reading of 46.9

329   mg/L, recorded in the MCD group, was found,on subsequent investigation to be due to an

330   unreported flu-like viral infection. At the conclusion of the study, all results for CRP were < 5

331   mg/L. This suggests a positive effect on systemic inflammation from low-carbohydrate diets

332   overall, but high baseline results may have been due to undisclosed illness or another stressor.

333   *Strengths and weaknesses of the study*

334   This study is one of the first to compare eucaloric diets differing in the magnitude of

335   carbohydrate restriction for anthropometric and cardiometabolic outcomes in healthy people. It

336   was a randomised trial, including food tracking with real-time researcher monitoring and

337   feedback, along with advice and information provided to participants from a competent team

338   with extensive experience in the prescription of LCDs and VLCKDs. As such, we believe it

339   provides a valuable addition to the literature to help inform clinical practice.

340   Our study was limited by small sample size and by the failure of 49% of participants to either

341   complete the intervention or present for follow-up testing. This was expected, as high dropout

342   rates are common in dietary studies. For example, a systematic review of low-carbohydrate diets

343   vs low-fat, calorie restricted diet interventions showed an overall attrition rate of 36%, with a

344   higher rate of attrition in low-fat, high-carbohydrate interventions. (Hession et al. 2009) Few

345   participants reported dropping out due to challenges with the diets and most dropouts were

346   instead due to failure to present for testing rather than failure to adhere to the diet, and these

347   numbers were almost identical between the intervention groups. Participants who failed to

348   present were asked to provide reasons for (not) doing so. Two participants responded, stating a

349   clash with work and inability to attend due to parental responsibilities. It is therefore unclear

350   whether there were other factors, outside of scheduling or other logistical challenges, that

351   affected participants completing the study.

352   The final numbers included in our analysis due to attrition, therefore lacked statistical power.

353   With larger numbers, greater statistical significance may be detected. This will be of value to

354   elucidate the impact of differing magnitudes of carbohydrate restriction on important markers of

355   cardiometabolic health in which there was a between group difference in change from baseline,

356   for example, TG and HDL-c. The small sample size also highlights a potential problem of

357   applying parametric tests i.e., whether or not the data collected fit the probability distributions

358   associated with them. An alternative that does not rely on such assumptions is a randomisation

359   test. Results from these tests in our study were very similar to those obtained from *t*-tests, for

360   example, the *p*-value for the between group differences in change from baseline Total-c was $p =$

361   0.658 which was very similar to the results of the ANOVA, $p = 0.686$.

362   The study also did not include a group with a higher carbohydrate allocation consistent with

363   existing dietary guidelines of 45-65% of energy derived from carbohydrate, (Council. 2006) (i.e.,

364   a true control group) and therefore, we cannot discount that higher-carbohydrate, lower-fat diets

365   with an emphasis on high quality food intake, a reduced preponderance of refined, energy-dense

366   foods, nutrition counselling as available in this study, and the accountability of being involved in

367   a study, could lead to similar beneficial results. In the recent DIETFITS study a higher- and

368   lower-carbohydrate intervention, with nutritional counselling and an emphasis on 'quality'

369   nutrition resulted in similar results for weight-loss over twelve months. (Gardner et al. 2018)

370   However, in this study there was a non-significant trend towards greater weight loss, and

371   statistically significant improvements in HDL-c and TG in the lower-carbohydrate group. In the

372   present study, these were improved in a dose-dependent fashion per carbohydrate restriction.

373   There is already a large body of evidence comparing low- to high-carbohydrate diets, and this

374   study helps to instead differentiate between differing lower-carbohydrate diets and their benefits.

375   *Meanings and implications of the study*

376   The consistency of the improvements in important predictors of mortality suggest a beneficial

377   effect of lower carbohydrate interventions overall, and similarly, towards greater improvement

378   on the most meaningful markers of health, concomitant to the magnitude of carbohydrate

379   restriction. This is of particular interest because the dietary interventions were not hypocaloric

380   and were designed to match habitual energy intake. Yet, despite matching the calorie intake at

381   baseline to the dietary prescription, meaningful anthropometric and blood measures of

382 cardiometabolic health, were improved and trended towards greater (non-significant)

383 improvements with greater carbohydrate restriction. However, the adherence to the carbohydrate

384 allocation was more likely to be achieved in those on more moderate carbohydrate-restricted

385 diets.

