

Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 mo¹⁻⁴

Grant D Brinkworth, Manny Noakes, Jonathan D Buckley, Jennifer B Keogh, and Peter M Clifton

ABSTRACT

Background: Long-term weight loss and cardiometabolic effects of a very-low-carbohydrate, high-saturated-fat diet (LC) and a high-carbohydrate, low-fat diet (LF) have not been evaluated under isocaloric conditions.

Objective: The objective was to compare an energy-controlled LC diet with an LF diet at 1 y.

Design: Men and women ($n = 118$) with abdominal obesity and at least one additional metabolic syndrome risk factor were randomly assigned to either an energy-restricted ($\approx 6-7$ MJ) LC diet (4%, 35%, and 61% of energy as carbohydrate, protein, and fat, respectively) or an isocaloric LF diet (46%, 24%, and 30% of energy as carbohydrate, protein, and fat, respectively) for 1 y. Weight, body composition, and cardiometabolic risk markers were assessed.

Results: Sixty-nine participants (59%) completed the trial: 33 in the LC group and 36 in the LF group. Both groups lost similar amounts of weight (LC: -14.5 ± 1.7 kg; LF: -11.5 ± 1.2 kg; $P = 0.14$, time \times diet) and body fat (LC: -11.3 ± 1.5 kg; LF: -9.4 ± 1.2 kg; $P = 0.30$). Blood pressure, fasting glucose, insulin, insulin resistance, and C-reactive protein decreased independently of diet composition. Compared with the LF group, the LC group had greater decreases in triglycerides (-0.36 ± 0.15 mmol/L; 95% CI: $-0.67, -0.05$ mmol/L; $P = 0.011$), increases in HDL cholesterol (0.23 ± 0.09 mmol/L; 95% CI: $0.06, 0.40$ mmol/L; $P = 0.018$) and LDL cholesterol (0.6 ± 0.2 mmol/L; 95% CI: $0.2, 1.0$ mmol/L; $P = 0.001$), and a greater but nonsignificant increase in apolipoprotein B (0.08 ± 0.04 g/L; 95% CI: $-0.004, 0.171$ g/L; $P = 0.17$).

Conclusions: Under planned isoenergetic conditions, as expected, both dietary patterns resulted in similar weight loss and changes in body composition. The LC diet may offer clinical benefits to obese persons with insulin resistance. However, the increase in LDL cholesterol with the LC diet suggests that this measure should be monitored. This trial was registered with the Australian New Zealand Clinical Trials Registry at <http://www.anzctr.org.au> as ACTR 12606000203550. *Am J Clin Nutr* 2009;90:23-32.

INTRODUCTION

Although a high-carbohydrate, low-fat (low saturated fat), moderate energy-restricted diet (LF) remains the conventional diet for weight management, carbohydrate continues to be at the center of the debate surrounding the optimal diet for weight loss. Hence, the obesity epidemic has led to widespread popularity of very-low-carbohydrate diets (LCs) that are high in saturated fat and protein. Several studies showed that, in comparison with a conventional LF diet, an LC diet results in greater weight loss

over 6 mo and at least comparable weight loss over 12 mo (1-8). These studies have also shown over the longer term (up to 1 y) that, compared with an LF diet, an LC diet has more favorable effects on triglyceride and HDL-cholesterol concentrations and similar reductions in blood pressure, insulin resistance, and glucose homeostasis. Although LDL-cholesterol concentrations in individual LC studies were not significantly increased with an LC diet (2-5, 7, 9, 10), a meta analysis showed a net increase in LDL cholesterol (8).

Despite this evidence, previous long-term trials have invariably studied the effects of LC diets when administered ad libitum without a fixed caloric intake and an overt attempt at energy restriction (2, 5-7, 10). Whereas this approach enables the effectiveness of an LC diet to be determined with a self-help format without intensive dietary advice and monitoring to reproduce what might typically occur in public practice, it is unable to evaluate the effects of these dietary patterns on cardiometabolic risk factors without related confounding variables, such as differences in energy intake. Additionally, these studies have often been associated with high attrition rates, poor long-term dietary compliance and modest long-term weight loss. Hence, although LC diets have caught the public's attention, the lack of understanding of the long-term efficacy and specific cardiometabolic effects of LC diets in the absence of potential confounding effects of differences in energy intake and weight loss has limited the applicability of these diets. We previously reported the findings of a 6-mo randomized study comparing the

¹ From the Preventative Health National Research Flagship, Commonwealth Scientific and Industrial Research Organization-Human Nutrition, Adelaide, Australia (GDB, MN, JBK, and PMC), and the Australian Technology Network, Centre for Metabolic Fitness and Nutritional Physiology Research Centre, University of South Australia, Adelaide, Australia (JDB).

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⁴ Address correspondence to GD Brinkworth, Commonwealth Scientific and Industrial Research Organisation-Human Nutrition, PO Box 10041 BC, Adelaide, South Australia 5000. E-mail: grant.brinkworth@csiro.au.

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effects of moderate-energy restricted LC and LF diets under isocaloric conditions in abdominally obese subjects with risk factors for cardiometabolic disease (11, 12). Both diets had similar effects on weight loss and reductions in blood pressure, plasma glucose, insulin, and C-reactive protein (CRP) concentrations, but there were differential effects on the blood lipid profile, with greater reductions in triglycerides and increases in HDL-cholesterol concentrations after an LC diet and a greater reduction in LDL cholesterol with an LF diet. In this article, we report the results of this study at 1 y to provide a greater understanding of the chronic effects of these dietary patterns.

SUBJECTS AND METHODS

Participants and study design

The participants, study design, and dietary interventions were previously described (11). Briefly, the subjects were recruited by public advertisement and included persons aged 18–65 y with abdominal obesity and at least one additional metabolic syndrome (MS) risk factor (13). Exclusion criteria were diabetes, pregnancy, malignancy, or a history of liver, cardiovascular, peripheral vascular, respiratory, or gastrointestinal disease. A total of 204 individuals were screened between February and March 2006; 122 were eligible for participation, but 4 withdrew before randomization. The remaining 118 participants were randomly assigned to either an energy-restricted LC diet ($n = 61$) or to an isocaloric conventional LF diet ($n = 57$) in April 2006. Data collection was completed in July 2007. The study was approved by the Human Research Ethics Committees of the Commonwealth Scientific and Industrial Research Organization and the University of South Australia. All participants provided written informed consent before participation.

