

BMJ Open Effect of a 6-month vegan low-carbohydrate ('Eco-Atkins') diet on cardiovascular risk factors and body weight in hyperlipidaemic adults: a randomised controlled trial

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ABSTRACT

Objective: Low-carbohydrate diets may be useful for weight loss. Diets high in vegetable proteins and oils may reduce the risk of coronary heart disease. The main objective was to determine the longer term effect of a diet that was both low-carbohydrate and plant-based on weight loss and low-density lipoprotein cholesterol (LDL-C).

Design, setting, participants: A parallel design study of 39 overweight hyperlipidaemic men and postmenopausal women conducted at a Canadian university-affiliated hospital nutrition research centre from April 2005 to November 2006.

Intervention: Participants were advised to consume either a low-carbohydrate vegan diet or a high-carbohydrate lacto-ovo vegetarian diet for 6 months after completing 1-month metabolic (all foods provided) versions of these diets. The prescribed macronutrient intakes for the low-carbohydrate and high-carbohydrate diets were: 26% and 58% of energy from carbohydrate, 31% and 16% from protein and 43% and 25% from fat, respectively.

Primary outcome: Change in body weight.

Results: 23 participants (50% test, 68% control) completed the 6-month ad libitum study. The approximate 4 kg weight loss on the metabolic study was increased to -6.9 kg on low-carbohydrate and -5.8 kg on high-carbohydrate 6-month ad libitum treatments (treatment difference (95% CI) -1.1 kg (-2.1 to 0.0), $p=0.047$). The relative LDL-C and triglyceride reductions were also greater on the low-carbohydrate treatment (treatment difference (95% CI) -0.49 mmol/L (-0.70 to -0.28), $p<0.001$ and -0.34 mmol/L (-0.57 to -0.11), $p=0.005$, respectively), as were the total cholesterol:HDL-C and apolipoprotein B:A1 ratios (-0.57 (-0.83, -0.32), $p<0.001$ and -0.05 (-0.09, -0.02), $p=0.003$, respectively).

Conclusions: A self-selected low-carbohydrate vegan diet, containing increased protein and fat from gluten and soy products, nuts and vegetable oils, had lipid lowering

Strengths and limitations of this study

- The study weaknesses include the relatively small sample size and the high dropout rate. Nevertheless, it is noteworthy that attrition rates were low in the metabolic study when all food was provided. Food availability and preparation may therefore be important factors. For those who did complete the study, however, there were benefits in weight loss and low-density lipoprotein cholesterol (LDL-C) reduction, an additional 2% advantage in body weight reduction compared with the high-carbohydrate diet and a 13% drop in LDL-C for participants consuming a more plant-based low-carbohydrate diet.
- The study's strength is that the prescribed hypocaloric diet was self-selected, meaning the results are more in line with what can be expected under free-living conditions. The breadth of application of the plant-based low-carbohydrate diet, however, remains to be determined, but it may provide an option for some individuals for whom LDL-C reduction is an equal concern to weight loss. If low-carbohydrate dietary options become more generally available the number of individuals who will benefit is likely to increase.
- A further strength of the study is that the reduction in Framingham cardiovascular disease risk score seen on the Eco-Atkins diet has been validated in a long-term cardiovascular disease outcome trial using key components of the Eco-Atkins diet (nuts and vegetable/olive oil).

advantages over a high-carbohydrate, low-fat weight loss diet, thus improving heart disease risk factors.

Trial Registration: [clinicaltrials.gov](http://www.clinicaltrials.gov) (<http://www.clinicaltrials.gov/>), #NCT00256516.

INTRODUCTION

Many popular weight loss diets emphasise carbohydrate restriction (Atkins, Eddies, South Beach, Zone). Their success is determined by the level of compliance with the prescribed diets.^{1–6} However, a high content of animal products, rich in saturated fat and cholesterol, may make conventional low-carbohydrate diets less appropriate for those with hypercholesterolaemia.^{2–7} Even during active weight loss, these high-saturated fat diets do not lower serum low-density lipoprotein cholesterol (LDL-C) below baseline^{2–7} and there is concern that if such diets continue to be eaten when weight loss has ceased, a more atherogenic blood lipid profile may result.⁸ These concerns have prompted exploration of other weight loss strategies, but only modest reductions in LDL-C have been observed.⁹

By contrast vegan diets significantly lower LDL-C.¹⁰ Trials of vegan and vegetarian diets also reduce progression of coronary heart disease (CHD)¹¹ and improve diabetes control.¹² Plant food components such as vegetable proteins, vegetable oils, nuts and viscous fibres, reduce serum lipids in many studies^{13–18} and may increase flow-mediated vasodilatation.^{19–22} Nuts, fibre and vegetarian diets in general, all reduce CHD and diabetes in cohort studies.^{23–28} Finally, in cohort studies, low-carbohydrate diets, high in vegetable oils and proteins as opposed to animal products, reduce CHD events and diabetes incidence in women,^{29–30} while lower red meat intake reduces total, cardiovascular and cancer mortality.³¹ Most recently a large randomised controlled trial confirmed the effect of nuts and increased vegetable oil (olive oil) intake in reducing cardiovascular events in the context of a Mediterranean diet.³²

In view of the apparent success of low-carbohydrate diets for weight loss and the demonstration that relatively high-carbohydrate vegetarian and vegan diets, and diets low in animal products, lower CHD risk factors,^{33–36} we designed a diet that combined both vegan and low-carbohydrate elements to determine whether such a diet captured both the weight loss and CHD risk reduction advantages. We have already reported the effect of this dietary strategy in producing a difference of 8% in LDL-C reduction between calorie-restricted diets (60% of estimated calorie requirements) when all food was provided.³⁷ We now report findings after these same participants continued on their respective diets for an additional 6 months, under self-selected conditions, in order to gain insights into the real-life effectiveness of this diet. The results of the metabolic (all foods provided) study have been reported previously and had demonstrated a CHD risk factor advantage, but with no greater weight loss than the control diet.³⁷

METHODS

Participants

Forty-seven overweight participants, recruited by newspaper advertisement and hospital clinic notices,

undertook the 1-month metabolic first phase of the study (figure 1) that has been previously reported.³⁷ At the start of the study, participants were given the option to participate in the metabolic and ad libitum phases or only the metabolic phase. On completion of the metabolic phase, 39 participants (19 control and 20 test participants) continued for an ad libitum 6-month study and their data (n=39) were used in the final analysis (table 1). The study was conducted at a Canadian university-affiliated hospital nutrition research centre from April 2005 to November 2006. All participants had high normal to raised LDL-C levels (>3.4 mmol/L at diagnosis) and a body mass index (BMI) >27 kg/m². Details of the eligibility criteria have been previously reported.³⁷ After recruitment, the 11/39 participants who were taking lipid lowering medications discontinued their medications at least 2 weeks prior to starting and for the study duration (table 1).