386 *Unanswered questions and directions for future research*

387 This study shows positive effects overall from reduced carbohydrate diets on select markers of

388 health and further suggests a potential benefit from a greater magnitude of carbohydrate

389 restriction, despite this greater carbohydrate restriction being more difficult to achieve.

390 Additional research with larger sample sizes is warranted to investigate this further. Due to the

391 large numbers that failed to present for follow-up testing, further investigation is warranted to

392 ascertain factors associated with adherence to the diet.

393 **Conclusion**

394 Low-carbohydrate diets are beneficial for the improvement of anthropometric and blood markers

395 of cardiometabolic health in healthy adults and are easily adhered to over 12-weeks. However,

396 the greatest restriction of carbohydrate to 5% of TE may not be realistically achievable for this

397 population. Our results demonstrate that non-hypocaloric, low-carbohydrate diets, matched to

398 habitual calorie intake, result in significant improvements in predictors of long-term health

399 including weight, waist and hip girth, waist-to-height ratio, TG and HDL-c, which increase in

400 magnitude with a greater degree of carbohydrate restriction. However, between-group

401 differences typically did not reach thresholds for statistical significance, and further research

402 with larger samples is required to investigate further, the effects of different degrees of

403 carbohydrate restrictions on outcomes in healthy populations.

Acknowledgements

404

405 We are grateful to the participants in this study. We acknowledge the support of our colleagues

406 at the Human Potential Centre, AUT University, especially Dee Holdsworth-Perks; and at the

407 Holistic Performance Institute. Specifically, we would like to acknowledge the assistance of

408 Amberleigh Jack, Bella Marinkovich, Emily White, and Lulu Caitcheon who assisted with data

409 collection; phlebotomists, Brenda Costa-Scorse and Claudia Barclay; Kirsten Beynon for lab

410 assistance during data collection and analysis, Dave Shaw for his co-operation during data-

411 collection, and Eric Helms and Nigel Harris for advice about the study design and methods.

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Figure 1

Flow of participants with dietary allocations during the study period.

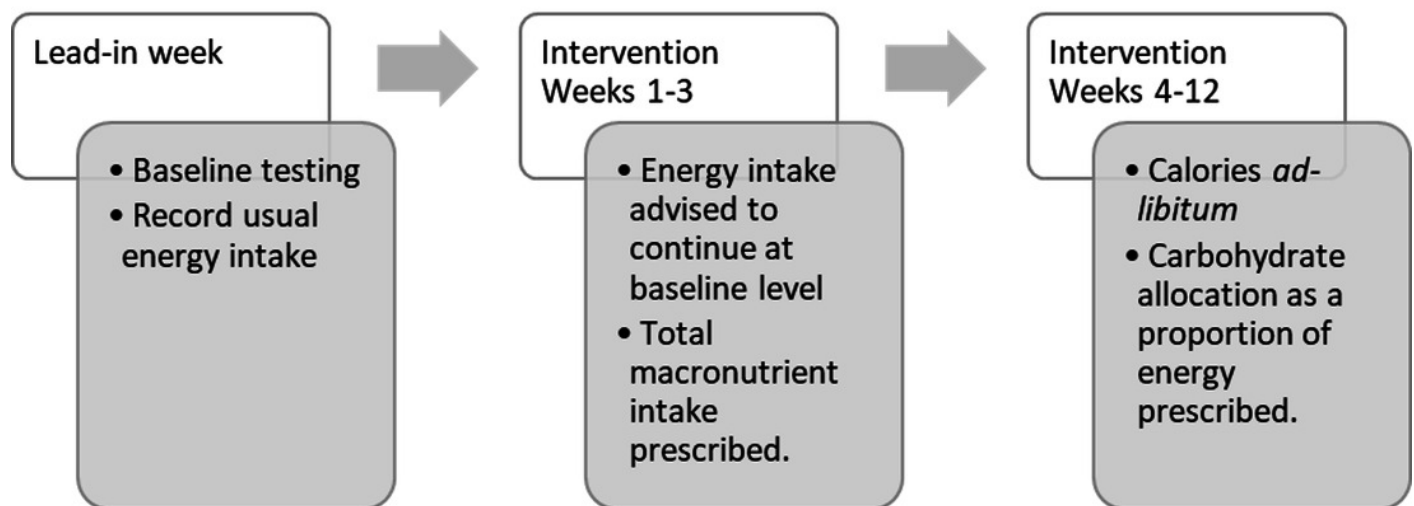



Figure 2

Participants included for participation, randomisation, allocation, and lost to follow up.