The diets were designed to be isocaloric with moderate energy restriction (≈ 6000 kJ/d for women, ≈ 7000 kJ/d for men). The planned macronutrient profile of the LC diet was 4% of total energy as carbohydrate, 35% as protein, 61% as total fat (20% saturated fat) with the objective to restrict carbohydrate intake to <20 g/d for the first 8 wk and to <40 g/d (with the inclusion of an approved 20-g carbohydrate exchange (14)) for the remainder of the study. The target profile for the LF diet was 46% of total energy as carbohydrate, 24% as protein, and 30% as total fat with the objective to restrict saturated fat intake to <10 g/d and $<8\%$ of total energy, with the inclusion of an approved food exchange (equivalent to the energy content of 20g of carbohydrate; 14) between weeks 9 and 52, so that the diets remained isocaloric. In an effort to maximize retention and compliance, participants attended the clinic fortnightly for the first 8 wk and monthly thereafter for consultation with a qualified dietitian during which time detailed individualized dietary advice, meal plans, and recipe information pertaining to each diet were provided. Apart from the dietary information, participants were also “coached” by the dietitians for sustained dietary change and compliance by reemphasizing clear dietary targets at each visit and teaching of behavioral self-management strategies. The dietitians also provided high levels of encouragement by using motivational techniques, including goal setting, feedback on weight loss, and dietary compliance achievements, information sharing between participants to troubleshoot common dietary issues, education on the nutritional value of foods, and techni-

ques to counteract situational/environmental influences that may hinder dietary compliance (eg, festive season). Participants were also provided with open-access phone contact with the dietitians throughout the intervention and were encouraged to contact the dietitians between diet visits to clarify dietary issues if necessary. In addition, to help establish the required eating pattern in the early phase of the study, participants were supplied with a selection of key foods ($\approx 30\%$ of total energy) representative of each diet’s macronutrient profile fortnightly for the first 8 wk and a \$40AU food voucher at each monthly diet visit during the remainder of the study. Both dietary patterns were also structured to include specific food quantities and weights to ensure the correct macronutrient and energy requirements were achieved (11). These foods were listed in a quantitative food record that was completed daily by the subjects. This provided participants with clear dietary targets and an opportunity for dietary self-management. The subjects were asked to weigh and measure their food daily using scales that were provided. Dietary composition was assessed on the basis of 3 d from the food records (2 weekdays and 1 weekend day) within each consecutive 2-wk period for the duration of the study by using computerized dietary software (Foodworks Professional Edition, version 4 software; Xyris Software 1998, Highgate Hill, Australia). This was done in the presence of the subjects to maximize accuracy and to clarify any ambiguities. The fortnightly food records were then used to calculate the average nutrient intakes for weeks 1–8, weeks 9–24, weeks 25–36, and weeks 37–52, which were subsequently used to represent the dietary intake for each of these study periods. No specific recommendations were given for physical activity, which was assessed at baseline and at 8, 24, and 52 wk with the use of a validated questionnaire (15).

Outcomes

Body composition was measured by using a dual-energy X-ray absorptiometry (DXA; Lunar Prodigy; General Electric Corporation, Madison, WI) to assess fat mass (FM) and fat-free mass (FFM) at baseline and at 8 and 52 wk. Abdominal fat mass was measured as previously described (12). Plasma ketones were assessed at baseline and at weeks 2, 4, 6, 8, 20, 24, 28, 36, 44, and 52 (11). All other outcome measures were assessed at baseline and at weeks 8, 24, and 52. These latter outcome measures included weight, which was measured by using calibrated electronic digital scales (AMZ14; Mercury, Tokyo, Japan), and seated blood pressure (mm Hg), which was measured with an automated sphygmomanometer (DYNAMAP 8100; Criticon, Tampa, FL). Plasma glucose, C-reactive protein, serum lipids, and apolipoprotein B (apo B) were also measured by using standard methods (11). The homeostasis model of assessment index 2 was used to assess insulin resistance (HOMA2-IR), β cell function (HOMA2%B), and insulin sensitivity (HOMA2%S) from fasting glucose and insulin concentrations (16). The Framingham 10-y coronary heart disease risk score (FRS) based on age, sex, smoking status, total and HDL cholesterol, blood pressure, and diabetes mellitus status was also calculated (17), which provides a global representation of coronary heart disease (CHD) risk. In addition, during the 24 h before the clinic visit at weeks 0, 8, and 52, the subjects collected a 24-h urine sample for assessment of 24-h urinary urea measured on a BM/Hitachi 902 Automatic Analyzer

with a standard enzymatic kit (Roche Diagnostics Co, Indianapolis, IN).

Statistical methods

Because the data for the first 6 mo of the intervention were previously published (11, 12), we present here the final outcomes at 12 mo. The distribution was normal for all variables except ketones, triglycerides, triglyceride:HDL cholesterol ratio, fasting insulin, HOMA2-IR, HOMA2%B, and HOMA2%S. Data for these variables were normalized by using logarithmic transformation before analysis, but the nonlog transformed values are presented. Differences in baseline characteristics between the groups and for study dropouts and completers were compared by using independent *t* tests for continuous variables and chi-square tests for categorical variables and indicated that the data for dropouts was missing at random. Two approaches were used to

analyze the effect of diet composition on the measured outcomes: 1) maximum likelihood mixed-effects models with fixed and random effects were used to analyze expected mean change over time, making efficient use of all available data (18), including data at baseline and at weeks 8, 24, and 52, and 2) a completers analysis that only included data for participants who completed the study to week 52 was also performed to compare changes between diets from baseline, week 24, and 52 by using repeated-measures analysis of variance. Change in weight was included as a covariate in the analysis models. Sex was also included as a factor in these analyses, but no significant effect of sex was observed for any of the outcomes, so individual gender data are not reported. The overall differences between diets (with 95% CIs for changes from baseline to week 52, ie, week 52 minus baseline) are presented for each outcome. Between-group differences in dietary intake data and plasma ketones at each point were assessed by analysis of variance with

