

Metabolic Effects of Weight Loss on a Very-Low-Carbohydrate Diet Compared With an Isocaloric High-Carbohydrate Diet in Abdominally Obese Subjects

Jeannie Tay, BNUTRDIET (HONS),*† Grant D. Brinkworth, PHD,* Manny Noakes, PHD,* Jennifer Keogh, MSc,* Peter M. Clifton, PHD*

Adelaide, Australia

- Objectives** This study was designed to compare the effects of an energy-reduced, isocaloric very-low-carbohydrate, high-fat (VLCHF) diet and a high-carbohydrate, low-fat (HCLF) diet on weight loss and cardiovascular disease (CVD) risk outcomes.
- Background** Despite the popularity of the VLCHF diet, no studies have compared the chronic effects of weight loss and metabolic change to a conventional HCLF diet under isocaloric conditions.
- Methods** A total of 88 abdominally obese adults were randomly assigned to either an energy-restricted (~6 to 7 MJ, 30% deficit), planned isocaloric VLCHF or HCLF diet for 24 weeks in an outpatient clinical trial. Body weight, blood pressure, fasting glucose, lipids, insulin, apolipoprotein B (apoB), and C-reactive protein (CRP) were measured at weeks 0 and 24.
- Results** Weight loss was similar in both groups (VLCHF -11.9 ± 6.3 kg, HCLF -10.1 ± 5.7 kg; $p = 0.17$). Blood pressure, CRP, fasting glucose, and insulin reduced similarly with weight loss in both diets. The VLCHF diet produced greater decreases in triacylglycerols (VLCHF -0.64 ± 0.62 mmol/l, HCLF -0.35 ± 0.49 mmol/l; $p = 0.01$) and increases in high-density lipoprotein cholesterol (HDL-C) (VLCHF 0.25 ± 0.28 mmol/l, HCLF 0.08 ± 0.17 mmol/l; $p = 0.002$). Low-density lipoprotein cholesterol (LDL-C) decreased in the HCLF diet but remained unchanged in the VLCHF diet (VLCHF 0.06 ± 0.58 mmol/l, HCLF -0.46 ± 0.71 mmol/l; $p < 0.001$). However, a high degree of individual variability for the LDL response in the VLCHF diet was observed, with 24% of individuals reporting an increase of at least 10%. The apoB levels remained unchanged in both diet groups.
- Conclusions** Under isocaloric conditions, VLCHF and HCLF diets result in similar weight loss. Overall, although both diets had similar improvements for a number of metabolic risk markers, an HCLF diet had more favorable effects on the blood lipid profile. This suggests that the potential long-term effects of the VLCHF diet for CVD risk remain a concern and that blood lipid levels should be monitored. (Long-term health effects of high and low carbohydrate, weight loss diets in obese subjects with the metabolic syndrome; <http://www.anzctr.org.au>; ACTR No. 12606000203550). (J Am Coll Cardiol 2008;51:59-67) © 2008 by the American College of Cardiology Foundation

Current dietary recommendations for weight management and obesity treatment advocate the consumption of a high-carbohydrate, low-fat (HCLF), moderate energy-restricted diet (1,2). However, there has been a resurgence

in public interest in and use of a very-low-carbohydrate, high-fat (VLCHF) diet fueled by the epidemic of obesity and type 2 diabetes (3), and several recent randomized controlled trials have demonstrated greater weight loss following the consumption of an VLCHF diet compared with a HCLF diet up to 6 months (4-7). However, these studies have been largely limited by high attrition rates, poor dietary compliance, and limited dietary assessment. More recently, Gardner et al. (8) published a study that used more intensive interventional strategies to achieve better dietary compliance and higher subject retention and demonstrated greater weight loss in overweight/obese women following an

From the *Commonwealth Scientific and Industrial Research Organisation—Human Nutrition, Adelaide, Australia; and the †Department of Nutrition and Dietetics, Flinders University, Adelaide, Australia. This study was supported by project grants from the National Heart Foundation of Australia and the National Health and Medical Research Council of Australia. For full author contribution and disclosure information, please see the end of this article.

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**Abbreviations
and Acronyms****apoB** = apolipoprotein B**BMI** = body mass index**CRP** = C-reactive protein**CVD** = cardiovascular
disease**HCLF** = high-carbohydrate,
low-fat**HDL-C** = high-density
lipoprotein cholesterol**HOMA-IR** = homeostatic
model assessment-insulin
resistance**ITT** = intention to treat**LDL-C** = low-density
lipoprotein cholesterol**TAG** = triacylglycerol**VLCHF** = very-low-
carbohydrate, high-fat

VLCHF diet after 12 months compared with higher carbohydrate diets.