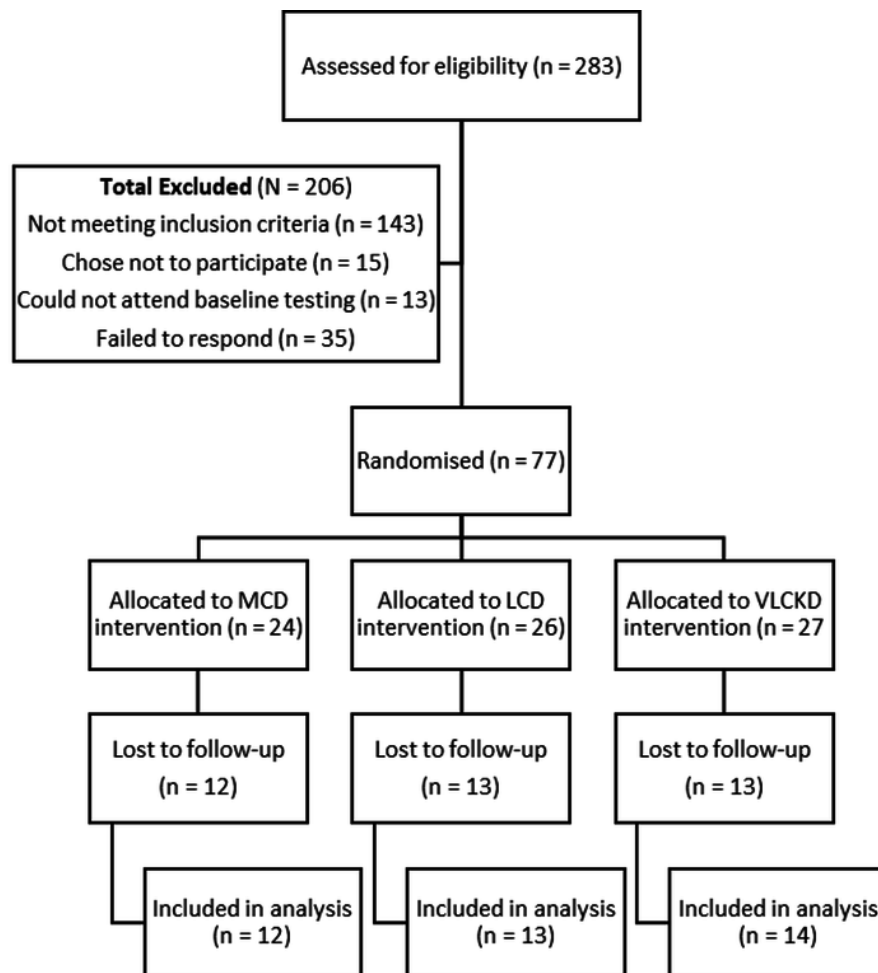