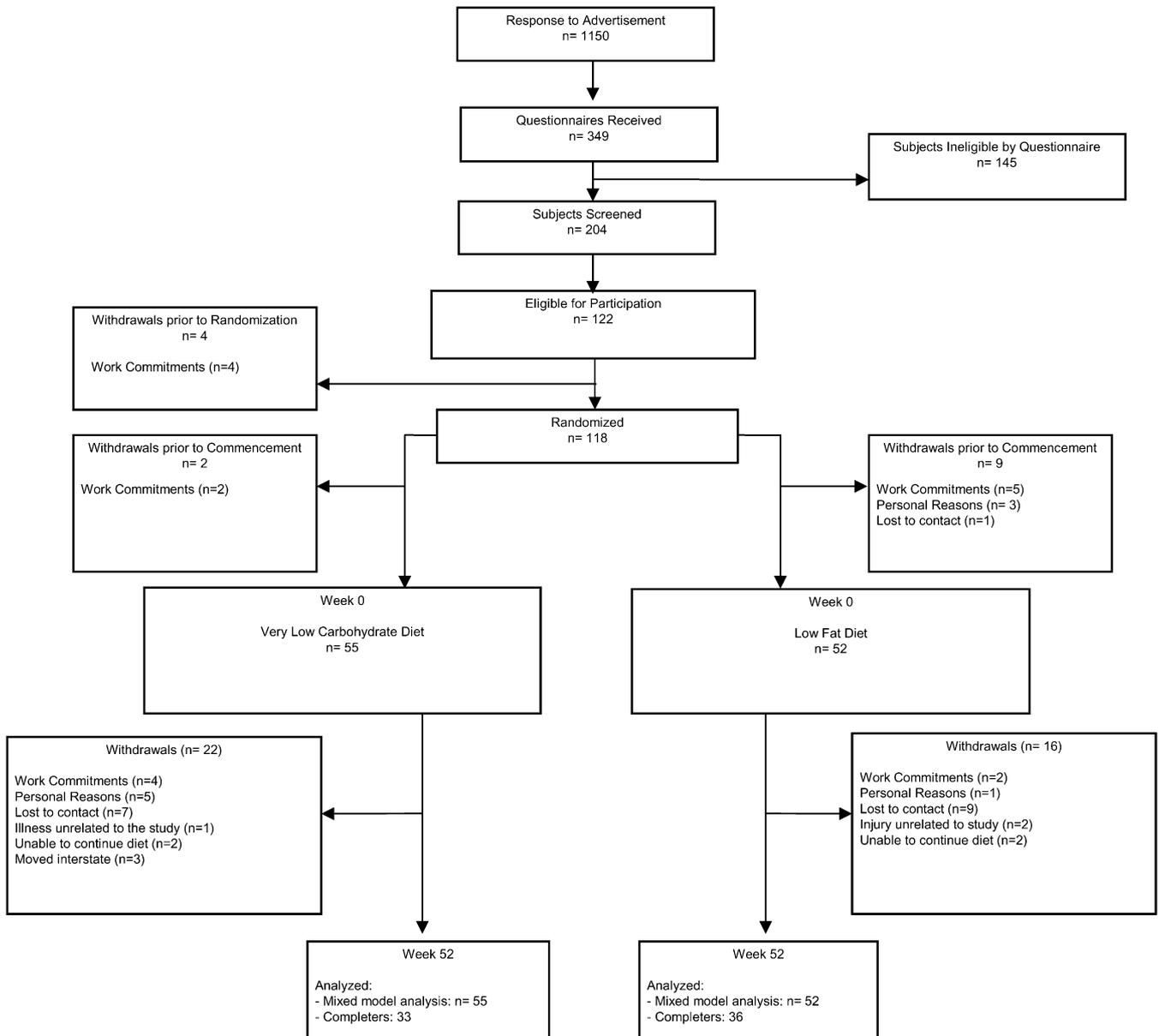


FIGURE 1. Participant flow.

Bonferroni adjustment. *P* values <0.05 were considered statistically significant. Data are presented as means \pm SEMs unless otherwise stated. Analyses were performed by using SPSS 14.0 for WINDOWS (SPSS Inc, Chicago, IL).

RESULTS

Of the 118 randomized participants, 11 dropped out before baseline assessments and were not included in the analysis; of the remaining 107 participants from whom baseline data were collected, a further 38 withdrew throughout the study but were included in the mixed-model analysis (**Figure 1**). There were no statistically significant differences in baseline characteristics or presence of MS risk factors between diet groups or between those who completed or did not complete the study (**Table 1**).

Dietary analysis, compliance, and physical activity

On the basis of the results of the food records, the participants showed good compliance with the prescribed diets. Total energy intake was similar in both groups across all stages of the intervention (**Table 2**). Over the course of the study, dietary composition was markedly different between the diet groups; the LC diet group consumed significantly less carbohydrate and more protein, total fat, unsaturated fat, monounsaturated fat, saturated fat, and cholesterol than did the LF diet group (*P* < 0.001 for all nutrients; **Table 2**). During the initial stages of the study, plasma β -hydroxybutyrate concentrations increased significantly more in the LC diet group than in the LF diet group, and, although concentrations decreased over time in the LC diet group, they remained higher than those in the LF diet group throughout the intervention (**Figure 2**), which indicated adherence to a low-carbohydrate intake in the LC group. Similarly, 24-h urinary urea excretion was similar in both groups at baseline (LC: 430.8 \pm 31.1 mmol/24 h; LF: 396.4 \pm 28.6 mmol/24 h; *P* = 0.42). There was a significant time \times diet interaction for

24-h urinary urea excretion (*P* = 0.004), such that excretion was significantly greater in the LC diet group than in the LF diet group at week 8 (LC: 532.7 \pm 32.5 mmol/24 h; LF: 358.5 \pm 20.1 mmol/24 h) and week 52 (LC: 508.9 \pm 32.7 mmol/24 h; LF: 430.0 \pm 26.7 mmol/24 h), which reflects a higher protein intake in the LC group during the study. Physical activity levels were similar in both groups at each time point throughout the intervention (data not shown).

Body weight and composition

Overall, volunteers lost weight during the first 24 wk of the study and continued to lose weight throughout the final 28 wk, albeit at a slower rate (**Figure 3**). By mixed-model analysis, using data from all participants who began the study, including those who discontinued the study, there was a significant reduction in weight (*P* < 0.001), but no significant difference between diets (LC: -13.1 \pm 1.6 kg; HC: -11.6 \pm 1.6 kg; *P* = 0.22). For the completers, mean weight change at 12 mo was -14.5 \pm 1.7 kg for the LC group and -11.5 \pm 1.2 kg for the LF group. Although absolute weight loss was greater in the LC diet group, the difference in weight loss between the diet groups was not statistically significant (-3.0 \pm 2.0 kg; 95% CI: -7.1 kg, 1.1 kg; *P* = 0.14; **Figure 3**). There was also no significant difference between the diet groups in the proportion of subjects who reported a weight loss of \geq 5% of body weight (LC: 30 of 33, 91%; LF: 27 of 36, 82%; χ^2 = 3.03, *P* = 0.08) and 10% (LC: 25 of 33, 76%; LF: 21 of 36, 58%; χ^2 = 2.352, *P* = 0.13).