Despite potential weight-loss advantages, concern remains that chronic consumption of an VLCHF diet, typically high in saturated fat and cholesterol, may have detrimental effects on blood lipids and cardiovascular disease (CVD) risk (9–12). Recent studies have consistently shown that compared with an HCLF diet, an VLCHF diet produces greater reductions in triacylglycerols (TAG) and increases in high-density lipoprotein cholesterol (HDL-C) and at least comparable changes in blood pressure and insulin resistance, without detrimental effects on low-density lipoprotein cholesterol (LDL-C) for periods up to 1 year (5–8,13). However, most of these studies have used a free-living, ad libitum approach that does not allow for the study of the metabolic effects of such dietary patterns without associated confounding variables such as differences in energy intake. For example, Gardner et al. (8) showed that weight-loss differences between an VLCHF and HCLF diet influenced the effect on CVD risk factor responses. Therefore, although ad libitum experimental designs are appropriate for evaluating effectiveness, there is still a lack of understanding of the specific metabolic effects of VLCHF diets when consumed long term without the confounding effect of differential weight loss. The aim of this study was to compare, under isocaloric and well-controlled diet conditions, weight loss and the metabolic effects at 6 months of a moderate energy-restricted VLCHF and HCLF diet in abdominally obese subjects with elevated cardiovascular risk.

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Methods

Participants. A total of 122 men and women, ages 18 to 65 years, with abdominal obesity and the presence of at least 1 additional metabolic syndrome risk factor (14) were recruited by public advertisement. Exclusion criteria included a history of liver, cardiovascular, peripheral vascular, respiratory, or gastrointestinal disease; diabetes, or a malignancy. Subjects provided written informed consent before participation, and all protocols and procedures were approved by the Human Ethics Committee of the Commonwealth Scientific and Industrial Research Organisation.

Figure 1 shows participant flow. Baseline characteristics between diet groups were not different (Table 1). Overall, 36% of subjects had elevated TAG, 25% had reduced HDL-C, 68% had elevated blood pressure, 42% had ele-

vated fasting blood glucose, and 55% had at least 2 of these risk factors and met the metabolic syndrome criteria (14). There was no difference between diet groups in the presence of these risk factors ($p \geq 0.29$). Subjects who withdrew before the end of the study were similar to those who completed the study for age, gender distribution, body mass index (BMI), waist circumference, and other CVD risk factors at baseline ($p \geq 0.22$).

Of the 88 subjects who completed the study, 15 were taking estrogens (hormone replacement therapy, $n = 11$; oral contraceptive pill, $n = 4$), 27 were taking antihypertensive medication, and 18 were taking lipid-lowering medication. No subjects were taking hypoglycemic medication.

Medication distribution between the treatment groups was not different. Throughout the study, 2 subjects increased their hypertensive medication (1 in each diet group), 7 decreased their antihypertensive medication ($n = 4$ for VLCHF and $n = 3$ for HCLF), and 1 from the VLCHF diet group decreased their lipid-lowering medication.

Study design. In a parallel study design, subjects were matched for age, gender, and BMI and randomly assigned to either an VLCHF or HCLF diet for 24 weeks. At weeks 0 and 24, subjects attended the clinic after an overnight fast. Body mass, height (baseline only), and blood pressure were measured before a venous blood sample for the determination of glucose, insulin, lipids, apolipoprotein B (apoB), C-reactive protein (CRP), and plasma ketones. Ketones were also measured at week 8. During the study, subjects attended the clinic fortnightly for 8 weeks and monthly thereafter for dietetic consultations and a weight check to quantify time-course changes. No specific recommendations were given for physical activity, which was assessed using an established questionnaire (15).

Dietary interventions. The planned macronutrient profiles of the dietary interventions were as follows: VLCHF diet = 4% of total energy as carbohydrate, 35% as protein, 61% as total fat (20% saturated fat); HCLF diet = 46% of total energy as carbohydrate, 24% as protein, 30% as total fat (<8% saturated fat). The diets were designed to be isocaloric, with a moderate energy restriction of ~30% (~6,000 kJ for women, ~7,000 kJ for men). In the VLCHF diet, carbohydrate intake was restricted to <20 g/day during the first 8 weeks of the study. Subjects were then given the option to increase carbohydrate intake to <40 g/day for the remaining 16 weeks to facilitate dietary compliance. Subjects in the HCLF diet were asked to restrict saturated fat intake to <10 g/day for the study duration. Key foods representative of each diet's macronutrient profile were supplied fortnightly for the first 8 weeks to aid compliance. These foods were generally uncooked but preweighed to provide about 30% of total energy. In the subsequent 16 weeks, \$40 food vouchers were provided to subjects monthly to facilitate continued adherence.

Both dietary patterns were structured to include specific food quantities to ensure the correct macronutrient and energy requirements (Table 2). These foods were listed in a