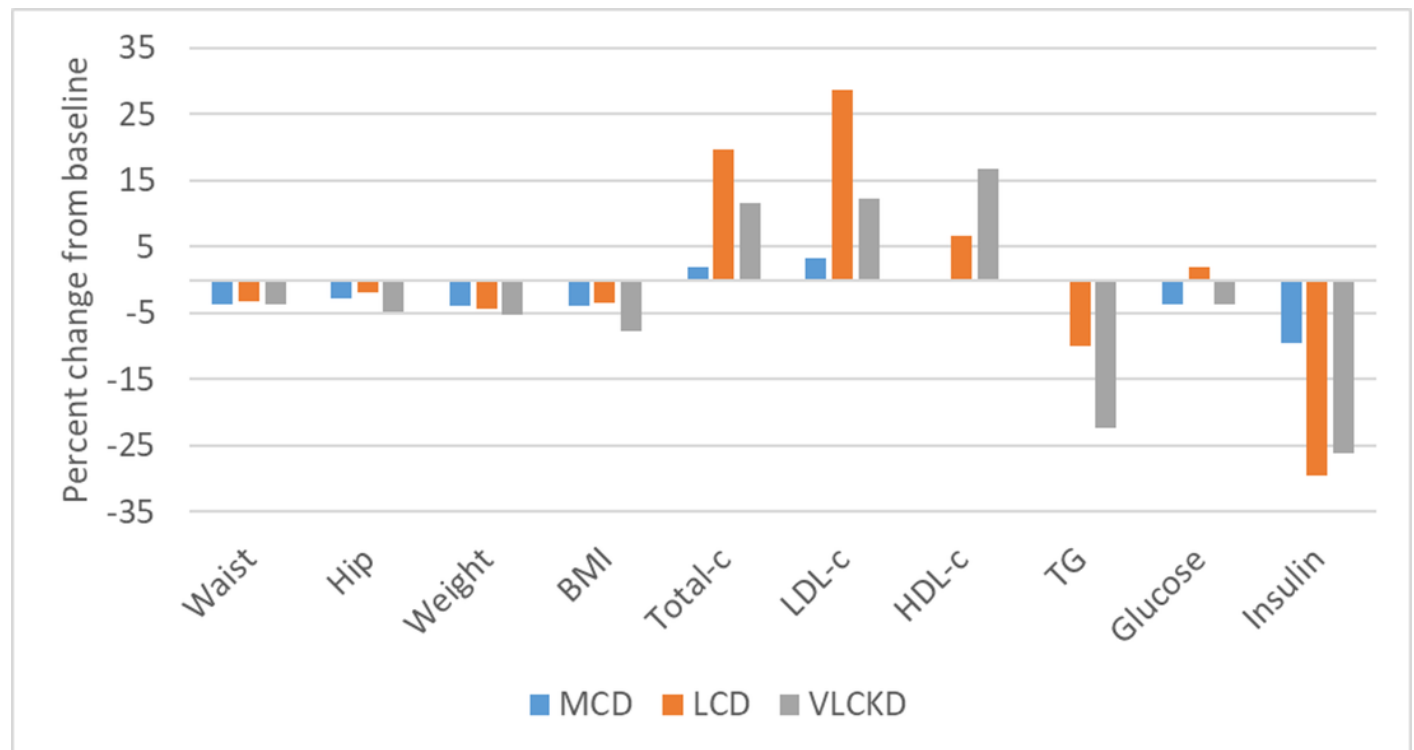
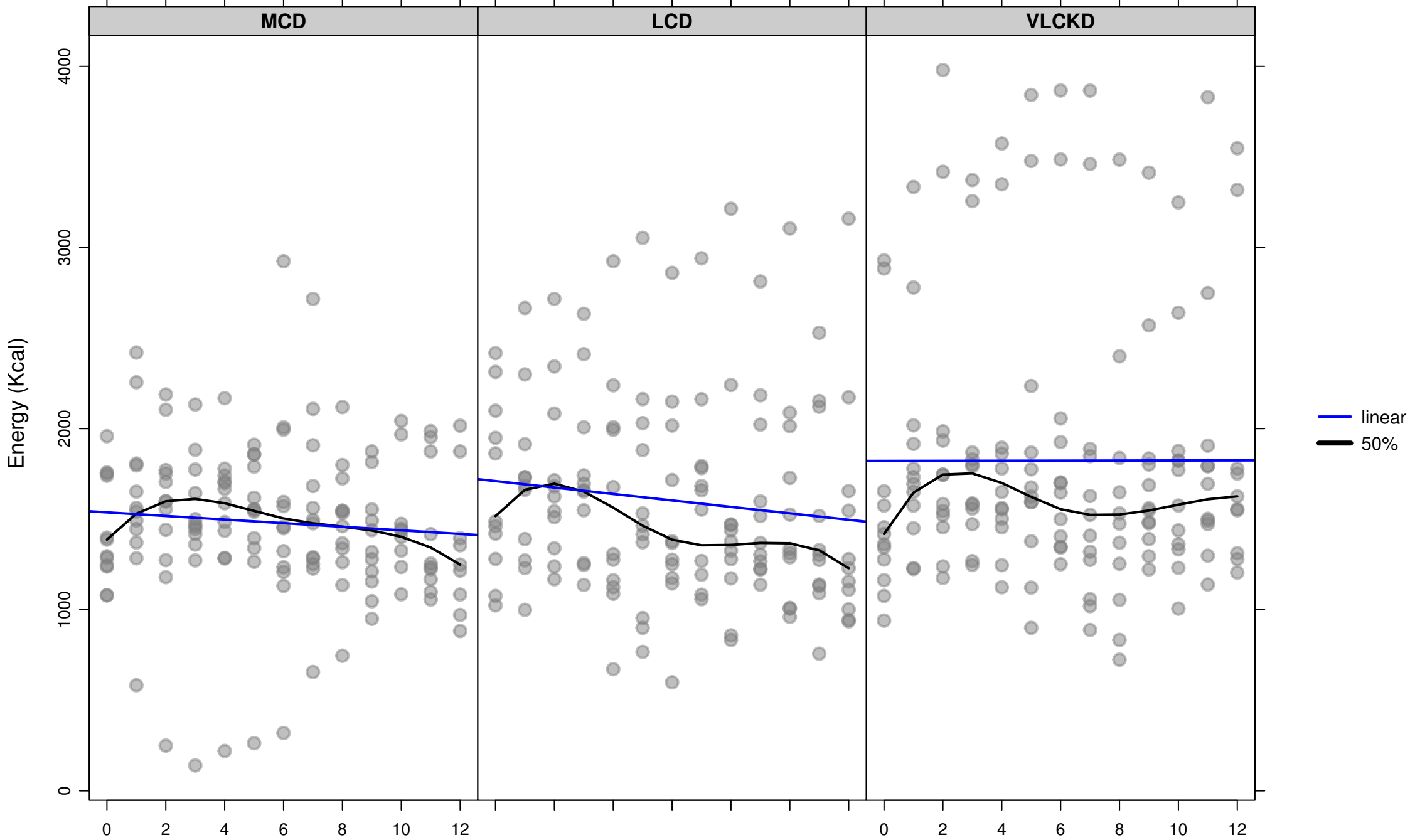