The overall trajectory over the course of the study showed that total FM and FFM and abdominal fat decreased in both diet groups (*P* < 0.001 for time), with no differential effect of diet composition or sex (*P* \geq 0.25). The completers analysis also showed no significant differences in reductions in FM and abdominal fat between the groups (*P* \geq 0.23 for time \times diet interaction; **Table 3**). FFM decreased to a greater extent in the LC

TABLE 1
Baseline participant characteristics¹

Characteristic	Very-low-carbohydrate-diet group		Low-fat-diet group	
	Completers (<i>n</i> = 33)	Noncompleters (<i>n</i> = 24)	Completers (<i>n</i> = 36)	Noncompleters (<i>n</i> = 25)
Age (y)	51.5 \pm 7.7 ²	49.0 \pm 8.6	51.4 \pm 6.5	47.2 \pm 9.5
Sex (no. male/female)	11/22	7/17	14/22	11/14
Weight (kg)	93.9 \pm 15.5	95.5 \pm 16.4	94.5 \pm 12.7	98.2 \pm 18.0
BMI (kg/m ²)	33.6 \pm 4.0	33.4 \pm 4.4	33.3 \pm 3.9	34.6 \pm 4.7
Waist circumference (cm)				
Men	112.6 \pm 2.3	109.5 \pm 3.7	108.5 \pm 1.8	115.5 \pm 4.0
Women	101.3 \pm 2.0	100.3 \pm 1.8	100.6 \pm 2.0	103.4 \pm 2.9
Elevated blood pressure [<i>n</i> (%)]	25 (76)	18 (75)	27 (75)	18 (72)
Antihypertensive medication [<i>n</i> (%)]	8 (33)	6 (24)	13 (39)	8 (22)
Elevated fasting blood glucose [<i>n</i> (%)]	12 (36)	11 (46)	15 (42)	11 (44)
Elevated triglycerides [<i>n</i> (%)]	17 (52)	11 (48)	18 (50)	13 (52)
Reduced HDL cholesterol [<i>n</i> (%)]	4 (12)	2 (8)	5 (14)	5 (20)
Lipid-lowering medication [<i>n</i> (%)]	8 (24)	4 (17)	6 (17)	6 (24)
Metabolic syndrome [<i>n</i> (%)]	19 (58)	11 (48)	20 (56)	15 (60)

¹ Metabolic risk factors and the metabolic syndrome were defined according to the criteria of the International Diabetes Federation (13). No subjects were taking hypoglycemic medications. Four subjects (1 man and 3 women) withdrew before randomization. The characteristics of the subject were not significantly different between diet groups or between completers and noncompleters by chi-square and independent Student's *t* tests.

² Mean \pm SD (all such values).

TABLE 2
Nutrient composition of the different diets¹

Variable and diet	Weeks 1–8	Weeks 9–24	Weeks 25–36	Weeks 37–52
Total energy (kJ)				
LC	6582.3 ± 119.3	6719.3 ± 168.6	6781.1 ± 148.2	6882.2 ± 156.6
LF	6319.8 ± 114.9	6364.0 ± 141.6	6508.8 ± 166.0	6800.4 ± 209.3
Carbohydrate (g)				
LC	19.8 ± 0.7	30.3 ± 2.4	33.1 ± 2.7	36.5 ± 3.4
LF	167.9 ± 4.3 ²	167.9 ± 4.4 ²	173.5 ± 5.4 ²	186.4 ± 7.3 ²
Carbohydrate (% of energy)				
LC	5.1 ± 0.2	7.6 ± 0.5	8.2 ± 0.6	8.9 ± 0.8
LF	45.1 ± 0.5 ²	44.9 ± 0.6 ²	45.2 ± 0.6 ²	46.4 ± 0.6 ²
Protein (g)				
LC	133.7 ± 1.7	130.4 ± 2.4	129.5 ± 2.4	129.8 ± 2.2
LF	85.8 ± 1.3 ²	84.7 ± 1.4 ²	84.4 ± 1.7 ²	85.6 ± 1.6 ²
Protein (% of energy)				
LC	34.7 ± 0.3	33.3 ± 0.5	32.6 ± 0.4	32.3 ± 0.4
LF	23.3 ± 0.3 ²	22.9 ± 0.3 ²	22.3 ± 0.3 ²	21.8 ± 0.4 ²
Total fat (g)				
LC	101.9 ± 2.3	101.8 ± 3.1	101.6 ± 2.8	102.3 ± 2.9
LF	45.1 ± 1.2 ²	46.0 ± 1.7 ²	46.3 ± 1.8 ²	48.3 ± 1.9 ²
Total fat (% of energy)				
LC	57.2 ± 0.5	55.9 ± 0.6	55.4 ± 0.7	54.9 ± 0.8
LF	26.5 ± 0.6 ²	26.8 ± 0.7 ²	26.5 ± 0.8 ²	26.4 ± 0.7 ²
Polyunsaturated fat (% of energy)				
LC	7.5 ± 0.2	7.4 ± 0.2	7.1 ± 0.1	7.2 ± 0.2
LF	6.5 ± 0.2 ²	6.4 ± 0.2 ²	6.2 ± 0.2 ²	6.0 ± 0.2 ²
Monounsaturated fat (% of energy)				
LC	24.5 ± 0.4	23.9 ± 0.5	23.8 ± 0.5	23.4 ± 0.5
LF	11.7 ± 0.4 ²	11.8 ± 0.4 ²	11.6 ± 0.5 ²	11.6 ± 0.4 ²
Saturated fat (g)				
LC	37.3 ± 0.9	37.1 ± 1.3	37.1 ± 1.0	37.9 ± 1.2
LF	9.6 ± 0.3 ²	10.5 ± 0.5 ²	10.7 ± 0.5 ²	11.5 ± 0.6 ²
Saturated fat (% of energy)				
LC	20.9 ± 0.4	20.4 ± 0.5	20.3 ± 0.4	20.4 ± 0.5
LF	5.6 ± 0.1 ²	6.1 ± 0.2 ²	6.1 ± 0.2 ²	6.2 ± 0.2 ²
Total cholesterol (mg)				
LC	597.1 ± 16.8	577.7 ± 18.7	573.9 ± 20.4	592.3 ± 21.3
LF	136.4 ± 5.0 ²	140.5 ± 4.1 ²	147.1 ± 4.6 ²	149.7 ± 5.8 ²