Study protocol

The intervention was a randomised parallel study stratified by sex in which participants were randomised to either low-carbohydrate or high-carbohydrate, calorie-reduced diets. The first month was the previously reported metabolically controlled study.³⁷ For the following 6 months, participants continued on the diet to which they had been assigned as a self-selected (ad libitum) diet. Anthropometric, blood pressure and blood lipid measurements were repeated at monthly intervals. Insulin and glycated haemoglobin (HbA1c) were measured at baseline and at the start and end of the ad libitum treatment. Percentage body fat was measured at baseline and end of the ad libitum treatment by bioelectrical impedance (Quantum II; RJL Systems, Clinton Township, Michigan). Seven-day diet and exercise histories were recorded in the week prior to each monthly visit. These histories were reviewed and discussed with the dietitian and appropriate dietary counselling was provided to enhance adherence. The overall feeling of satiety for the previous week was assessed at each study visit using a 9-point bipolar semantic scale, where -4 was extremely hungry, 0 was neutral and +4 was uncomfortably full.^{34–37} No exercise advice was given during the study, but alterations in exercise were allowed and recorded.

Written informed consent was obtained from the participants. The study's clinical trial registration number was #NCT00256516.

Diets

As with the previous metabolic study, participants were encouraged to eat only 60% of their estimated caloric requirements in order to continue the body weight reduction started on their metabolic phase.^{38–40} The prescribed test diet was a low-carbohydrate vegan diet containing 26% of calories from carbohydrate, 31% of calories from vegetable proteins and 43% from fat (primarily vegetable oils). Carbohydrate sources on the low-carbohydrate diet featured viscous fibre-containing

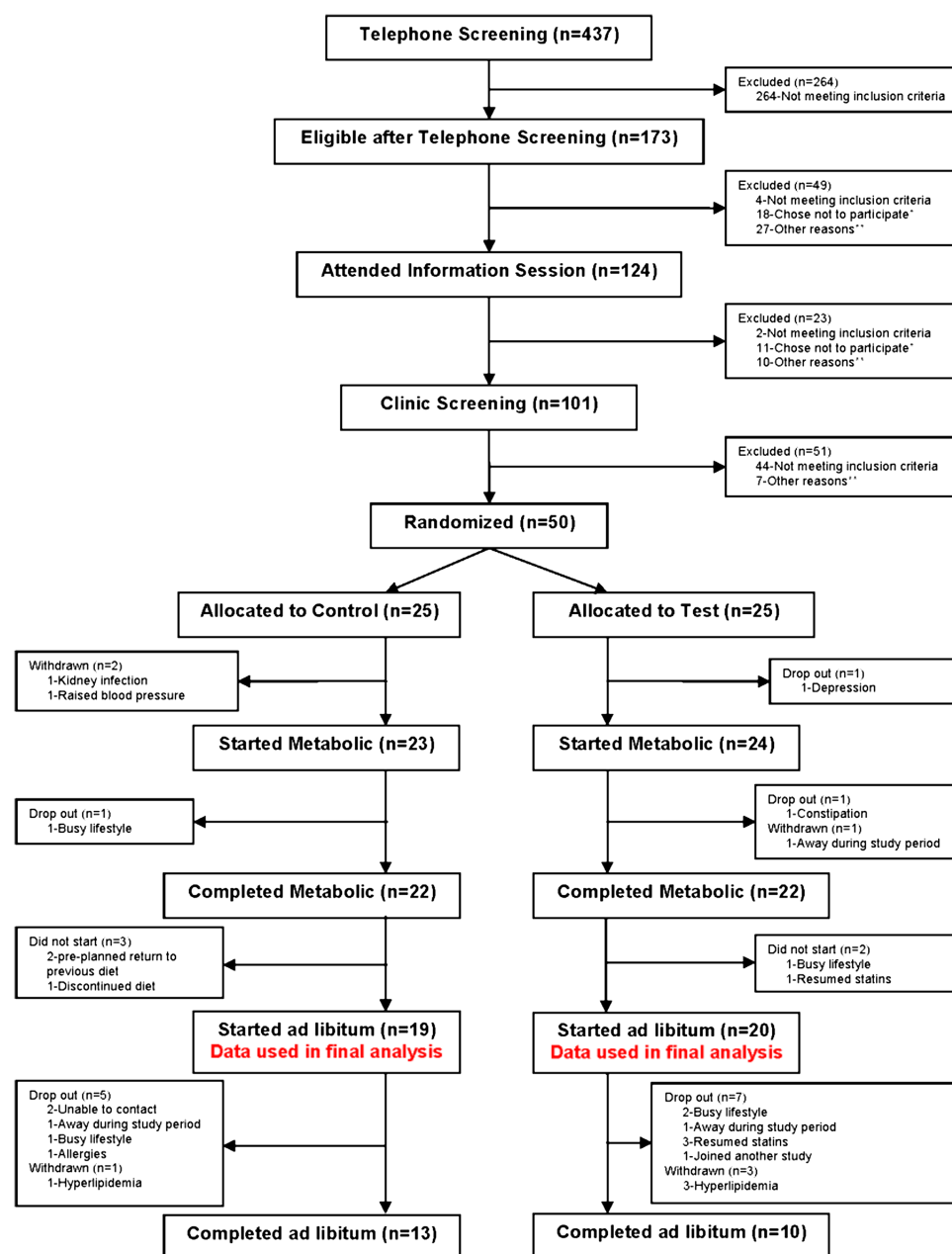


Figure 1 Patient flow diagram. *Chose not to participate (29): busy lifestyle (13); not interested (6); study too demanding (3); currently on another diet (2); no compensation (2); work-related (2); dislike prepackaged foods (1). **Other reasons (44): unable to contact (19); unable to come to clinic (13); away (5); throat surgery (1); bowel resection (1); high potassium and BP (1); high potassium (1); raised liver function tests (1); not interested (1); medical insurance issue (1).

foods (such as oats and barley) and low-starch vegetables (emphasising okra and eggplant) for the relatively limited amount of carbohydrate allowed. The vegetable proteins were prescribed as gluten (54.8% of total protein), soy (23%), fruits and vegetables (8.7%), nuts (7.5%), and cereals (6%). Gluten was contained in the nut bread and wheat gluten (also called 'seitan') products. Soy protein was present in the form of burgers, deli slices, breakfast links, veggie bacon, tofu and soy milks. Nuts included almonds, cashews, hazelnuts, macadamia, pecans and pistachios. The fat sources were nuts (43.6% of total fat), vegetable oils (24.4%), soy products

(18.5%), avocado (7.1%), cereals (2.7%), fruits and vegetables (2.3%), and seitan products (1.4%). Participants were able to purchase at the research centre the 'no' starch high protein nut bread and three of the seitan (wheat gluten) products used in the study which were not available in Canada. The control, high-carbohydrate lacto-ovo vegetarian diet (58% carbohydrate, 16% protein and 25% fat) emphasised whole wheat cereals and cereal fibre, as well as low-fat or skim milk dairy products and liquid egg substitute to reduce saturated fat and cholesterol intakes. These diets have been published previously.³⁷ Participants were given a

Table 1 Baseline characteristics for those who started the 6-month self-selected diets (n=39)

	High carbohydrate (n=19)	Low carbohydrate (n=20)
Age (years)	55.3±1.8	57.6±1.4
Males/females	6/13	9/11
Body weight (kg)	85.4 (79.3 to 91.6)	83.7 (78.5 to 89.0)
Body mass index (kg/m ²)	31.1 (29.9 to 32.4)	31.1 (29.8 to 32.4)
Blood pressure (mm Hg)		
Systolic	122 (116 to 128)	128 (123 to 132)
Diastolic	75 (72 to 79)	77 (74 to 80)
Cholesterol (mmol/L)		
Total	6.75 (6.28 to 7.21)	6.76 (6.21 to 7.31)
LDL-C	4.40 (3.99 to 4.82)	4.53 (4.14 to 4.93)
HDL-C	1.36 (1.22 to 1.50)	1.21 (1.06 to 1.36)
Triglycerides (mmol/L)	2.16 (1.62 to 2.70)	2.23 (1.65 to 2.80)
Ratios		
TC:HDL-C	5.17 (4.54 to 5.80)	5.81 (5.20 to 6.41)
LDL-C:HDL-C	3.35 (2.95 to 3.75)	3.89 (3.49 to 4.29)
Medications		
Lipid lowering (prior to start of study)	4	7
Blood pressure	3	6
Diabetes	0	0
Thyroid	2	1

Values represent mean±SEM or 95% CIs.