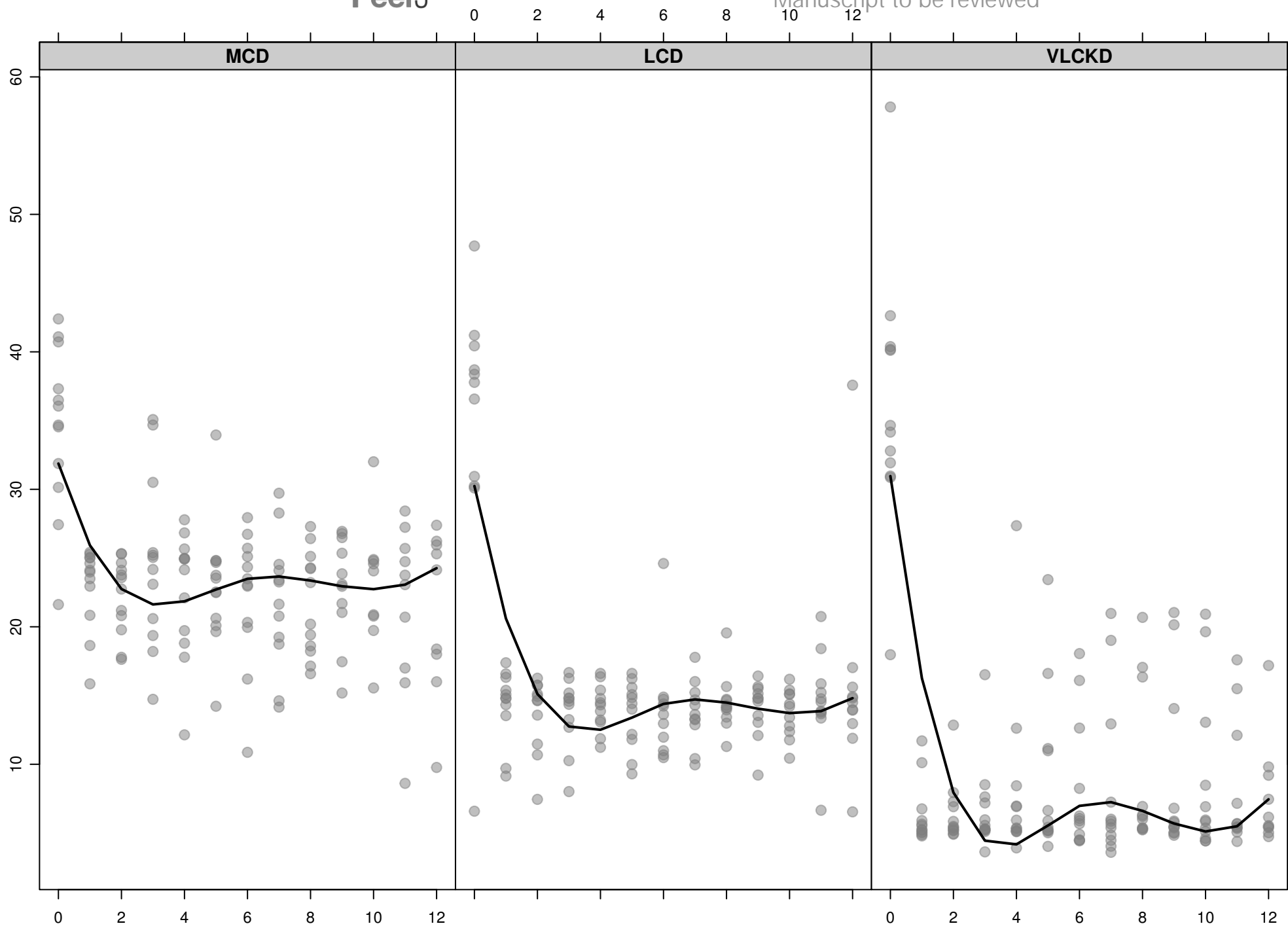