¹ All values are means ± SEMs for the 69 participants who completed the study. LC, very-low-carbohydrate diet (*n* = 33); LF, conventional low-fat diet (*n* = 36). Dietary targets: total energy intake (women: 6000 kJ/d; men: 7000 kJ/d). Macronutrient profile of the LC diet: 4% of total energy as carbohydrate, 35% as protein, 61% as total fat, 20% as saturated fat; the objective was to restrict the carbohydrate intake to <20 g/d for weeks 0–8 and to <40 g/d for weeks 9–52. Macronutrient profile of the LF diet: 46% of total energy as carbohydrate, 24% as protein, 30% as total fat, <8% as saturated fat; the objective was to restrict saturated fat intake to <10 g/d and <8% of total energy throughout the study, with the inclusion of an approved food exchange (equivalent to the energy content of 20 g carbohydrate) between weeks 9 and 52.

² Significantly different from LC at the corresponding time point, *P* < 0.001 (repeated-measures ANOVA with Bonferroni adjustment).

group than in the LF group (*P* = 0.03 for time × diet interaction; Table 3); however, this difference was no longer significant after differences in FM loss were controlled for (*P* = 0.06), which suggests that the greater reduction in FFM in the LC diet group was a direct effect of the greater absolute weight loss observed in those subjects. In this way, the FFM:FM ratio had increased in both groups by week 52 (*P* < 0.001 for time effect) but with no effect of diet composition or sex.

Blood pressure, glucose, insulin, and CRP

Mixed-model analysis showed that blood pressure, fasting glucose, insulin, HOMA2-IR, and HOMA2%B all decreased, and

HOMA2%S increased over time in both groups (*P* < 0.001 for time effect for all variables), with no effect of diet or sex. The completers’ analysis showed a similar pattern of results for these variables (Table 3). There was still no effect of diet in all of these analyses after adjustment for weight-loss differences. Participants with an isolated CRP concentration of >10.0 mg/L were excluded from the CRP analysis (LC: *n* = 2; LF: *n* = 7) because concentrations above this level may be associated with the presence of infection or inflammation (19). Mixed-model analysis showed that CRP concentrations decreased during the study (*P* < 0.001 for time), with no effect of diet or sex. The completers analysis showed a similar response between the between diets at 1 y (Table 3).

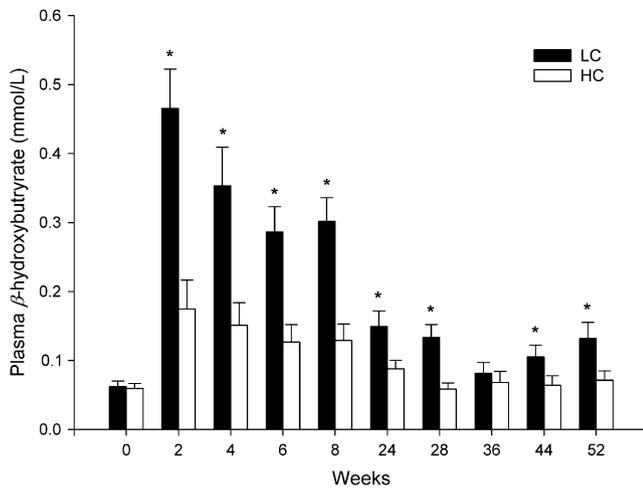


FIGURE 2. Mean (\pm SEM) plasma β -hydroxybutyrate concentrations before and after 2, 4, 6, 8, 24, 28, 36, 44, and 52 wk of energy restriction with either a very-low-carbohydrate diet (LC; $n = 33$) or a conventional low-fat diet (LF; $n = 36$). The data available at each time point were as follows: week 0 (LC: 33; HC: 36), week 2 (LC: 32; HC: 36), week 4 (LC: 32; HC: 36), week 6 (LC: 33; HC: 36), week 8 (LC: 33; HC: 36), week 24 (LC: 33; HC: 36), week 28 (LC: 31; HC: 36), week 36 (LC: 33; HC: 35), week 44 (LC: 33; HC: 35), and week 52 (LC: 33; HC: 36). There was a significant time \times diet interaction, $P < 0.001$. *Significantly different from LF at the corresponding time point, $P < 0.05$ (repeated-measures ANOVA with Bonferroni adjustment).

Lipids, apo B, and FRS

The overall trajectory (ie, all time points) of changes in total cholesterol, LDL cholesterol, and HDL cholesterol showed these variables increased more with the LC diet than with the LF diet ($P \leq 0.02$ for time \times diet interaction), whereas triglyceride concentrations and the triglyceride:HDL cholesterol ratio decreased to a greater extent in the LC diet group than in the LF diet group ($P = 0.001$ for time \times diet interaction). There was no significant effect of diet composition on non-HDL cholesterol ($P = 0.17$). The completers' analysis confirmed these differences between diets at 1 y (Table 4). These outcomes were not af-

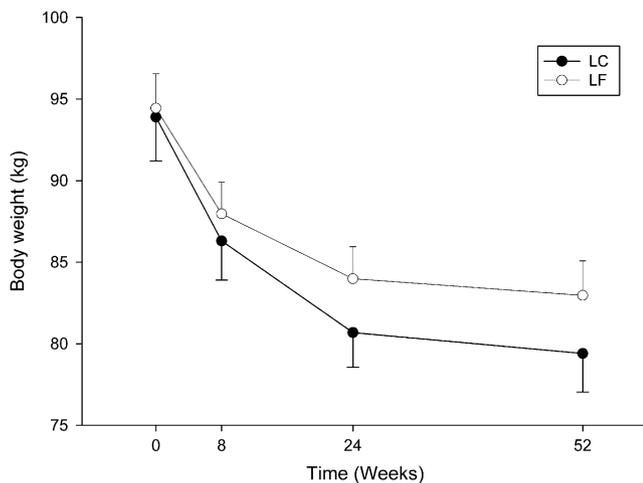


FIGURE 3. Mean (\pm SEM) body weight before and after 52 wk of energy restriction with either a very-low-carbohydrate diet (LC; $n = 33$) or a conventional low-fat diet (LF; $n = 36$) in the participants who completed the study. $P < 0.001$ for the main effect of time, and $P = 0.14$ for the time \times diet interaction (repeated-measures ANOVA).