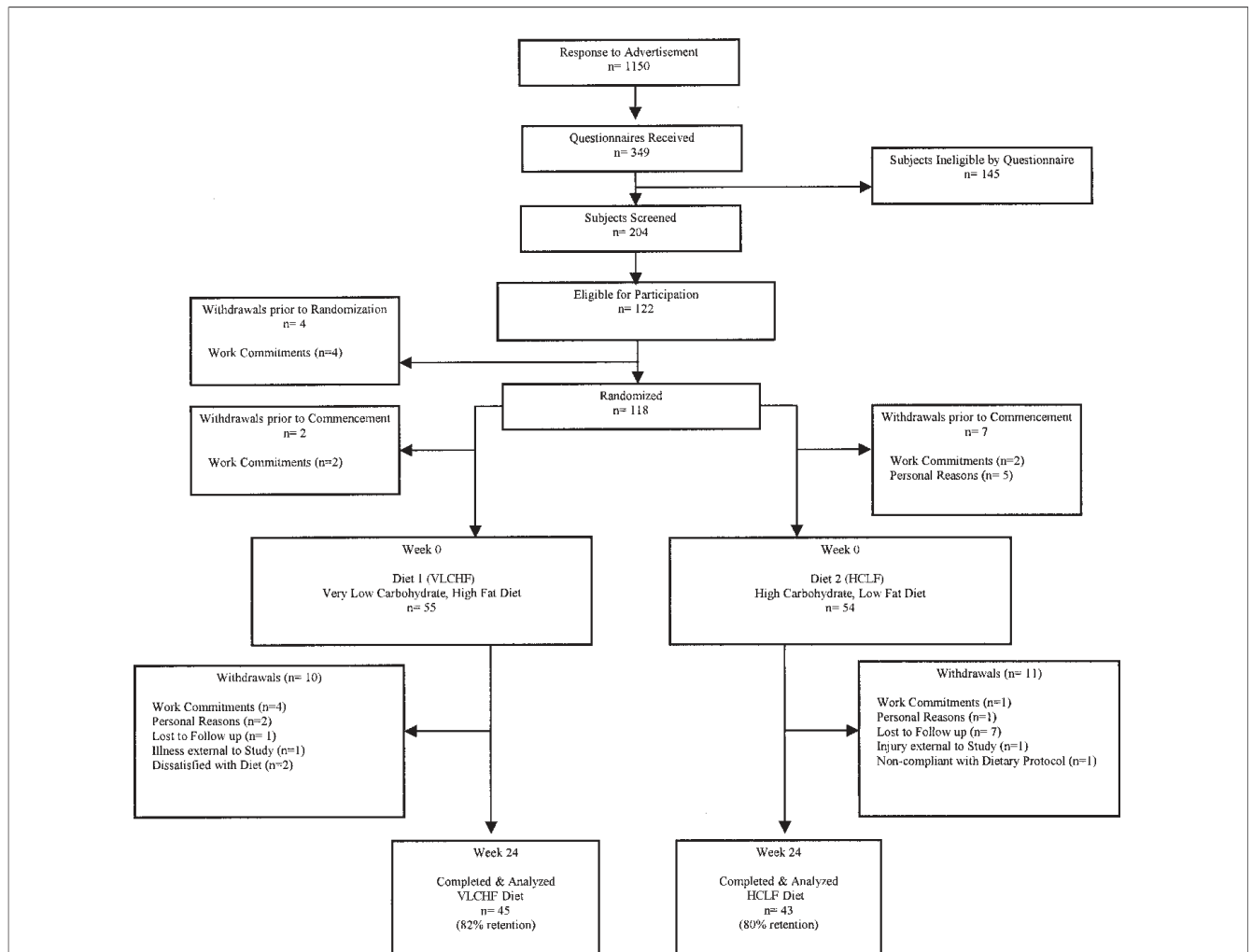


Figure 1 CONSORT Diagram of the Study

HCLF = high-carbohydrate, low-fat diet; VLCHF = very-low-carbohydrate, high-fat diet.

semiquantitative food record that subjects completed daily. Scales for weighing food were provided. At each clinic visit, subjects attended individual consultations with a qualified dietitian during which detailed, individualized dietary advice, meal planning, and recipe information for each diet was provided. Diet composition during the study was assessed using 3-day food records recorded every 2 weeks and analyzed using Foodworks Professional Edition version 4 software (Xyris Software 1998, Highgate Hill, Australia). At baseline and week 24, dietary intake was assessed using a food frequency questionnaire (16).

Anthropometric measurements and blood pressure. Body mass was measured using calibrated electronic digital scales (Mercury AMZ14, Tokyo, Japan) to the nearest 0.05 kg, with subjects wearing light clothing and no footwear. Waist circumference was measured to the nearest millimeter using a standard nonstretching tape measure 3 cm above the iliac crest. The average of 2 measures was recorded as the measured value (cm). Resting blood pressure (mm Hg) was measured by

an automated sphygmomanometer (DYNAMAP 8100, Criticon, Tampa, Florida) with subjects in a seated position after having rested for a minimum of 5 min. Three readings were taken, each separated by 2 min, with the average score recorded as the measured value.