Figure 3

Percentage change from baseline in cardiometabolic and athropometric outcome measures

Mean daily energy intake by week per participant.

The blue line indicates the linear trend. Black line indicates the 50th percentile.

13 missing values (13 in Calories)

Mean percent of total energy derived from carbohydrate by participant, per week.

The black line indicates the 50th percentile.

13 missing values (13 in percent_TE_carbohydrate)

Baseline characteristics of study participants.

1 Table 1. Baseline characteristics of study participants

	MCD	**LCD**	**VLCKD**	**Total**	**Test**	**_p_-value**
	Treatment group					
	12	13	14	39		
Age mean (SD)	39.1 (6.6)	38.9 (8.3)	38.7 (7.1)	38.9 (7.1)	ANOVA	0.992
Gender (%)					Fisher's	0.198
Female	10 (83.3)	6 (46.2)	9 (64.3)	25 (64.1)		
Male	2 (16.67)	7 (53.85)	5 (35.71)	14 (35.9)		
Ethnicity (%)					Fisher's	0.733
Asian	1 (8.3)	0 (0.0)	1 (7.1)	2 (5.1)		
European	8 (66.7)	11 (84.6)	10 (71.4)	29 (74.4)		
Maori	2 (16.7)	1 (7.7)	3 (21.4)	6 (15.4)		
Other ethnicity	1 (8.3)	0 (0.0)	0 (0.0)	1 (2.6)		
Pacific peoples	0 (0.0)	1 (7.7)	0 (0.0)	1 (2.6)		
Total energy (Kcal) mean (SD)	1435 (293)	1567 (666)	1805 (857)	1603 (649)	ANOVA	0.378
Weight (kg) mean (SD)	76.3 (14.9)	90.4 (20.0)	76.8 (11.2)	81.2 (16.6)	ANOVA	0.046
Height (m) mean (SD)	1.70 (0.10)	1.76 (0.08)	1.74 (0.09)	1.73 (0.09)	ANOVA	0.245
BMI (kg/m^2) mean (SD)	26.4 (3.23)	29.1 (4.92)	25.5 (2.77)	27.0 (3.96)	ANOVA	0.050
Glucose (mmol/L) mean (SD)	5.54 (0.43)	5.38 (0.47)	5.44 (0.44)	5.45 (0.44)	ANOVA	0.673
Total cholesterol (mmol/L) mean (SD)	5.20 (1.3)	4.57 (0.61)	6.10 (1.37)	5.31 (1.29)	ANOVA	0.005
Triglyceride (mmol/L) mean (SD)	0.79 (0.2)	0.99 (0.36)	0.92 (0.22)	0.90 (0.27)	ANOVA	0.184
Insulin (pmol/L) mean (SD)	63.1 (37.3)	81.1 (39.4)	41.6 (17.6)	61.4 (35.8)	ANOVA	0.012

2 SD: standard deviation; BMI: body mass index

Change in outcome measures, overall, and by group.