ected by sex and remained after weight loss was adjusted for. LDL cholesterol was increased by $>10\%$ in 18 individuals (18/33, 55%) in the LC diet group and in 8 individuals (8/34, 24%) in the LF diet group ($\chi^2 = 6.78$, $P = 0.009$). Apo B concentrations tended to increase with the LC diet and decrease with the LF diet, but this difference was not statistically significant by using either the mixed model ($P = 0.10$ time \times diet effect) or the completers' analysis ($P = 0.17$ for time \times diet effect; Table 4). Based on the data for the completers, FRS decreased in both groups at week 52 ($P = 0.01$ for time effect; Table 4), with no effect of diet or sex.

DISCUSSION

This study showed that the isocaloric LC and LF diets resulted in similar weight loss and reductions in blood pressure, glucose, insulin, insulin resistance, and CRP after 12 mo. However, the diets resulted in differential effects on blood lipids, with greater increases in total cholesterol, LDL cholesterol, and HDL cholesterol and reductions in triglycerides with the LC diet than with the LF diet, independent of differences in energy intake and weight loss. We used the FRS to ascertain differential effects between the diets on estimated overall cardiovascular disease (CVD) risk. Using the FRS, weight loss on both diets was effective in decreasing 10-y predicted CHD risk and diet composition did not affect this response. However, the FRS has not been validated for use in overweight populations.

Distinct from previous studies that compared the effects of ad libitum LC and LF diets, this study was designed to evaluate whether there were any long-term differences in weight loss and/or cardiometabolic outcomes between these diet patterns when delivered as isocaloric eating patterns. In contrast with our findings, previous studies have shown greater weight loss after an ad libitum LC diet than after an LF diet after 12 mo (5, 6). Several mechanisms for this effect have been postulated, with most relating to spontaneous reductions in energy intake (1–3, 11, 20, 21). A meta-regression of 87 studies (22) showed that lower-carbohydrate diets were associated with greater weight loss than were higher-carbohydrate diets, which was independent of energy intake. However, no trials longer than 26 wk were included in this analysis. Our results suggest that, over the long term, any additional weight-loss advantage of an LC diet over an HC diet was not evident. Despite this, we estimated that a sample size of ≈ 130 persons per group would have been needed for the observed difference of 3 kg between the groups to have been statistically significant (80%, $P < 0.05$). Hence, the possibility that a larger study may have realized a statistically significant difference in weight loss between diets cannot be entirely dismissed. Other studies have reported greater weight loss after an LC diet than after an LF diet, despite reported total energy intakes being similar between groups (1, 5). It is possible that dietary records may not be sensitive enough to detect small differences in energy intake that may result from underreporting (1, 3).

Irrespective of any group differences, both groups achieved substantial weight loss by 12 mo (≈ 13 kg), with most subjects achieving weight loss of $\geq 10\%$. This is at least comparable with, if not greater than, the effects observed with pharmacotherapy (23) and markedly superior to the modest weight loss (≈ 5 kg) often reported in long-term dietary interventions (2, 6, 7, 23).

TABLE 3

Change in body composition, blood pressure, glucose, insulin, homeostasis model assessment index 2 (HOMA-2), and C-reactive protein (CRP) concentrations at 1 y¹

Variable and diet	Baseline	Week 24	Week 52	Change	Mean difference ²	95% CI ²	P for time × diet ³
BMI (kg/m ²)							
LC	33.6 ± 0.7	28.9 ± 0.5	28.4 ± 0.6	-5.2 ± 0.6	-1.1 ± 0.7	-2.6, 0.3	0.116
LF	33.7 ± 0.7	29.6 ± 0.6	29.2 ± 0.7	-4.1 ± 0.4			
Fat mass (kg) ⁴							
LC	40.0 ± 1.7	—	28.7 ± 1.7	-11.3 ± 1.5	-1.9 ± 1.9	-5.6, 1.9	0.304
LF	39.2 ± 1.5	—	29.8 ± 1.6	-9.4 ± 1.2			
Fat-free mass (kg) ⁴							
LC	53.7 ± 2.2	—	50.5 ± 2.0	-3.2 ± 0.4	-0.9 ± 0.4	-1.8, -0.08	0.033
LF	55.9 ± 2.0	—	53.6 ± 2.0	-2.3 ± 0.2			
Fat-free mass:fat mass (kg/kg) ⁴							
LC	1.36 ± 0.08	—	1.80 ± 0.13	0.42 ± 0.08	-0.04 ± 0.2	-0.27, 0.20	0.760
LF	1.50 ± 0.09	—	2.0 ± 0.15	0.51 ± 0.09			
Abdominal fat mass (kg) ⁴							
LC	3.1 ± 0.2	—	2.2 ± 0.2	-0.9 ± 0.1	-0.2 ± 0.2	-0.5, 0.1	0.226
LF	3.1 ± 0.1	—	2.4 ± 0.1	0.7 ± 0.1			
Systolic BP (mm Hg)							
LC	132.7 ± 2.3	118.5 ± 1.7	118.9 ± 2.0	-13.8 ± 2.5	0.8 ± 3.2	-5.5, 7.1	0.536
LF	135.2 ± 2.1	122.1 ± 2.2	120.6 ± 2.9	-14.6 ± 2.0			
Diastolic BP (mm Hg)							
LC	72.3 ± 1.8	66.3 ± 1.7	66.0 ± 2.0	-6.3 ± 1.6	1.6 ± 2.3	-3.0, 6.2	0.746
LF	77.1 ± 1.8	70.7 ± 1.3	69.2 ± 1.7	-7.9 ± 1.6			
Glucose (mmol/L)							
LC	5.7 ± 0.1	5.5 ± 0.1	5.4 ± 0.1	-0.3 ± 0.01	0.01 ± 0.1	-0.2, 0.2	0.932
LF	5.6 ± 0.1	5.4 ± 0.1	5.3 ± 0.1	-0.3 ± 0.1			
Insulin (mU/L)							
LC	7.9 ± 0.6	4.8 ± 0.3	4.8 ± 0.5	-3.4 ± 0.6	0.2 ± 0.8	-1.4, 1.8	0.540
LF	9.8 ± 0.6	6.9 ± 0.6	6.5 ± 0.5	-3.3 ± 0.5			
HOMA2-IR							
LC	1.20 ± 0.12	0.75 ± 0.08	0.72 ± 0.09	-0.49 ± 0.12	0.04 ± 0.15	-0.26, 0.35	0.769
LF	1.42 ± 0.11	0.95 ± 0.07	0.89 ± 0.07	-0.53 ± 0.10			
HOMA2%B							
LC	81.4 ± 4.6	62.3 ± 3.0	63.7 ± 5.5	-17.7 ± 4.6	-0.2 ± 6.2	-12.6, 12.1	0.584
LF	93.2 ± 4.0	79.2 ± 4.6	75.7 ± 3.1	-17.5 ± 4.2			
HOMA2%S							
LC	105.7 ± 9.3	163.7 ± 12.8	184.9 ± 15.7	79.2 ± 14.2	27.2 ± 15.7	-4.2, 58.6	0.683
LF	83.3 ± 5.5	125.2 ± 8.8	135.2 ± 10.3	52.0 ± 7.6			
CRP (mg/L) ⁵							
LC	2.7 ± 0.3	2.2 ± 0.3	1.5 ± 0.2	-1.3 ± 0.2	0.1 ± 0.5	-0.8, 1.0	0.903
LF	2.8 ± 0.4	2.0 ± 0.4	1.4 ± 0.2	-1.4 ± 0.3			