Biochemical analysis. Serum total cholesterol, HDL-C, TAG, total apoB (B100 and B48), CRP, and plasma glucose were measured on a Roche Hitachi 902 auto-analyzer (Roche Diagnostics, Indianapolis, Indiana) using standard Roche enzymatic kits (Roche Diagnostics, Basel, Switzerland) compared to control sera. The LDL-C was calculated according to the method described by Friedewald et al. (17). Plasma insulin concentrations were determined using a commercial enzyme immunoassay kit (Mercodia ELISA, ALPCO Diagnostics, Uppsala, Sweden). The homeostatic model assessment (HOMA) was used as a surrogate measure of insulin resistance based on fasting glucose and insulin concentrations, calculated as fasting plasma insulin concentration (mU/l) \times fasting plasma

Table 1 Subject Characteristics at Baseline

Characteristic	VLCHF (n = 45)	HCLF (n = 43)
n (men/women)	14/31	17/26
Age (yrs)	50.3 ± 8.4	51.0 ± 7.5
BMI (kg/m ²)	33.9 ± 4.3	33.5 ± 4.1
Weight (kg)	94.4 ± 15.5	95.2 ± 12.6
Waist circumference (cm)		
Men	109.1 ± 10.0	109.8 ± 7.2
Women	102.4 ± 8.3	100.7 ± 8.9
Systolic blood pressure (mm Hg)	133.5 ± 14.5	136.1 ± 12.6
Diastolic blood pressure (mm Hg)	73.6 ± 11.6	77.8 ± 10.1
Glucose (mmol/l)	5.7 ± 0.6	5.7 ± 0.8
Insulin (mU/l)	9.2 ± 4.8	10.9 ± 5.4
Cholesterol (mmol/l)		
Total	5.4 ± 0.9	5.4 ± 0.8
HDL-C	1.4 ± 0.3	1.3 ± 0.4
LDL-C	3.2 ± 0.9	3.3 ± 0.7
Triacylglycerol (mmol/l)*	1.6 ± 0.7	1.8 ± 0.8

Values are mean ± SD. To convert mmol/l to mg/dl, multiply value by 18 for glucose, 38.7 for cholesterol, and 88.6 for triacylglycerol. All baseline characteristics were not significantly different between diet groups ($p > 0.05$) by independent samples *t* test (continuous variables) and Pearson chi-square (categorical variables). *Triacylglycerol represents triglycerides.

BMI = body mass index; HCLF = high-carbohydrate, low-fat diet; HDL-C = high-density lipoprotein cholesterol; VLCHF = very-low-carbohydrate, high-fat diet; LDL-C = low-density lipoprotein cholesterol.

glucose concentration (mmol/l)/22.5 (18). Plasma ketone concentrations were analyzed in duplicate on a Roche Hitachi auto-analyzer using a RANBUT D-3-Hydroxybutyrate kit (RANDOX Laboratories Ltd., Antrim, United Kingdom).

Statistical analysis. All statistical analyses were performed using SPSS 14.0 for Windows (SPSS Inc., Chicago, Illinois). Distribution was normal for all variables except ketones and insulin, which were normalized using logarithmic transformation before analysis with normal-scale values presented. Differences in baseline characteristics between

groups and dietary data were compared using independent *t* tests for continuous variables and Pearson chi-square test for categorical variables. Repeated-measures analysis of variance (ANOVA) with diet (i.e., VLCHF or HCLF) and gender set as between-subjects factors and time (weeks 0 and 24) as a within-subject factor was used to assess the effects of dietary intervention by comparing changes on the dependent variables between the groups over time. Where there was a significant main effect, post-hoc comparisons were performed as appropriate with Bonferroni's adjustment for multiple comparisons to determine differences between group means. Intention-to-treat (ITT) analysis was performed using baseline weight or weight at last follow-up visit carried forward for those who did not complete the study to examine the change in weight from baseline to week 24. Pearson correlation analyses were conducted to assess the association of change between variables. Statistical significance was set at $p \leq 0.05$. All data are presented as mean ± SD unless otherwise stated.

Results

Dietary analysis, compliance, and physical activity. The reported dietary intakes over the 24-week period were consistent with the prescribed dietary interventions. Total energy intake was not different between the groups (VLCHF 6,714 ± 764 kJ, HCLF 6,402 ± 731 kJ; $p > 0.05$), and the level of energy restriction significantly correlated with the degree of weight loss (VLCHF $r = -0.31$, $p = 0.04$; HCLF $r = -0.30$, $p = 0.05$). Compared to baseline, saturated fat intake increased by 6.8 ± 16.7 g/day in the VLCHF diet and decreased by 14.6 ± 16.7 g/day in the HCLF diet. From baseline, carbohydrate intake decreased by 141.4 ± 77.6 g/day in the VLCHF diet and

Table 2 Food Profile of Dietary Interventions

VLCHF, 6,000 kJ	HCLF, 6,000 kJ
125 ml full-fat milk	300 ml skim milk
70 g full-fat cheddar cheese*	2 slices whole-grain bread (35 g/slice)
1 medium (50 to 55 g) egg	40 g high-fiber cereal, (e.g., Fibre Plus, All Bran)*
300 g (raw protein food) beef, chicken, fish	20 g reduced-fat cheese (2 times/wk)*
100 g (cooked weight) ham, tuna, beef, chicken, turkey*	150 g raw meat, beef, chicken, pork, lamb (5 times/wk)*
At least 2.5 cups (green) vegetables	300 g fruit
25 g (5 tsp) oil/butter	150 g fish (once/wk)
40 g raw unsalted mixed nuts*	At least 2.5 cups vegetables
2 standard alcoholic drinks/wk (optional)	1 medium potato (3 times/wk)
	100 g (dry wt.) pasta/rice (4 times/wk)*
	100 g beans/lentils (2 times/wk)*
	200 g diet yogurt (3 times/wk)
	20 g raw unsalted nuts*
	50 g tinned fish (3 times/wk)*
	2 tsp polyunsaturated margarine
	3 tsp vegetable oil (e.g., olive or canola oil)
	2 standard alcoholic drinks/wk (optional)

*Key food items provided in the first 8 weeks. Abbreviations as in Table 1.

22.2 ± 71.6 g/day in the HCLF diet with energy restriction. Plasma ketone concentrations were not different between the groups at baseline. There was a significant time by diet interaction for ketone bodies ($p < 0.001$) such that levels had increased more in the VLCHF diet compared with the HCLF diet by week 8 (Fig. 2). Ketone concentrations declined in the VLCHF diet during the subsequent 16 weeks but remained 2-fold higher compared to the HCLF diet at week 24, indicating compliance to a very-low-carbohydrate intake on the VLCHF diet. At week 24, carbohydrate intake negatively correlated with ketone concentration in the VLCHF diet ($r = -0.37$, $p = 0.01$), but not the HCLF diet ($r = -0.17$, $p = 0.29$). At baseline, physical activity levels were similar in both groups ($p = 0.55$) and did not change in either group during the intervention ($p = 0.83$).

Weight loss. Over the 24 weeks, there were substantial reductions in body weight in both groups ($p < 0.001$), with no significant difference between the diets, expressed either in absolute terms (VLCHF -11.9 ± 6.3 kg, HCLF -10.1 ± 5.7 kg; $p = 0.17$) (Fig. 3) or as percentage weight loss (VLCHF $-12.3 \pm 5.5\%$, HCLF $-10.5 \pm 5.5\%$; $p = 0.14$). There was no effect of gender. The ITT with either baseline values carried forward or the last follow-up visit carried forward for those who did not complete the study also showed no difference in weight loss between the diets ($p \geq 0.23$). Furthermore, there were no differences between the diets for the proportion of subjects that exhibited $>5\%$ weight loss (VLCHF 41 of 45, HCLF 35 of 43; chi-square = 1.76; $p = 0.18$) and 10% weight loss (VLCHF 30 of 45, HCLF 23 of 43; chi-square = 1.594; $p = 0.21$). Subjects in the highest

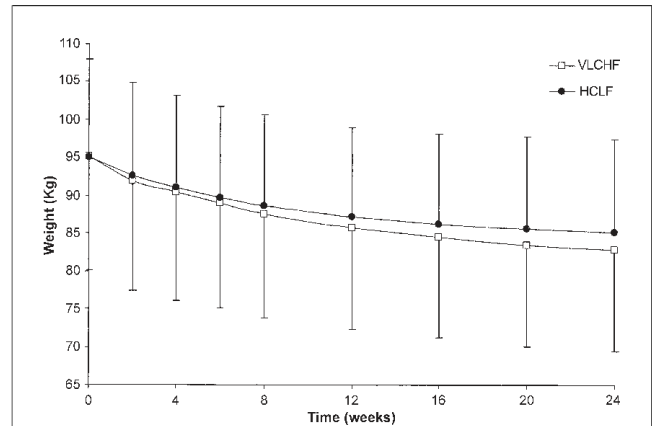


Figure 3 Body Weight Before and After Intervention

Body weight at baseline and after 24 weeks of energy restriction consumption of an VLCHF diet ($n = 45$) or an HCLF diet ($n = 43$). Both diets significantly different ($p < 0.001$) from baseline (time effect). There was no significant time by diet interaction ($p > 0.05$) over 24 weeks by repeated-measures analysis of variance. Abbreviations as in Figure 1.

tertile of carbohydrate intake at baseline (>214 g/day) did not experience greater weight loss on the VLCHF diet compared with the HCLF diet ($p = 0.10$, time by diet interaction). At week 24, weight loss correlated with ketone concentration in the VLCHF diet ($r = 0.45$, $p = 0.002$), but not in the HCLF diet ($r = 0.20$, $p = 0.20$).

Lipids and apoB. There was a significant effect of diet on total and LDL-C ($p \leq 0.005$, time by diet interaction) whereby these parameters decreased in the HCLF diet ($p < 0.001$) but did not change in the VLCHF diet ($p \geq 0.52$) (Table 3). Subjects in the highest tertile according to baseline LDL-C (>4.11 mmol/l, $n = 29$) showed larger LDL-C reductions in the HCLF diet compared with the VLCHF diet (VLCHF -0.23 ± 0.54 mmol/l, HCLF -0.76 ± 0.72 mmol/l; $p = 0.03$). A greater proportion of subjects on the VLCHF diet compared with the HCLF diet experienced an increase in LDL-C of at least 5% (VLCHF 36% [16 of 45]; HCLF 12% [5 of 42]; chi-square = 6.64, $p = 0.01$) and 10% (VLCHF 24% [11 of 45]; HCLF 10% [4 of 42]; chi-square = 3.39, $p = 0.06$). The LDL decreased in 58% (26 of 45) and 79% (33 of 42) of subjects on the VLCHF and HCLF diets, respectively (chi-square = 4.30, $p = 0.04$). For LDL-C, a significant effect of gender was also observed ($p = 0.04$ time \times diet \times gender interaction), such that LDL-C decreased in both genders on the HCLF diet (men -0.57 ± 0.97 mmol/l, women -0.39 ± 0.51 mmol/l; $p = 0.57$) but increased in men and decreased in women on the VLCHF diet (men 0.21 ± 0.62 mmol/l, women -0.18 ± 0.52 mmol/l; $p = 0.03$). Compared to baseline, apoB concentrations were reduced by 1% in the VLCHF diet and 4.9% in the HCLF diet, but this did not reach statistical significance, and there was no difference between the diets ($p = 0.52$) (Table 3).

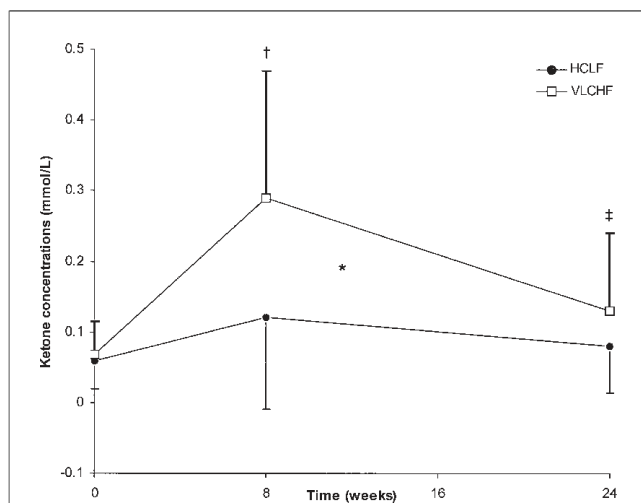


Figure 2 Plasma Ketone Concentrations Before and After Intervention

Ketone concentration at baseline and after 8 and 24 weeks of energy restriction with an VLCHF diet ($n = 45$) or an HCLF diet ($n = 43$). *Significant time by diet interaction between the groups ($P < 0.001$) by repeated measures analysis of variance. † $p < 0.001$, ‡ $p = 0.01$ significantly greater than HCLF by post-hoc comparisons at each time point with Bonferroni adjustment for 3 comparisons. Abbreviations as in Figure 1.

Table 3 Serum Lipids and Apo-B Concentrations Before and After the 24-Week Dietary Intervention

	VLCHF			HCLF		
	Week 0	Week 24	Change	Week 0	Week 24	Change
Total cholesterol (mmol/l)*	5.39 ± 0.93	5.37 ± 1.19	-0.02 ± 0.81	5.39 ± 0.77	4.85 ± 0.84	-0.54 ± 0.79†
LDL-C (mmol/l)*	3.24 ± 0.93	3.19 ± 0.94	0.06 ± 0.58	3.26 ± 0.72	2.80 ± 0.74	-0.46 ± 0.71†
HDL-C (mmol/l)*	1.42 ± 0.28	1.67 ± 0.36	0.25 ± 0.28†	1.33 ± 0.35	1.41 ± 0.30	0.08 ± 0.17†
TAG (mmol/l)*	1.60 ± 0.69	0.96 ± 0.35	-0.64 ± 0.62†	1.78 ± 0.79	1.43 ± 0.96	-0.35 ± 0.49†
ApoB (g/l)	0.98 ± 0.22	0.96 ± 0.25	-0.02 ± 0.18	1.00 ± 0.19	0.95 ± 0.26	-0.05 ± 0.19

Values are mean ± SD. *Significant time × diet interaction ($p < 0.05$) by repeated measures analysis of variance. † $p < 0.001$: significantly different from baseline (time effect) by post-hoc within group comparisons, with Bonferonni adjustment for 2 comparisons.

ApoB = apolipoprotein B; TAG = triacylglycerol; other abbreviations as in Table 1.

High-density lipoprotein increased more in the VLCHF diet than in the HCLF diet (VLCHF 18% vs. HCLF 6%, $p = 0.002$ time × diet interaction). There was no effect of gender. For subjects in the lowest tertile of baseline HDL-C (<1.23 mmol/l; $n = 29$), HDL-C increased more in the VLCHF diet compared with the HCLF diet (VLCHF 0.41 ± 0.20 mmol/l, HCLF 0.11 ± 0.09 mmol/l; $p < 0.001$). Similarly, for subjects in the highest tertile of baseline HDL-C (>1.49 mmol/l; $n = 29$), there was a significant time by diet interaction ($p = 0.003$), with an increase in the VLCHF diet (0.25 ± 0.24 mmol/l, $p < 0.001$), but no change in the HCLF diet (-0.05 ± 0.24 mmol/l, $p = 0.52$).

Diet composition had a significant effect on TAG, with a 2-fold greater reduction in the VLCHF diet compared with the HCLF diet ($p = 0.01$ time × diet effect). No effect of gender was observed. For subjects in the highest tertile of baseline TAG (>1.83 mmol/l; $n = 29$), those in the VLCHF diet displayed greater reductions in TAG compared with the HCLF diet (VLCHF -1.31 ± 0.61 mmol/l, HCLF -0.34 ± 0.67 mmol/l; $p < 0.001$). A significant effect of diet composition on TAG according to HOMA status was also observed whereby subjects in the highest tertile according to baseline HOMA scores (>2.72 , $n = 29$) corresponding to those with the highest degree of insulin resistance showed a larger reduction in the VLCHF diet compared with the HCLF diet (VLCHF -0.89 ± 0.53 mmol/l, HCLF -0.25 ± 0.67 mmol/l, $p = 0.009$).

Blood pressure, glucose, insulin, and CRP. Blood pressure, fasting glucose, insulin, and HOMA were all reduced with weight loss, with no significant effect of diet compo-

sition ($p \geq 0.57$) (Table 4). At baseline, CRP was positively correlated with BMI in both diet groups (VLCHF $r = 0.33$, $p = 0.04$; HCLF $r = 0.51$, $p = 0.003$). Subjects with CRP levels >10 mg/l (VLCHF = 7, HCLF = 11) were excluded from analysis. C-reactive protein decreased significantly with weight loss in both groups ($p < 0.001$), independent of diet composition ($p = 0.64$) (Table 4). The change in CRP negatively correlated with percentage weight loss ($r = -0.29$, $p = 0.02$). Similarly, a subanalysis of subjects with elevated CVD risk indicated by CRP >3 mg/l at baseline ($n = 33$) showed a reduction in CRP with weight loss, with no significant diet effect ($p = 0.38$).

Discussion

The results of this study demonstrate that under isocaloric conditions, an energy-restricted VLCHF diet results in similar weight loss, as well as reductions in blood pressure, plasma glucose, insulin, and CRP concentrations compared with an HCLF diet. However, differential diet effects on lipid profile were observed, and a large individual variability in LDL-C response was associated with the VLCHF diet, which may limit the generalizability of this diet.

A high level of dietary compliance was achieved, as evidenced by both the dietary data and objectively by the plasma ketones response observed. Ketone levels remained low in the HCLF diet but were elevated in the VLCHF diet, with an inverse correlation between carbohydrate intake and ketone concentrations.

The current study differs from previous investigations that have compared the chronic effects of VLCHF and

Table 4 Blood Pressure, Glucose, Insulin, HOMA-IR, and CRP Concentrations Before and After the 24-Week Dietary Intervention

	VLCHF			HCLF		
	Week 0	Week 24	Change	Week 0	Week 24	Change
Systolic blood pressure (mm Hg)	133.1 ± 14.4	120.8 ± 11.5	-12.3 ± 14.1*	136.1 ± 12.6	125.2 ± 15.8	-10.8 ± 13.2*
Diastolic blood pressure (mm Hg)	73.6 ± 11.6	69.0 ± 11.7	-4.58 ± 9.78*	77.8 ± 10.1	72.3 ± 9.01	-5.50 ± 8.60*
Glucose (mmol/l)	5.67 ± 0.57	5.49 ± 0.48	-0.18 ± 0.40*	5.60 ± 0.55	5.38 ± 0.49	-0.21 ± 0.40*
Insulin (mU/l)	9.15 ± 4.82	6.17 ± 3.48	-2.99 ± 3.31*	10.9 ± 5.40	7.45 ± 3.44	-3.43 ± 4.63*
HOMA-IR	2.35 ± 1.42	1.54 ± 1.32	-0.81 ± 1.03*	2.81 ± 1.62	1.84 ± 1.05	-0.97 ± 1.34*
CRP (mg/l)	3.21 ± 2.00	2.01 ± 1.58	-1.11 ± 1.46*	3.62 ± 2.66	2.35 ± 1.92	-1.27 ± 1.95*

Values are mean ± SD. No significant time × diet interaction ($p > 0.05$) for these parameters. * $p < 0.01$: significantly different from baseline (time effect).

CRP = C-reactive protein; HOMA-IR = homeostatic model assessment insulin resistance; other abbreviations as in Table 1.

HCLF diets when consumed ad libitum, as our purpose was to specifically assess the metabolic effects of these diets when matched in energy intake. After 6 months, we did not observe a metabolic weight loss advantage with the VLCHF diet, although numerically there was a greater weight loss with the VLCHF diet. In contrast, we previously showed (19) over a shorter period (12 weeks) that an energy-restricted VLCHF produced greater weight loss compared with an isocaloric HCLF diet (9.2% vs. 7.0%). Collectively, this suggests that under energy-controlled conditions, the VLCHF diet may confer a small, transient weight-loss advantage that does not persist over the longer term. Reduced thermodynamic efficiency associated with VLCHF diets has been proposed to explain this metabolic advantage, although the supporting evidence is scant (20,21). Measurement of resting energy expenditure and the thermic effect of meals in future isocaloric studies may provide some explanation. Although proponents of VLCHF diets suggest (22) that ketosis from severe carbohydrate restriction is essential to maximize weight loss, previous studies have shown no association between ketonuria and weight loss (4,5). However, these studies were limited by high withdrawal rates and poor dietary adherence. In the present study, although we observed a positive correlation between ketone concentration and weight loss and markedly elevated ketone levels in the VLCHF diet, weight loss in both groups remained similar at 24 weeks. This suggests that ketosis may be a reflection of dietary compliance rather than causation.

In contrast to our findings, recent long-term ad libitum studies have demonstrated greater weight loss following consumption of the VLCHF diet compared with the HCLF diet after 6 months (4–7,13) and 1 year (8). This could be related to greater satiety associated with a higher protein intake (23), the severely limited food choices (24), the simplicity of the carbohydrate avoidance strategy, or a combination of these. Conversely, the larger variety of foods permitted in ad libitum HCLF diets may have promoted a greater potential for small but cumulative overconsumption of more food items. A greater food variety could also result in more complex meals, with a potential for the underreporting of some food items in dietary records. This may provide an explanation for the observations of previous studies that report greater weight loss following the consumption of the VLCHF diet compared with the HCLF diet, despite reported total energy intake being lower or comparable in the VLCHF diet (4,8).

Consistent with other recent studies (5–7,13,19), the VLCHF diet produced greater reductions in TAG and increases in HDL-C than the HCLF diet. This suggests that the VLCHF diet as a weight loss strategy may confer the greatest clinical benefits in patients who present with hypertriglyceridemia, low HDL levels, abdominal adiposity, and insulin resistance (14). In contrast, greater reductions in total cholesterol and LDL-C were observed with the HCLF diet, although levels in the VLCHF diet remained unchanged. This is consistent with a number of previous

studies (4,5,7,25,26). It has been suggested (27) that apoB, which represents the actual number of atherogenic lipoprotein particles, may be a more reliable indicator of CVD risk. Although there was some evidence for a reduction compared with baseline, apoB levels did not change significantly by week 24 in either diet group, suggesting that atherogenicity did not change despite a high or low saturated fat intake and the absence of an expected reduction in LDL-C with weight loss in the VLCHF diet (28). A meta-analysis showed that apoB levels were not affected by the replacement of dietary carbohydrate with saturated fat (29).

It is possible that the anticipated increase in LDL-C secondary to a high saturated fat intake in the VLCHF diet may have been mitigated by the effects of energy restriction and weight loss (28). However, there was no correlation between the change in LDL-C and the change in saturated fat intake or weight loss, suggesting the influence of other factors. A high saturated fat intake in the context of a carbohydrate-restricted diet has been shown to increase larger rather than smaller atherogenic LDL particles (30,31). This evidence suggests that the LDL-C elevating effects of saturated fat may be dependent on specific dietary conditions and that the VLCHF diet may differentially alter lipoprotein metabolism. On the basis of these findings, the effect of replacing saturated fat with cis-unsaturated fat in the context of an VLCHF diet is worthy of investigation.

Although no large increases in mean LDL-C concentration occurred in the VLCHF diet, it is important to note that substantial variability in LDL response was observed, with approximately one-half of the group showing a decrease and vice versa. This high individual variability has been previously reported in smaller studies (32). Therefore, it is possible that some individuals may have a more sensitive lipoprotein response to increases in saturated fat intake (33), but this has remained largely unexplained. In the present study, we showed a differential gender response for LDL-C with consumption of the VLCHF diet such that the mean change decreased in women and increased in men. Other studies in humans (34,35) have also observed gender difference in lipoprotein responses to diets. Our results suggest that LDL-C in men could be of some concern because of the strong level of evidence that lipid lowering reduces the risk of coronary heart disease (36). The exact reason for the gender differences and high variability in the responsiveness of LDL-C to the VLCHF diet cannot be determined from the present data, but interactions between diet and genetic traits could play a role (37). Hence, monitoring lipid level may be prudent in patients adopting the VLCHF diet.

Conclusions

After 6 months, isocaloric energy-restricted VLCHF and HCLF diets produced similar weight loss and substantial reductions in a number of CVD risk markers. Neither diet displayed adverse atherogenic effects, suggesting that diverse dietary patterns, including VLCHF diets, may be tailored to

an individual's metabolic profile and dietary preference for weight management. The HCLF diet had more favorable effects on LDL-C, whereas the VLCHF diet had more favorable effects on TG and HDL-C, suggesting that the latter approach may have relevance for the management of the metabolic syndrome. However, individual metabolic responsiveness remains an important consideration. Further research is warranted to determine the impact of both dietary patterns on longer term cardiovascular and other health outcomes and in individuals with advanced metabolic disease, such as type 2 diabetes.

Author Contributions

Ms. Tay completed this study as part of the requirement of her honors degree in Nutrition and Dietetics. She participated in study implementation, performed data analyses, and contributed to results interpretation and to the writing of the manuscript. Dr. Brinkworth was responsible for conception and design of the study, coordinated the study, contributed to the statistical analyses, interpreted the data, and coordinated the writing of the manuscript. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Noakes was responsible for the design of the study and the experimental diets, and contributed to the statistical analyses, interpretation of the data, and the writing of the manuscript. Ms. Keogh assisted in the design of the dietary protocol. Dr. Clifton contributed to the experimental design, data interpretation, and writing of the manuscript.

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Reprint requests and correspondence: Dr. Grant D. Brinkworth, CSIRO-Human Nutrition, P.O. Box 10041 BC, Adelaide, South Australia 5000, Australia. E-mail: grant.brinkworth@csiro.au.

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