No significant differences between treatments at baseline assessed by two sample t test (two-tailed).

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

copy of the menu plans that outlined the food items and amounts prescribed during the metabolic phase. These menu plans served as a reference during the ad libitum phase. Furthermore, participants were given an exchange list of the items prescribed on the menu plan. The goal was to enhance adherence.

Self-taring electronic scales (My Weigh Scales, Vancouver, BC or Tanita Corporation, Arlington Heights, Illinois) were provided to all participants and they were instructed to weigh all food items while recording the 7-day food diary in the week prior to monthly clinic visits. Adherence to the three principal cholesterol-lowering components (vegetable proteins (soy and gluten), nuts and viscous fibres) of the low-carbohydrate diet was assessed from the completed monthly 7-day food records. The amount of each component provided during the metabolic phase remained the same as that prescribed during the ad libitum phase.

Neither the dietitians nor participants could be blinded, but equal emphasis was placed on the potential importance for health of both diets. The analytical technicians were blinded to diet allocation, as was the statistician, up to analysis of the primary outcome. Participants were offered no financial compensation for participation in the study.

Analyses

The analytical techniques have been reported previously.³⁷ Serum was analysed in the J. Alick Little Lipid Research Laboratory. LDL-C (in mmol/L) was calculated by the method of Friedewald *et al* using all data including the two participants who had baseline and

during study triglyceride values above 4.5 mmol/L (3 values on low-carbohydrate diet and 2 on high-carbohydrate diet, maximum triglyceride <6.5 mmol/L; exclusion of these two individuals did not alter the findings). The methods for analysing apolipoproteins A1 (ApoA1) and B (ApoB), high sensitivity C reactive protein (hs-CRP), blood glucose, insulin, HbA1c and homoeostasis model assessment—insulin resistance model (HOMA-IR) have been described previously.³⁷ Exercise data were calculated as metabolic equivalents (METs).⁴¹ The absolute 10-year CHD risk score was calculated using the Framingham risk equation.⁴²

Diets were assessed for macronutrients, fatty acids, cholesterol and fibre using a computer programme based on the US Department of Agriculture (USDA) database⁴³ and developed in our laboratory to allow the addition of the macronutrient content of study foods obtained from food labels or directly from food manufacturers. The nutritional profiles of the diets were calculated from the 7-day food records completed once a month throughout the study and mean intakes are presented.

Adherence to the three principal cholesterol-lowering components (vegetable proteins (soy and gluten), nuts and viscous fibres) of the low-carbohydrate diet was estimated from the 7-day food records. Each component was assessed as contributing 1/3 or 33.3% to the LDL-C reduction. When the amount consumed was equivalent to the amount prescribed a 33.3% compliance would be recorded for that component. The sum of the three components if consumed as prescribed would equal 100% adherence.

Statistical analyses

Results are expressed as means \pm SEM or 95% CIs. Time zero was used as the baseline and refers to the premetabolic study baseline.³⁷ Treatment differences in physical and biochemical measures were assessed using all available data from the 39 participants and a repeated measures mixed model accounting for time of assessment (SAS V.9.2)⁴⁴ in tables 2 and 3 and the Results section. The response variable was change from baseline, with diet and week as fixed effects and subject ID nested in diet. There was no adjustment for baseline. Any participant who started the ad libitum treatment was included in the analysis (N=39). The completer analysis included the 23 participants who completed the study (figure 1).

Multiple imputation (taking the mean of five sets of randomly imputed values) was used to present baseline and treatment values in tables 2 and 3 and figures 2 and 3 by generating data for those who dropped out or had missing values.⁴⁴

RESULTS

Compliance with the major dietary components (vegetable proteins (soy and gluten), nuts and viscous fibres) was 33.6% or one-third of that prescribed during the metabolic phase (table 2). Saturated fat intakes were similar on both treatments whereas intake of monounsaturated fats (MUFAs), vegetable proteins and soy protein were significantly higher on the low-carbohydrate diet (table 2). Available carbohydrate intake was significantly lower on the low-carbohydrate diet (table 2).

The attrition rate was 50% (10/20) on the low-carbohydrate and 32% (6/19) on the high-carbohydrate (figure 1) diets, this equates to a total attrition rate of 41% (16/39). The number of participants who did not complete the study (including dropouts and withdrawals) did not differ between treatments. Three participants were withdrawn by the study physician due to failure to attain LDL-C targets on the low-carbohydrate diet (mean LDL-C=5.24 mmol/L) and one participant on the high-carbohydrate diet (LDL-C=7.78 mmol/L). Participants on the low-carbohydrate diet tended to have larger reductions in body weight over time (figure 2). The weight loss from baseline to the end of the 6-month ad libitum treatment was -6.9 kg (95% CI -7.7 to -6.1) on the low-carbohydrate and -5.8 kg (95% CI -6.6 to -5.1) on the control diet with a significant difference between groups (treatment difference (95% CI) -1.1 kg (-2.1 to 0.0); p=0.047; table 3). The final reduction in BMI was also greater on the low-carbohydrate versus high-carbohydrate diet (treatment difference (95% CI) -0.4 kg/m² (-0.8 to 0.0); p=0.039; table 3). Among the completers, there were numerically larger differences between treatments for both body weight and BMI (treatment difference (95% CI) -1.8 kg (-3.0 to -0.6); p=0.004 and -0.7 kg/m² (-1.1 to -0.2); p=0.004, respectively).

There was a relative increase in recorded exercise by the high-carbohydrate diet participants, whereas there was no relative change in the low-carbohydrate participants (treatment difference (95% CI) -9.3 (-16.4 to -2.2) METs; p=0.012), but this was not reflected in a greater weight loss (table 3). There were no treatment differences in percent body fat, waist circumference or satiety (table 3).

Lipids

At the end of the study, the reduction on the low-carbohydrate versus high-carbohydrate diet was greater for LDL-C (treatment difference (95% CI) -0.49 mmol/L (-0.70 to -0.28); p<0.001, for total cholesterol (TC) -0.62 mmol/L (-0.86 to -0.37); p<0.001, for TC:high-density lipoprotein carbohydrate (HDL-C) -0.57 (-0.83 to -0.32); p<0.001, for LDL-C:HDL-C -0.42 (-0.60 to -0.24); p<0.001 and for triglycerides (-0.34 mmol/L (-0.57 to -0.11); p=0.005). No treatment difference was seen in HDL-C (table 3). A similar pattern was observed in the completers. The treatment difference was numerically larger for LDL-C (-0.60 mmol/L (-0.84 to -0.36); p<0.0001), TC (-0.73 mmol/L (-1.00 to -0.45); p<0.0001), TC:HDL-C (-0.68 (-0.97 to -0.39); p<0.0001) and LDL-C:HDL-C (-0.53 (-0.73 to -0.32); p<0.0001). Values for LDL-C and the TC:HDL-C ratio were consistently lower in participants on the low-carbohydrate diet throughout the study while HDL-C values were not different from baseline (figure 3A-C).

Apolipoproteins

ApoB and the ApoB:ApoA1 ratio were reduced more on the low-carbohydrate versus the high-carbohydrate diet at the end of the study (treatment different (95% CI) -0.11 g/L (-0.16 to -0.06); p<0.001 and -0.05 (-0.09 to -0.02); p=0.003, respectively; table 3). No significant difference between the diets was observed for ApoA1 concentrations. The pattern of change in the apolipoproteins in the completers reflected the changes seen in the whole group. Figure 3D,F show that the low-carbohydrate diet resulted in lower ApoB and ApoB:ApoA1 ratios relative to baseline over the course of the study.

CRP, HbA1c, blood glucose, serum insulin, insulin resistance and blood pressure

Both treatments reduced hs-CRP with no difference between treatments (table 3). HbA1c, fasting blood glucose, insulin and insulin resistance (calculated using the HOMA model) fell similarly on both treatments during the course of the study (table 3). Systolic and diastolic blood pressure decreased similarly with no treatment differences (table 3). The completers also failed to show a difference between treatments.

Calculated CHD risk

The low-carbohydrate diet significantly reduced the calculated 10-year CHD risk relative to the high-

Table 2 Nutritional profiles on the high-carbohydrate and low-carbohydrate diets (n=39)

	High carbohydrate		Low carbohydrate		Between-treatment difference†	p Value‡
	Week 0*	Ad libitum*	Week 0*	Ad Libitum*		
Calories (kcal)	1598 (1421 to 1775)	1347 (1140 to 1553)	1840 (1550 to 2130)	1388 (1234 to 1541)	-248 (-391 to -106)	0.001
Percentage of total calories						
Available carbohydrate	46.3 (42.2 to 50.4)	53.9 (50.2 to 57.5)	43.8 (40.2 to 47.4)	39.6 (35.7 to 43.6)	-10.5 (-13.6 to -7.5)	<0.001
Protein	20.6 (18.7 to 22.5)	18.4 (17.4 to 19.5)	20.1 (18.0 to 22.2)	22.7 (20.1 to 25.4)	5.9 (4.3 to 7.5)	<0.001
Vegetable protein	5.6 (5.0 to 6.1)	6.7 (6.1 to 7.3)	5.7 (5.3 to 6.1)	15.0 (11.7 to 18.2)	8.2 (6.5 to 9.9)	<0.001
Soy protein	0 (0 to 0)	0.2 (0.1 to 0.2)	0 (0 to 0)	4.7 (2.7 to 6.8)	3.6 (2.9 to 4.4)	<0.001
Fat	30.8 (27.3 to 34.4)	27.5 (24.6 to 30.4)	34.4 (31.4 to 37.5)	36.0 (31.5 to 40.5)	5.2 (2.6 to 7.7)	<0.001
Saturated	10.8 (9.1 to 12.6)	7.6 (6.2 to 8.9)	11.8 (10.3 to 13.3)	7.5 (6.6 to 8.4)	-0.4 (-1.4 to 0.6)	0.401
Monounsaturated	12.3 (10.7 to 13.8)	10.4 (9.3 to 11.6)	13.0 (11.9 to 14.2)	14.8 (13.1 to 16.6)	4.6 (3.1 to 6.1)	<0.001
Polyunsaturated§	5.2 (4.6 to 5.8)	6.3 (5.4 to 7.2)	6.6 (5.5 to 7.8)	8.4 (7.5 to 9.4)	0.4 (-0.5 to 1.4)	0.350
Alcohol	2.2 (0.3 to 4.2)	1.9 (0.7 to 3.2)	1.6 (0.0 to 3.3)	1.1 (0.1 to 2.1)	-0.5 (-1.3 to 0.2)	0.160
Dietary fibre (g/1000 kcal)	10.9 (9.2 to 12.5)	18.2 (15.2 to 21.1)	12.1 (9.9 to 14.4)	21.3 (18.8 to 23.8)	1.5 (-0.5 to 3.5)	0.127
Dietary cholesterol (mg/1000 kcal)	149 (129 to 169)	87 (61 to 113)	157 (136 to 177)	117 (44 to 189)	11 (-22 to 23)	0.954
Adherence with 'Eco-Atkins' components¶						
Viscous fibre (of 33.3%)	-	-	-	14.0 (9.4 to 18.6)	-	-
Vegetable protein (soy and gluten; of 33.3%)	-	-	-	14.7 (10.3 to 19.1)	-	-
Nuts (of 33.3%)	-	-	-	6.3 (3.3 to 9.3)	-	-
Total adherence (of 100%)	-	-	-	33.6 (22.1 to 45.2)	-	-

Values represent mean±95% CIs.

*Values represent multiple imputation (taking the mean of 5 sets of randomly imputed values) to generate data for those who dropped out or had missing values.

†Between-treatment difference, change from baseline between the two diets using all available data.

‡p-Values assessed using all available data and a repeated measures mixed model accounting for time of assessment. The response variable was change from baseline, with diet and week as fixed effects and subject ID nested in diet. There was no adjustment for baseline.

§Significantly different between-treatments at baseline assessed by two sample t test (two tailed), p=0.025.

¶Adherence represents the mean percentage intake of the prescribed intake of the three cholesterol-lowering components (viscous fibre, vegetable protein (soy and gluten), nuts) by expressing the recorded intake for each component as 33.3%. The sum of the three components if consumed as prescribed would equal 100% adherence.

Table 3 Effect of high-carbohydrate and low-carbohydrate diets on body weight, blood lipids, apolipoproteins and 10-year CHD risk (n=39)

	High carbohydrate		Low carbohydrate		Between-treatment difference†	p Value‡
	Week 0*	Ad libitum*	Week 0*	Ad libitum*		
Body weight (kg)	85.4 (79.3 to 91.6)	80.4 (74.2 to 86.6)	83.7 (78.5 to 89.0)	76.9 (71.9 to 81.9)	-1.1 (-2.1 to 0.0)	0.047
BMI	31.1 (29.9 to 32.4)	29.2 (27.9 to 30.5)	31.1 (29.8 to 32.4)	28.7 (27.3 to 30.1)	-0.4 (-0.8 to 0.0)	0.039
Body fat (%)	38.9 (34.0 to 43.8)	35.0 (30.7 to 39.2)	35.6 (30.1 to 41.1)	31.4 (26.1 to 36.6)	-1.7 (-4.0 to 0.7)	0.161
Waist circumference (cm)	102.8 (99.4 to 106.2)	97.4 (93.1 to 101.6)	99.8 (96.1 to 103.5)	93.7 (89.8 to 97.7)	0.1 (-1.1 to 1.3)	0.861
Fasting glucose	5.2 (4.9 to 5.4)	4.6 (4.5 to 4.7)	5.2 (5.0 to 5.4)	4.6 (4.4 to 4.9)	0.1 (-0.1 to 0.2)	0.447
HbA1c (%)	5.2 (5.0 to 5.4)	5.2 (5.0 to 5.3)	5.3 (5.0 to 5.5)	5.2 (5.0 to 5.4)	0.0 (-0.2 to 0.1)	0.852
Fasting insulin	50.0 (38.3 to 61.7)	36.4 (27.5 to 45.4)	47.3 (36.9 to 57.6)	33.3 (22.8 to 43.9)	-0.6 (-9.1 to 8.0)	0.898
HOMA-IR	1.65 (1.17 to 2.13)	1.11 (0.81 to 1.41)	1.53 (1.19 to 1.88)	0.99 (0.68 to 1.30)	0.01 (-0.30 to 0.33)	0.937
Satiety (-4 to 4)	1.0 (0.7 to 1.4)	0.9 (0.7 to 1.2)	1.2 (0.8 to 1.7)	1.1 (0.8 to 1.4)	-0.1 (-0.4 to 0.2)	0.440
Exercise, METs	17.4 (12.4 to 22.4)	25.8 (21.1 to 30.6)	24.0 (12.9 to 35.0)	23.9 (15.3 to 32.6)	-9.3 (-16.4 to -2-2)	0.012
Cholesterol (mmol/L§)						
Total	6.75 (6.28 to 7.21)	6.49 (5.97 to 7.02)	6.76 (6.21 to 7.31)	6.10 (5.67 to 6.53)	-0.62 (-0.86 to -0.37)	<0.001
LDL-C	4.40 (3.99 to 4.82)	4.40 (3.91 to 4.90)	4.53 (4.14 to 4.93)	4.06 (3.71 to 4.42)	-0.49 (-0.70 to -0.28)	<0.001
HDL-C	1.36 (1.22 to 1.50)	1.35 (1.22 to 1.48)	1.21 (1.06 to 1.36)	1.25 (1.10 to 1.39)	0.03 (-0.02 to 0.07)	0.245
Triglycerides	2.16 (1.62 to 2.70)	1.71 (1.35 to 2.07)	2.23 (1.65 to 2.80)	1.50 (1.22 to 1.77)	-0.34 (-0.57 to -0.11)	0.005
Ratios						
TC:HDL-C	5.17 (4.54 to 5.80)	4.92 (4.49 to 5.34)	5.81 (5.20 to 6.41)	5.13 (4.65 to 5.62)	-0.57 (-0.83 to -0.32)	<0.001
LDL-C:HDL-C	3.35 (2.95 to 3.75)	3.34 (3.00 to 3.68)	3.89 (3.49 to 4.29)	3.48 (3.06 to 3.90)	-0.42 (-0.60 to -0.24)	<0.002
Apolipoproteins (g/L¶)						
ApoA1	1.69 (1.60 to 1.78)	1.69 (1.60 to 1.77)	1.57 (1.45 to 1.69)	1.57 (1.46 to 1.67)	-0.02 (-0.06 to 0.02)	0.316
ApoB	1.38 (1.26 to 1.50)	1.23 (1.13 to 1.33)	1.42 (1.30 to 1.54)	1.20 (1.10 to 1.31)	-0.11 (-0.16 to -0.06)	<0.001
ApoB: ApoA1	0.83 (0.74 to 0.91)	0.74 (0.68 to 0.80)	0.92 (0.84 to 0.99)	0.78 (0.70 to 0.86)	-0.05 (-0.09 to -0.02)	0.003
Hs-CRP (mg/dL)	2.1 (1.0 to 3.3)	1.9 (1.3 to 2.4)	3.0 (1.5 to 4.5)	2.6 (1.0 to 4.1)	-0.4 (-0.9 to 0.1)	0.082
Blood pressure (mm Hg)						
Systolic	122 (116 to 128)	118 (114 to 122)	128 (123 to 132)	123 (119 to 128)	-2 (-5 to 2)	0.356
Diastolic	75 (72 to 79)	74 (71 to 77)	77 (74 to 80)	76 (71 to 80)	-1 (-3 to 1)	0.288
10-year CHD risk (%)**	8 (6 to 9)	7 (6 to 9)	12 (9 to 14)	9 (7 to 11)	-2 (-2 to -1)	<0.001

Values represent mean±95% CIs.

*Values represent multiple imputation (taking the mean of 5 sets of randomly imputed values) to generate data for those who dropped out or had missing values.

†Between-treatment difference, change from baseline between the two diets using all available data.

‡p-values assessed using all available data and a repeated measures mixed model accounting for time of assessment. The response variable was change from baseline, with diet and week as fixed effects and subject ID nested in diet. There was no adjustment for baseline.

§To convert total cholesterol, LDL-C, and HDL-C to mg/dL, divide by 0.0259; to convert triglycerides to mg/dL, divide by 0.0113.

¶To convert apolipoprotein A1 and B to mg/dL, multiply by 100.

**Significantly different between-treatments at baseline assessed by two sample t test (two tailed), p=0.007.

BMI, body mass index; CHD, coronary heart disease; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homoeostasis model assessment—insulin resistance model; Hs-CRP, high-sensitivity C reactive protein; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalents; TC, total cholesterol.

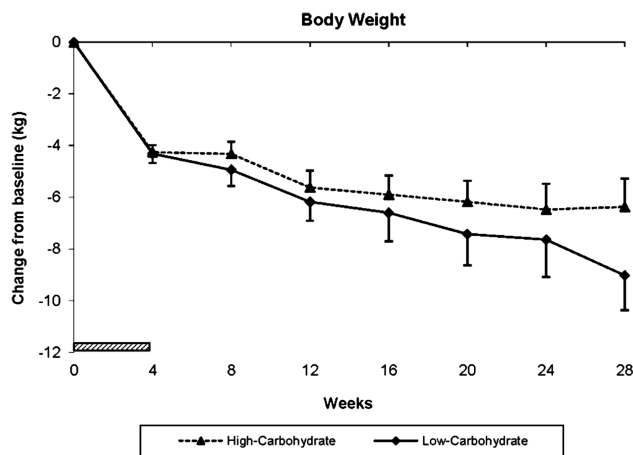


Figure 2 Weight loss during the study on both diets. Weight loss during the study on both diets. Values represent mean \pm SEM of the change from baseline during the metabolic and ad libitum phases, using multiple imputation (taking the mean of 5 sets of randomly imputed values) to generate data for those who dropped out or had missing values on the ad libitum phase. The change in weight during the ad libitum phase was significantly reduced ($P=0.047$) on the low versus the high carbohydrate diet using all available data in the repeated measures mixed model analysis. Cross hatched bar represents the metabolic phase.

carbohydrate diet (2% (-2% to -1%); $p<0.001$; table 3). A reduced CHD risk on the low-carbohydrate diet was also observed in the completers (2% (-3% to -1%); $p<0.001$).

Adverse events

No serious adverse events or events that involved hospitalisation occurred during the study.

DISCUSSION

The present study demonstrated that consumption of a low-carbohydrate vegan diet resulted in a modestly greater body weight reduction compared with a high-carbohydrate diet (7% vs 6% reductions, respectively) over a 6-month ad libitum period. These reductions were similar to those reported for low-carbohydrate 'Atkins-like' diets.^{1 2 5 9} However, by comparison with the high-carbohydrate diet, consumption of the low-carbohydrate diet containing vegetable proteins and oils was also associated with significantly reduced concentrations of LDL-C. This LDL-C reduction has not been reported for other low-carbohydrate diet studies in which a large part of the protein and fat originated from animal sources and in which no significant LDL-C reductions were seen.^{1-5 7} The sustained reduction in LDL-C, associated with a small incremental weight loss on the 6-month self-selected diet, is a potentially important attribute of the diet in reducing long-term CHD risk.^{45 46} Furthermore, as seen in the present study, a low-carbohydrate diet, in which vegetable fat and

protein options were encouraged, demonstrated a larger reduction in the TC:HDL-C ratio than that reported at 6 months in weight loss studies employing either a Mediterranean or a high-carbohydrate diet.⁹

The majority of studies undertaken to date have been 6 months to 1 year in duration^{1-5 47} with recent studies of up to 2 years.^{1 7} The high dropout rate in the present 6-month study did not prevent identification of significant LDL-C and body weight differences in the intent-to-treat analysis (using all available data). However, the completer data demonstrated an even larger treatment difference in LDL-C favouring the low-carbohydrate treatment. Those on the low-carbohydrate diet showed overall adherence to the major dietary components (vegetable proteins (soy and gluten), nuts and viscous fibres) at 33.6% of that provided during the metabolic phase.³⁷ This adherence is similar to the 43.3% seen with the dietary portfolio in the comparison of the metabolic 1 month³⁴ and the ad libitum 6-month studies.⁴⁸ In this study, the LDL-C reduction on the low-carbohydrate metabolic month was also greater than that on the ad libitum 6 months, although the treatment differences were similar.³⁴

The effect of low-carbohydrate diets on CHD events has not been assessed in randomised controlled trials. Nevertheless, low-carbohydrate diets high in vegetable proteins and oils have been associated with a 30% reduced CHD risk and an 18% reduced incidence of diabetes in cohort studies.^{29 30} The median interquartile difference in these studies between the 1st and 10th decile for vegetable protein and MUFA intakes, as a marker of increased vegetable oil consumption, was 1.4% and 9.3% expressed as a percentage of total calorie intake.²⁹ These figures compare with an 8.2% and a 4.6% relative increase in vegetable protein and oil consumption from baseline on the Eco-Atkins diet compared with the control diet. The increases in MUFA were therefore seen in both studies. Recently a Spanish Mediterranean diet emphasising increased nut or olive oil consumption, and so increasing MUFA intake by 2-3%, has been shown to significantly reduce cardiovascular events also by approximately 30%.³² These data provide consistent support for the view that the Eco-Atkins approach would reduce CHD risk in the long term.

The present diet, while lowering LDL-C by 9%, did not result in any significant depression of HDL-C. Lowering LDL-C while maintaining HDL-C would be expected to reduce CHD risk.^{45 46} Similarly, reductions in ApoB and the ApoB:ApoA1 ratio were also observed in the present study. These findings further support the potential CHD benefit that this weight loss diet may have.⁴⁹⁻⁵¹ It has also been claimed that apolipoproteins may be stronger predictors of CHD events than conventional lipid variables.⁵²⁻⁵⁴

In contrast to the metabolic study, the reductions in systolic and diastolic blood pressure were not significant between the low-carbohydrate and high-carbohydrate

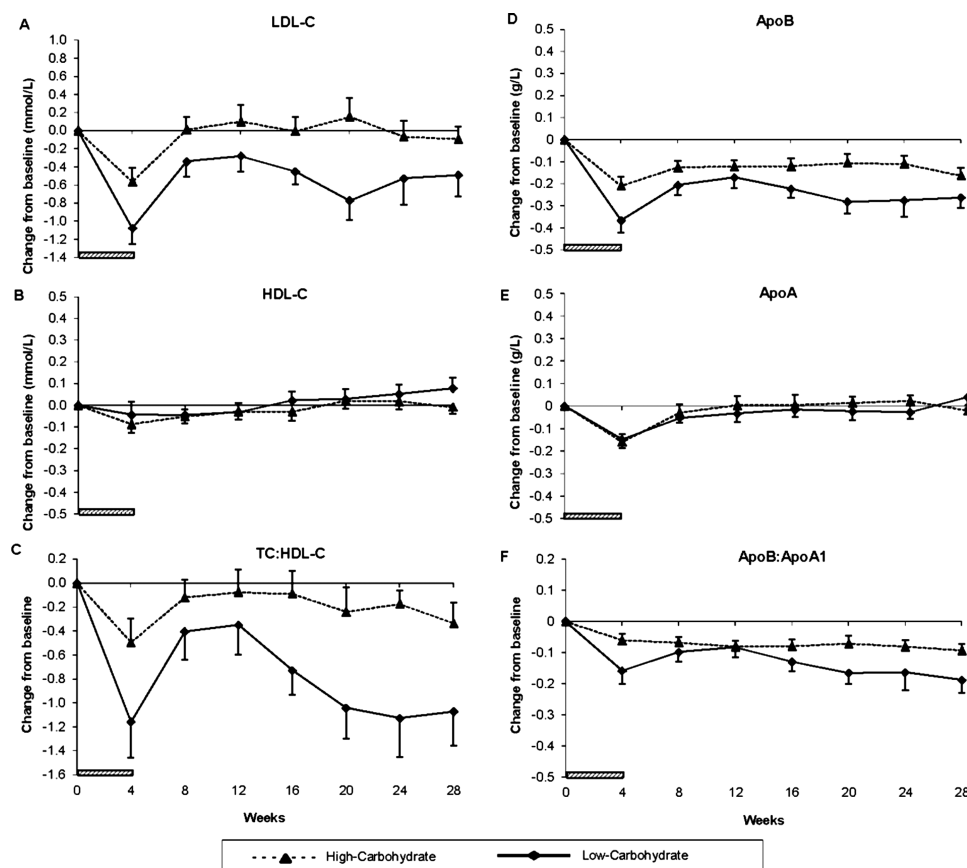


Figure 3 Change in (A) LDL-C, (B) HDL-C, (C) TC:HDL-C, (D) Apolipoprotein B (apoB), (E) Apolipoprotein A1 (apoA1), (F) ApoB:ApoA1 ratio between the two treatments during the metabolic and ad libitum phases. Values represent mean \pm SEM of the change from baseline using multiple imputation (taking the mean of 5 sets of randomly imputed values) to generate data for those who dropped out or had missing values for the ad libitum phase. Significant treatment differences were seen for LDL-C ($p < 0.001$), apo B ($p < 0.001$) and the ratios TC:HDL-C ($p < 0.001$) and apoB:apoA1 ($p = 0.003$), using all available data in the repeated measures mixed model analysis during the ad libitum phase. Cross hatched bar represents the metabolic phase.

diets. Similarly, hs-CRP was unchanged between treatments, however, the level was significantly reduced with the low-carbohydrate diet compared with baseline. Studies have shown that hs-CRP tended to be lowest in the diets containing the highest proportion of carbohydrate.⁴ Low-glycaemic index and low-glycaemic load diets have also been associated with lower hs-CRP concentrations.^{55 56} These advantages of the higher carbohydrate diet may have reduced any hs-CRP difference between the two diets in the present study.

Soy-containing foods as well as nuts have cholesterol-lowering effects^{14 16 17 57 58} and may explain the reduction in LDL-C. Viscous fibre in low starch vegetables and β -glucan in oats and barley may also have contributed to the overall cholesterol-lowering effect of the diet.^{8 13 45} Furthermore, nuts and high fibre food consumption have been associated with lower body weight.⁵⁹

The study weaknesses include the relatively small sample size and the high dropout rate. Nevertheless, it is noteworthy that attrition rates were low in the metabolic study when all food was provided.³⁷ Food availability and preparation may therefore be important factors. Future studies will need to focus on strategies to increase and

maintain adherence, especially to the cholesterol-lowering components, which all bear US Food and Drug Administration (FDA) health claims for cardiovascular disease risk reduction. Furthermore, collaboration with food industry may be helpful in addressing concerns of availability, variety and ease of preparation. In retrospect, a simplified one page eating plan for breakfast, lunch and dinner with a number of options and amounts for each meal, as we have used in our dietary portfolio studies, might also be helpful.⁴⁸ For those who did complete the study, however, there were benefits in weight loss and LDL-C reduction, an additional 2% advantage in body weight reduction compared with the high-carbohydrate diet and a 13% drop in LDL-C for participants consuming a more plant-based low-carbohydrate diet. Unfortunately it was not possible to predict who would complete the diet based on prestudy data or changes observed during the metabolic phase.

The study's strength is that the prescribed hypocaloric diet was self-selected, meaning the results are more in line with what can be expected under free-living conditions. The breadth of application of the plant-based low-carbohydrate diet, however, remains to be determined, but it may provide

an option for some individuals for whom LDL-C reduction is an equal concern to weight loss. If low-carbohydrate dietary options become more generally available the number of individuals who will benefit is likely to increase.

We conclude that a weight loss diet which reduced carbohydrate in exchange for increased intakes of vegetable sources of protein, such as gluten, soy and nuts, together with vegetable oils offers an opportunity to improve both LDL-C and body weight, both being risk factors for CHD. Further trials are warranted to evaluate low-carbohydrate diets, including more plant-based low-carbohydrate diets, on CHD risk factors and ultimately on CHD.

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Competing interests DJAJ has served on the Scientific Advisory Board of Sanitarium Company, Agri-Culture and Agri-Food Canada (AAFC), Canadian Agriculture Policy Institute (CAPI), California Strawberry Commission, Loblaw Supermarket, Herbal Life International, Nutritional Fundamental for Health, Pacific Health Laboratories, Metagenics, Bayer Consumer Care, Orafit, Dean Foods, Kellogg's, Quaker Oats, Procter & Gamble, Coca-Cola, NuVal Griffin Hospital, Abbott, Pulse Canada, Saskatchewan Pulse Growers, and Canola Council of Canada; received honoraria for scientific advice from Sanitarium Company, Orafit, the Almond Board of California, the American Peanut Council, International Tree Nut Council Nutrition Research and Education Foundation and the Peanut Institute, Herbal Life International, Pacific Health Laboratories, Nutritional Fundamental for Health, Barilla, Metagenics, Bayer Consumer Care, Unilever Canada and Netherlands, Solae LLC, Oldways, Kellogg's, Quaker Oats, Procter & Gamble, Coca-Cola, NuVal Griffin Hospital, Abbott, Canola Council of Canada, Dean Foods,

California Strawberry Commission, Haine Celestial, Pepsi, and Alpro Foundation; has been on the speakers panel for the Almond Board of California; received research grants from Saskatchewan Pulse Growers, the Agricultural Bioproducts Innovation Program (ABIP) through the Pulse Research Network (PURENet), Advanced Food Materials Network (AFMNet), Loblaw, Unilever, Barilla, Almond Board of California, Coca-Cola, Solae LLC, Haine Celestial, Sanitarium Company, Orafit, International Tree Nut Council Nutrition Research and Education Foundation and the Peanut Institute, the Canola and Flax Councils of Canada, Calorie Control Council, Canadian Institutes of Health Research (CIHR), Canada Foundation for Innovation, and the Ontario Research Fund; and received travel support to meetings from the Solae LLC, Sanitarium Company, Orafit, AFMNet, Coca-Cola, The Canola and Flax Councils of Canada, Oldways Preservation Trust, Kellogg's, Quaker Oats, Griffin Hospital, Abbott Laboratories, Dean Foods, the California Strawberry Commission, American Peanut Council, Herbal Life International, Nutritional Fundamental for Health, Metagenics, Bayer Consumer Care, AAFC, CAPI, Pepsi, Almond Board of California, Unilever, Alpro Foundation, International Tree Nut Council, Barilla, Pulse Canada, and the Saskatchewan Pulse Growers. CWCK reported being on speakers bureaus for Almond Board of California, Solae LLC, and Unilever; and receiving research grants from CIHR, Unilever, Solae LLC, Loblaw Brands Ltd, International Tree Nut Council, and Almond Board of California. EV has received partial salary funding from research grants provided by Unilever, Loblaw's, and the Almond Board of California. GP, RM and ESK are employees of Solae, LLC. JMW was a recipient of a Canadian Institutes of Health Research (CIHR) Doctoral Research Award and is now a holder of a CIHR randomised controlled trials—mentoring program Training Grant.

Ethics approval The Ethics Committees of St. Michael's Hospital and the University of Toronto, and the Therapeutic Products Directorate of Health Canada approved the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement We can make available the raw data used for this report. Additional data may be made available on request if we have it.

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REFERENCES

1. Samaha FF, Iqbal N, Seshadri P, *et al.* A low-carbohydrate as compared with a low-fat diet in severe obesity. *N Engl J Med* 2003;348:2074–81.
2. Foster GD, Wyatt HR, Hill JO, *et al.* A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* 2003;348:2082–90.
3. Stern L, Iqbal N, Seshadri P, *et al.* The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med* 2004;140:778–85.
4. Dansinger ML, Gleason JA, Griffith JL, *et al.* Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA* 2005;293:43–53.
5. Gardner CD, Kiazand A, Alhassan S, *et al.* Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A to Z Weight Loss Study: a randomized trial. *JAMA* 2007;297:969–77.
6. Sacks FM, Bray GA, Carey VJ, *et al.* Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med* 2009;360:859–73.
7. Foster GD, Wyatt HR, Hill JO, *et al.* Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. *Ann Intern Med* 2010;153:147–57.
8. Anderson JW, Randles KM, Kendall CW, *et al.* Carbohydrate and fiber recommendations for individuals with diabetes: a quantitative assessment and meta-analysis of the evidence. *J Am Coll Nutr* 2004;23:5–17.
9. Shai I, Schwarzfuchs D, Henkin Y, *et al.* Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med* 2008;359:229–41.

10. Sacks FM, Ornish D, Rosner B, *et al.* Plasma lipoprotein levels in vegetarians. The effect of ingestion of fats from dairy products. *JAMA* 1985;254:1337–41.
11. Ornish D, Brown SE, Scherwitz LW, *et al.* Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. *Lancet* 1990;336:129–33.
12. Barnard ND, Cohen J, Jenkins DJ, *et al.* A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. *Diabetes Care* 2006;29:1777–83.
13. Jenkins DJ, Newton C, Leeds AR, *et al.* Effect of pectin, guar gum, and wheat fibre on serum-cholesterol. *Lancet* 1975;1:1116–17.
14. Sirtori CR, Agradi E, Conti F, *et al.* Soybean-protein diet in the treatment of type-II hyperlipoproteinaemia. *Lancet* 1977;1:275–7.
15. Grundy SM. Comparison of monounsaturated fatty acids and carbohydrates for lowering plasma cholesterol. *N Engl J Med* 1986;314:745–8.
16. Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med* 1995;333:276–82.
17. Kris-Etherton PM, Yu-Poth S, Sabate J, *et al.* Nuts and their bioactive constituents: effects on serum lipids and other factors that affect disease risk. *Am J Clin Nutr* 1999;70(3 Suppl):504S–11S.
18. Sabate J, Oda K, Ros E. Nut consumption and blood lipid levels: a pooled analysis of 25 intervention trials. *Arch Intern Med* 2010;170:821–7.
19. Ros E, Nunez I, Perez-Heras A, *et al.* A walnut diet improves endothelial function in hypercholesterolemic subjects: a randomized crossover trial. *Circulation* 2004;109:1609–14.
20. Zhao G, Etherton TD, Martin KR, *et al.* Dietary alpha-linolenic acid reduces inflammatory and lipid cardiovascular risk factors in hypercholesterolemic men and women. *J Nutr* 2004;134:2991–7.
21. West SG, Krick AL, Klein LC, *et al.* Effects of diets high in walnuts and flax oil on hemodynamic responses to stress and vascular endothelial function. *J Am Coll Nutr* 2010;29:595–603.
22. Ma Y, Njike VY, Millet J, *et al.* Effects of walnut consumption on endothelial function in type 2 diabetic subjects: a randomized controlled crossover trial. *Diabetes Care* 2010;33:227–32.
23. Appleby PN, Thorogood M, Mann JI, *et al.* The Oxford Vegetarian Study: an overview. *Am J Clin Nutr* 1999;70(3 Suppl):525S–31S.
24. Fraser GE. *Diet, life expectancy, and chronic disease: studies of Seventh-Day Adventists and other vegetarians.* New York: Oxford University Press, 2003.
25. Pereira MA, O'Reilly E, Augustsson K, *et al.* Dietary fiber and risk of coronary heart disease: a pooled analysis of cohort studies. *Arch Intern Med* 2004;164:370–6.
26. Li TY, Brennan AM, Wedick NM, *et al.* Regular consumption of nuts is associated with a lower risk of cardiovascular disease in women with type 2 diabetes. *J Nutr* 2009;139:1333–8.
27. Kris-Etherton PM, Hu FB, Ros E, *et al.* The role of tree nuts and peanuts in the prevention of coronary heart disease: multiple potential mechanisms. *J Nutr* 2008;138:1746S–51S.
28. Pan A, Sun Q, Manson JE, *et al.* Walnut consumption is associated with lower risk of type 2 diabetes in women. *J Nutr* 2013;143:512–18.
29. Halton TL, Willett WC, Liu S, *et al.* Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med* 2006;355:1991–2002.
30. Halton TL, Liu S, Manson JE, *et al.* Low-carbohydrate-diet score and risk of type 2 diabetes in women. *Am J Clin Nutr* 2008;87:339–46.
31. Pan A, Sun Q, Bernstein AM, *et al.* Red meat consumption and mortality: results from 2 prospective cohort studies. *Arch Intern Med* 2012;172:555–63.
32. Estruch R, Ros E, Salas-Salvado J, *et al.* Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;368:1279–90.
33. Sacks FM, Kass EH. Low blood pressure in vegetarians: effects of specific foods and nutrients. *Am J Clin Nutr* 1988;48(3 Suppl):795–800.
34. Jenkins DJ, Kendall CW, Marchie A, *et al.* Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. *JAMA* 2003;290:502–10.
35. Appel LJ, Sacks FM, Carey VJ, *et al.* Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. *JAMA* 2005;294:2455–64.
36. Gardner CD, Coulston A, Chatterjee L, *et al.* The effect of a plant-based diet on plasma lipids in hypercholesterolemic adults: a randomized trial. *Ann Intern Med* 2005;142:725–33.
37. Jenkins DJ, Wong JM, Kendall CW, *et al.* The effect of a plant-based low-carbohydrate ('Eco-Atkins') diet on body weight and blood lipid concentrations in hyperlipidemic subjects. *Arch Intern Med* 2009;169:1046–54.
38. Harris JA, Benedict FG. *A biometric study of basal metabolism in man.* Washington, DC: Carnegie Institute of Washington, 1919 (Publication no. 279.).
39. Shetty PS, Henry CJ, Black AE, *et al.* Energy requirements of adults: an update on basal metabolic rates (BMRs) and physical activity levels (PALs). *Eur J Clin Nutr* 1996;50 (Suppl 1):S11–23.
40. Pereira MA, Swain J, Goldfine AB, *et al.* Effects of a low-glycemic load diet on resting energy expenditure and heart disease risk factors during weight loss. *JAMA* 2004;292:2482–90.
41. Ainsworth BE, Haskell WL, Leon AS, *et al.* Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc* 1993;25:71–80.
42. Anderson KM, Wilson PW, Odell PM, *et al.* An updated coronary risk profile. A statement for health professionals. *Circulation* 1991;83:356–62.
43. USDA Nutrient Database for Standard Reference, Release 19. *Nutrient data laboratory home page.* U.S. Department of Agriculture, Agricultural Research Service, 2006.
44. SAS Institute. *SAS/STAT user's guide (ed 9.2) [program].* Cary, NC: SAS Institute, 2008.
45. Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–97.
46. Grundy SM, Cleeman JI, Merz CN, *et al.* Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227–39.
47. Westman EC, Yancy WS, Edman JS, *et al.* Effect of 6-month adherence to a very low carbohydrate diet program. *Am J Med* 2002;113:30–6.
48. Jenkins DJ, Jones PJ, Lamarche B, *et al.* Effect of a dietary portfolio of cholesterol-lowering foods given at 2 levels of intensity of dietary advice on serum lipids in hyperlipidemia: a randomized controlled trial. *JAMA* 2011;306:831–9.
49. Gotto AM Jr, Whitney E, Stein EA, *et al.* Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Circulation* 2000;101:477–84.
50. Sniderman AD, Furberg CD, Keech A, *et al.* Apolipoproteins versus lipids as indices of coronary risk and as targets for statin treatment. *Lancet* 2003;361:777–80.
51. Yusuf S, Hawken S, Ounpuu S, *et al.* Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937–52.
52. McQueen MJ, Hawken S, Wang X, *et al.* Lipids, lipoproteins, and apolipoproteins as risk factors of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. *Lancet* 2008;372:224–33.
53. Contois JH, McConnell JP, Sethi AA, *et al.* Apolipoprotein B and cardiovascular disease risk: position statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices. *Clin Chem* 2009;55:407–19.
54. Sniderman AD, Williams K, Contois JH, *et al.* A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. *Circ Cardiovasc Qual Outcomes* 2011;4:337–45.
55. Liu S, Manson JE, Buring JE, *et al.* Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity C-reactive protein in middle-aged women. *Am J Clin Nutr* 2002;75:492–8.
56. Wolever TM, Gibbs AL, Mehling C, *et al.* The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-y controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: no effect on glycated hemoglobin but reduction in C-reactive protein. *Am J Clin Nutr* 2008;87:114–25.
57. Sabate J, Fraser GE, Burke K, *et al.* Effects of walnuts on serum lipid levels and blood pressure in normal men. *N Engl J Med* 1993;328:603–7.
58. Jenkins DJ, Kendall CW, Marchie A, *et al.* Dose response of almonds on coronary heart disease risk factors: blood lipids, oxidized low-density lipoproteins, lipoprotein(a), homocysteine, and pulmonary nitric oxide: a randomized, controlled, crossover trial. *Circulation* 2002;106:1327–32.
59. Mozaffarian D, Hao T, Rimm EB, *et al.* Changes in diet and lifestyle and long-term weight gain in women and men. *N Engl J Med* 2011;364:2392–404.