¹ All values are means ± SEMs for the 69 participants who completed the study. LC, very-low-carbohydrate diet (*n* = 33); LF, conventional low-fat diet (*n* = 36); BP, blood pressure; HOMA2-IR, homeostasis model of assessment index 2 of insulin resistance; HOMA2%B, homeostasis model of assessment index 2 of β cell function; HOMA2%S, homeostasis model of assessment index 2 of insulin sensitivity.

² For changes from baseline to week 52.

³ P values are for the LC diet relative to the conventional LF diet (time × diet interaction) by repeated-measures ANOVA.

⁴ Dual-energy X-ray absorptiometry scans were not performed at baseline for 3 participants (LC: *n* = 1; LF: *n* = 2) and for 1 participant in the LF diet group at week 52.

⁵ CRP data were excluded for 9 persons (LC: *n* = 2; LF: *n* = 7) because CRP values were >10 mg/L.

Self-monitoring, including self-observation and recording, dietary structure, and professional support, including frequency of dietary counseling, are key factors to achieving dietary compliance and weight-loss success (24–27). In our study, participants were provided with a well-structured program, including a highly prescriptive diet plan with clear targets, regular clinic weight checks, and continual professional support with individualized visits with a registered dietitian who provided intensive dietary instruction. This could explain, at least in part, the greater weight loss observed in comparison with other trials

providing minimal professional contact (2, 7, 28). Other possible contributing factors include high levels of self monitoring promoted by the daily requirement to record food intake, reimbursement for food costs, and the use of motivational techniques. Although the specific components of the structured program that led to weight-loss success could not be determined, the current data highlight that substantial long-term weight loss can be achieved via moderate caloric restriction with professional support. Nevertheless, a moderate dropout rate was still observed, and future studies need to compare the cost-

TABLE 4Change in serum lipids and apolipoprotein B concentrations and Framingham 10-y coronary heart disease risk score at 1 y¹

Variable and diet	Baseline	Week 24	Week 52	Change	Mean difference ²	95% CI ²	<i>P</i> for time × diet ³
Total cholesterol (mmol/L)					0.6 ± 0.2	0.1, 1.1	0.004
LC	5.4 ± 0.2	5.4 ± 0.2	6.0 ± 0.2	0.7 ± 0.2			
LF	5.5 ± 0.1	4.8 ± 0.2	5.5 ± 0.2	0.1 ± 0.1			
LDL-C (mmol/L) ⁴					0.6 ± 0.2	0.2, 1.0	0.001
LC	3.2 ± 0.1	3.3 ± 0.2	3.8 ± 0.2	0.6 ± 0.2			
LF	3.4 ± 0.1	2.8 ± 0.1	3.4 ± 0.2	0.1 ± 0.1			
HDL-C (mmol/L)					0.23 ± 0.09	0.06, 0.40	0.018
LC	1.45 ± 0.05	1.68 ± 0.07	1.75 ± 0.09	0.30 ± 0.07			
LF	1.36 ± 0.06	1.44 ± 0.05	1.43 ± 0.06	0.07 ± 0.06			
TG (mmol/L)					-0.36 ± 0.15	-0.67, -0.05	0.011
LC	1.67 ± 0.13	0.95 ± 0.06	1.09 ± 0.11	-0.58 ± 0.11			
LF	1.80 ± 0.14	1.38 ± 0.17	1.58 ± 0.19	-0.22 ± 0.11			
TG/HDL-C					-0.32 ± 0.19	-0.71, 0.06	0.009
LC	1.28 ± 0.15	0.66 ± 0.09	0.73 ± 0.11	-0.55 ± 0.11			
LF	1.50 ± 0.17	1.05 ± 0.14	1.28 ± 0.21	-0.23 ± 0.15			
Non-HDL-C (mmol/L)					0.26 ± 0.19	-0.12, 0.63	0.088
LC	3.91 ± 0.16	3.56 ± 0.17	4.15 ± 0.18	0.24 ± 0.15			
LF	4.12 ± 0.14	3.38 ± 0.16	4.11 ± 0.17	-0.02 ± 0.12			
apo B (g/L)					0.08 ± 0.04	-0.004, 0.171	0.168
LC	0.97 ± 0.04	0.95 ± 0.05	0.99 ± 0.04	0.03 ± 0.04			
LF	1.00 ± 0.03	0.93 ± 0.05	0.94 ± 0.04	-0.06 ± 0.03			
FRS (%)					1 ± 1	-1, 2	0.601
LC	6 ± 1	4 ± 0	5 ± 1	-1 ± 1			
LF	7 ± 1	5 ± 0	6 ± 1	-1 ± 1			

¹ All values are means ± SEMs for the 69 participants who completed the study. LC, very-low-carbohydrate diet (*n* = 33); LF, conventional low-fat diet (*n* = 36); apo B, apolipoprotein B; FRS, Framingham 10-y coronary heart disease risk score; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TG, triglycerides.

² For changes from baseline to week 52.

³ *P* values are for the LC diet relative to the conventional LF diet (time × diet interaction) by repeated-measures ANOVA.

⁴ LDL-C was not calculated in 2 persons in the LF diet group because of a TG concentration >4.5 mmol/L.

effectiveness of these types of dietary programs with other weight-loss interventions.

Consistent with previous studies (5, 29, 30), reductions in FM accounted for most of the weight loss. There was a small, greater reduction in FFM in the LC group, which was no longer significant after changes in FM were controlled for. This, taken together with the fact the FFM:FM ratio remained similar in both groups, which indicated that body-composition changes paralleled those of weight, suggests that greater reductions in FFM in the LC group paralleled the loss of FM. Moreover, the effects of the different diets on body composition are consistent with those of a previous study that compared an LC Atkins diet with a conventional LF diet (3) and with a meta-regression analysis of low- and high-carbohydrate diets (22). These findings support the view that the proportional changes in FM and FFM during weight loss with either diet are similar over the long term. The fact that FFM is closely related to resting metabolic rate (31) with importance for long-term weight maintenance (32); therefore, a comparison of the effects of the LC and LF diets on resting energy expenditure would be useful in future studies.

The present study showed substantial improvements in blood pressure, glucose, insulin resistance and CRP with weight loss that were independent of diet composition. This supports the results of other previous long-term studies that compared LC and LF diets (2–5, 7, 9, 10). These improvements reduce the cardiometabolic disease risk.

The LC diet also provided greater improvements in triglycerides and HDL cholesterol than did the LF diet, which occurred independently of differences in energy intake and weight loss. This finding is consistent with those of long-term ad libitum studies (2, 5, 7, 10). High triglyceride and low HDL-cholesterol concentrations are 2 of the MS risk factors, a syndrome that is associated with an increased risk of type 2 diabetes and CVD (13, 33). Elevated triglyceride concentrations have also been identified as an independent CVD risk factor (34), and the triglyceride:HDL cholesterol ratio is considered a strong predictor of future cardiac events (35) and is a surrogate measure of insulin resistance (36). Our data show that the triglyceride:HDL cholesterol ratio was halved after the LC diet and was approximately double the improvement observed with the LF diet. A recent review suggests that biological markers typically associated with the MS are those improved by carbohydrate restriction (37), which suggests that LC diets may offer the greatest clinical benefits for overweight populations who are insulin resistant and have several metabolic risk factors. However, no endpoint studies of either diet or drugs have shown that increasing HDL cholesterol or reducing triglyceride concentrations lowers coronary events.

Whereas the LC diet improved a range of cardiometabolic risk factors, greater increases in total and LDL cholesterol also occurred. Other studies that compared LC and LF diets reported similar findings (2, 7, 10), although the overall magnitude of the differences was smaller (8): 0.60 and 0.20 mmol/L in favor of the

LF diet. This lower response between the diets in previous studies could be attributed to the notion that greater reductions in energy intakes and weight loss occur after an ad libitum LC diet (2, 3), which may reduce the LDL-cholesterol response to an LC diet. In support of this, the differential effects between the LC and LF diets on LDL cholesterol are more prominent in other short-term studies in which energy intake was controlled for and matched between diets (38–41). Alternatively, other long-term studies that compared LC and LF diets are associated with poor compliance with the prescribed macronutrient compositions (2, 3, 5, 7), which may have suppressed the differential LDL cholesterol response between diets. Despite the unfavorable effect on LDL cholesterol, the overall trajectory (ie, across all time points) in the apo B response between diets was not different. At 12 mo, although there was a trend toward an increase in apo B on LC and a reduction in LF, this was not statistically significant ($P = 0.168$). This suggests that the increase in LDL cholesterol with an LC diet may be due to an increase in LDL cholesterol particle size as well as particle number. Previous studies have shown that an LC diet increases large LDL cholesterol particle size and decreases small LDL cholesterol particle size (38, 42, 43) and is considered to reduce the atherogenicity of LDL cholesterol (44). Krauss et al (45) also reported a strong relation between carbohydrate intake and the prevalence of small LDL particles. Further studies are required to better characterize the long-term effects of LC diets on lipoprotein particle subfractions. Nevertheless, based on data from the Health Professionals Follow-Up Study (46), it can be calculated that the increase and decrease in apo B with LC and LF diets, respectively, can increase and decrease cardiac risk by 16% and 32%, respectively. However, this is based on an isolated study conducted only in men and should be interpreted with some caution.

Using the FRS, which provides a global representation of CHD risk, the improvements in risk factors achieved in the current study resulted in an overall $\approx 21\%$ relative reduction in 10-y CHD risk, with no difference between diets. However, it has not been confirmed that a reduction in the FRS reduces CVD event risk, in contrast with studies showing that a reduction in LDL cholesterol is associated with such a reduction (47). A limitation of the FRS model is the absence of potentially important risk markers of CHD, such as LDL cholesterol, which remains a primary target (48), elevated fasting glucose, which may be as powerful as established diabetes, and the use of antihypertensive medication, which may lower blood pressure but does not reduce CVD risk to the degree expected. Hence, whether long-term consumption of LC and LF diets positively or adversely affects clinical endpoints remains speculative.

In summary, similar weight loss and improvements in many CVD risk factors occurred after consumption of an energy-restricted LC diet and an isocaloric LF diet for 12 mo. The LC diet was associated with greater increases in HDL cholesterol and decreases in triglycerides and the triglyceride:HDL cholesterol ratio, which may be clinically beneficial to obese persons with insulin resistance. However, these potential benefits may be counteracted by the detrimental effects of an increase in LDL cholesterol, which should be monitored, although predictions of overall lower CHD risk based on the FRS are similar with both diets.

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The authors' responsibilities were as follows—GDB: had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis, conceived and designed the study, coordinated the study, contributed to the statistical analyses, interpreted the data, and coordinated the writing of the manuscript; MN: conceived and designed the study and the experimental diets, interpreted the data, and wrote the manuscript; JDB: contributed to the experimental design, the statistical analysis, the data interpretation, and the writing of the manuscript; JBK: contributed to the experimental design, data interpretation, and writing of the manuscript; and PMC: conceived and designed the study and contributed to the data interpretation and writing of the manuscript. All authors agreed on the final version of the manuscript. None of the authors had a conflict of interest in relation to this manuscript.

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