1   Table 2. Change in outcome measures

Measure	Overall change† Mean change from baseline [95% CI]	Treatment group‡ Mean change from baseline [95% CI]		
		Moderate-low carbohydrate diet	Low carbohydrate diet	Very low carbohydrate ketogenic diet
Weight (kg)	-3.70 [-4.72, -2.68] *p* < 0.01	-2.97 [-5.03, -0.90]	-3.93 [-6.17, -1.69] *p* = 0.63	-4.12 [5.58, -2.65]
Waist circumference (cm)	-2.85 [-3.82, -1.88] *p* < 0.01	-2.95 [-5.57, -0.33]	-2.80 [-4.62, -0.98] *p* = 0.99	-2.81 [-3.88, -1.75]
Hip circumference (cm)	-3.43 cm [-4.95, -1.92] *p* < 0.01	-3.56 [-5.00, -2.12]	-1.19 [-4.29, 1.91] *p* = 0.06	-5.40 [-8.34, -2.46]
Waist-height ratio	-0.02 [-0.02, -0.01] *p* < 0.001	-0.02 [-0.03, -0.002]	-0.02 [-0.03, -0.006] *p* = 0.98	-0.02 [-0.02, -0.01]
Waist-hip ratio	-0.003 [-0.016, 0.010] *p* = 0.66	-0.004 [-0.026, 0.018]	-0.017 [-0.046, 0.011] *p* = 0.16	0.011 [-0.008, 0.030]
BMI (kg/m^2)	-1.223 [-1.556, -0.889] p < 0.001	-1.031 [-1.757, -0.306]	-1.22 [-1.894, -0.546] *p* = 0.686	-1.39 [-1.899, -0.881]
Total cholesterol (mmol/L)	0.58 [0.11, 1.05] *p* = 0.02	0.08 [-0.57, 0.72]	0.94 [0.08, 1.80] *p* = 0.33	0.68 [-0.33, 1.69]
LDL-c (mmol/L)	0.49 [0.06, 0.92] *p* = 0.03	0.14 [-0.39, 0.67]	0.80 [-0.02, 1.62] *p* = 0.47	0.50 [-0.44, 1.44]
HDL-c (mmol/L)	0.11 [0.00, 0.23] *p* = 0.05	-0.05 [-0.33, 0.24]	0.13 [-0.02, 0.27] *p* = 0.10	0.24 [0.07, 0.42]
Triglycerides (mmol/L)	-0.12 [0.20, -0.02] *p* = 0.02	-0.04 [-0.22, 0.15]	-0.09 [-0.27, 0.09] *p* = 0.41	-0.18 [-0.32, -0.04]
TG-HDL ratio	-0.101 [-0.173, -0.030] *p* = 0.006	-0.023 [-0.123, 0.078]	-0.118 [-0.294, 0.058] *p* = 0.31	-0.154 [-0.259, -0.048]
Insulin (pmol/L)	-13.58 [-21.61, -5.56] *p* < 0.01	-6.45 [-23.38, 10.48]	-23.68 [-42.49, -4.86] *p* = 0.19	-10.33 [-17.03, -3.62]
Glucose (mmol/L)	-0.11 [-0.26, 0.04] *p* = 0.14	-0.22 [-0.55, 0.11]	0.08 [-0.19, 0.34] *p* = 0.20	-0.20 [-0.45, 0.04]
c-reactive protein (mg/L)	-2.16 [-4.55, 0.22] *p* = 0.07	-3.90 [-11.90, 4.10]	-3.04 [-5.39, -0.68] *p* = 0.34	0.14 [-0.50, 0.77]

2 †Mean change from baseline [95% CI]; *p*-value relates to repeated measures t-test. ‡Mean change from baseline [95%
3 CI]; *p*-value relates to Anova comparing change from baseline within treatment group. BMI, body mass index; LDL-c,
4 low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol