

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

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AGENCIES CONCERNED WITH cardiovascular health have uniformly stressed the importance of diet and lifestyle as the primary means of lowering serum lipids and coronary heart disease (CHD) risk.¹⁻³ Nevertheless, the introduction of statins in the late 1980s highlighted the relative ineffectiveness of conventional dietary advice.⁴ As a result, alternative dietary paradigms have been proposed⁵⁻⁷ and efforts have been made to enhance the ability of conven-

Context Combining foods with recognized cholesterol-lowering properties (dietary portfolio) has proven highly effective in lowering serum cholesterol under metabolically controlled conditions.

Objective To assess the effect of a dietary portfolio administered at 2 levels of intensity on percentage change in low-density lipoprotein cholesterol (LDL-C) among participants following self-selected diets.

Design, Setting, and Participants A parallel-design study of 351 participants with hyperlipidemia from 4 participating academic centers across Canada (Quebec City, Toronto, Winnipeg, and Vancouver) randomized between June 25, 2007, and February 19, 2009, to 1 of 3 treatments lasting 6 months.

Intervention Participants received dietary advice for 6 months on either a low-saturated fat therapeutic diet (control) or a dietary portfolio, for which counseling was delivered at different frequencies, that emphasized dietary incorporation of plant sterols, soy protein, viscous fibers, and nuts. Routine dietary portfolio involved 2 clinic visits over 6 months and intensive dietary portfolio involved 7 clinic visits over 6 months.

Main Outcome Measures Percentage change in serum LDL-C.

Results In the modified intention-to-treat analysis of 345 participants, the overall attrition rate was not significantly different between treatments (18% for intensive dietary portfolio, 23% for routine dietary portfolio, and 26% for control; Fisher exact test, $P = .33$). The LDL-C reductions from an overall mean of 171 mg/dL (95% confidence interval [CI], 168-174 mg/dL) were -13.8% (95% CI, -17.2% to -10.3%; $P < .001$) or -26 mg/dL (95% CI, -31 to -21 mg/dL; $P < .001$) for the intensive dietary portfolio; -13.1% (95% CI, -16.7% to -9.5%; $P < .001$) or -24 mg/dL (95% CI, -30 to -19 mg/dL; $P < .001$) for the routine dietary portfolio; and -3.0% (95% CI, -6.1% to 0.1%; $P = .06$) or -8 mg/dL (95% CI, -13 to -3 mg/dL; $P = .002$) for the control diet. Percentage LDL-C reductions for each dietary portfolio were significantly more than the control diet ($P < .001$, respectively). The 2 dietary portfolio interventions did not differ significantly ($P = .66$). Among participants randomized to one of the dietary portfolio interventions, percentage reduction in LDL-C on the dietary portfolio was associated with dietary adherence ($r = -0.34$, $n = 157$, $P < .001$).

Conclusion Use of a dietary portfolio compared with the low-saturated fat dietary advice resulted in greater LDL-C lowering during 6 months of follow-up.

Trial Registration clinicaltrials.gov Identifier: NCT00438425

JAMA. 2011;306(8):831-839

www.jama.com

tional dietary therapy to reduce serum cholesterol through the inclusion of specific foods or food components with known cholesterol-lowering proper-

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ties,^{1,8} singly or in combination (dietary portfolio).⁹ Use of these cholesterol-lowering dietary components in combination in short-term studies with all food provided has been shown to reduce serum low-density lipoprotein cholesterol (LDL-C) to a similar extent as first-generation statins.^{10,11} The longer-term effect of such diets compared with conventional dietary advice has not been assessed.

We therefore undertook a multicenter trial to determine whether advice to eat a dietary portfolio consisting of foods recognized by the US Food and Drug Administration (FDA) as associated with lowering serum cholesterol achieved significantly greater percentage decreases in LDL-C compared with a control diet at 6-month follow-up. The control diet emphasized high fiber and whole grains but lacked portfolio components. To increase the relevance of the study for routine clinical application, the advice was given at 2 levels of intensity, either as a routine dietary portfolio (2 clinic visits of 40- to 60-minute sessions) or an intensive dietary portfolio (7 clinic visits of 40- to 60-minute sessions).

METHODS

Participants

Three hundred fifty-one participants with hyperlipidemia (137 men and 214 postmenopausal women) were randomized after recruitment through advertisement by 4 participating centers across Canada (Quebec City, Toronto, Winnipeg, and Vancouver). Six randomized participants (3 men and 3 women) were either withdrawn for medical reasons before starting the study (n=3) or failed to attend for baseline measurements (n=3), resulting in 345 participants with data available for the final (modified intention-to-treat) analysis (FIGURE 1). Inclusion criteria included men and postmenopausal women in the low (0%-10%) and intermediate (10%-19%) Framingham 10-year risk categories who had LDL-C values ranging from 135 to 205 mg/dL and 116 to 178 mg/dL, respectively (to convert to millimoles per liter, multiply by

0.0259). Exclusion criteria included a history of cardiovascular disease, cancer or a strong family history of cancer, untreated hypertension (blood pressure >140/90 mm Hg), diabetes, renal or liver disease, and currently taking lipid-lowering medications.

Study Protocol

Recruitment was achieved by advertising in newspapers, subway cars, lipid clinics, and family practice offices, and randomization took place between June 25, 2007, and February 19, 2009. Participants were stratified by center, sex, and pretreatment LDL-C levels (≥ 158 vs < 158 mg/dL), and randomized in blocks of 75 participants. The blocks were created by a statistician (E.V.) and the allocations were placed in numbered envelopes to be opened by the dietitian in the presence of the participants. Neither the dietitian nor the participants could be blinded to treatment; however, the statistician, investigators, and laboratory staff who analyzed the samples were unaware of participant allocation. Treatments were coded as 1, 2, and 3. Participants were randomized to a parallel-design study of dietary advice to take either a therapeutic low-fat diet (control) or dietary portfolio of cholesterol-lowering foods with either 2 visits (routine) or 7 visits (intensive) during a 6-month period.

Study visits occurred at baseline (week 0) and at 3 and 6 months for the control and routine dietary portfolio interventions, and baseline, 2 weeks, and subsequently at monthly follow-up for the intensive dietary portfolio intervention (eFigure, available at <http://www.jama.com>). At each study visit, the preceding 7-day diet histories were assessed by the dietitian and discussed with the participant. Body weight was measured and a fasting blood sample was obtained (eFigure). At each visit, blood pressure was measured 3 times in the nondominant arm using a digital blood pressure monitor (Omron HEM-907XL, Omron Healthcare Inc, Vernon Hills, Illinois). Participants completed a race/ethnicity questionnaire at week 0 with pre-

defined options to determine the applicability of the results to the general population.

The study was approved by the ethics committees of St Michael's Hospital and the universities of Toronto, Manitoba, British Columbia, and Laval, and the National Health Products Directorate, Health Canada. Informed consent was obtained in writing from the participants.

Diets

TABLE 1 shows diets for participants in each study group before enrollment. During the 6-month study period, dietitians counseled participants to follow weight-maintaining vegetarian diets from foods available in supermarkets and health food stores. Counseling periods were 1-hour duration for the first visit and 30 to 40 minutes at subsequent visits. For participants in the dietary portfolio interventions, dietitians focused on incorporating study foods (eTable 1) into the participants' regular diets using their 7-day food diaries as templates. Participants were provided with a 7-day study food checklist and an illustrated study booklet. The goal of the dietary portfolio was to provide 0.94 g of plant sterols per 1000 kcal of diet in a plant sterol ester-enriched margarine; 9.8 g of viscous fibers per 1000 kcal of diet from oats, barley, and psyllium; 22.5 g of soy protein per 1000 kcal as soy milk, tofu, and soy meat analogues; and 22.5 g of nuts (including tree nuts and peanuts) per 1000 kcal of diet. Consumption of peas, beans, and lentils was also encouraged. This dietary portfolio has been described in detail previously.¹⁰

The control dietary advice focused on low-fat dairy and whole grain cereals together with fruit and vegetables and avoidance of the specific portfolio components. Participants were provided with measuring cups and measuring spoons to assist in portion control.

Analyses

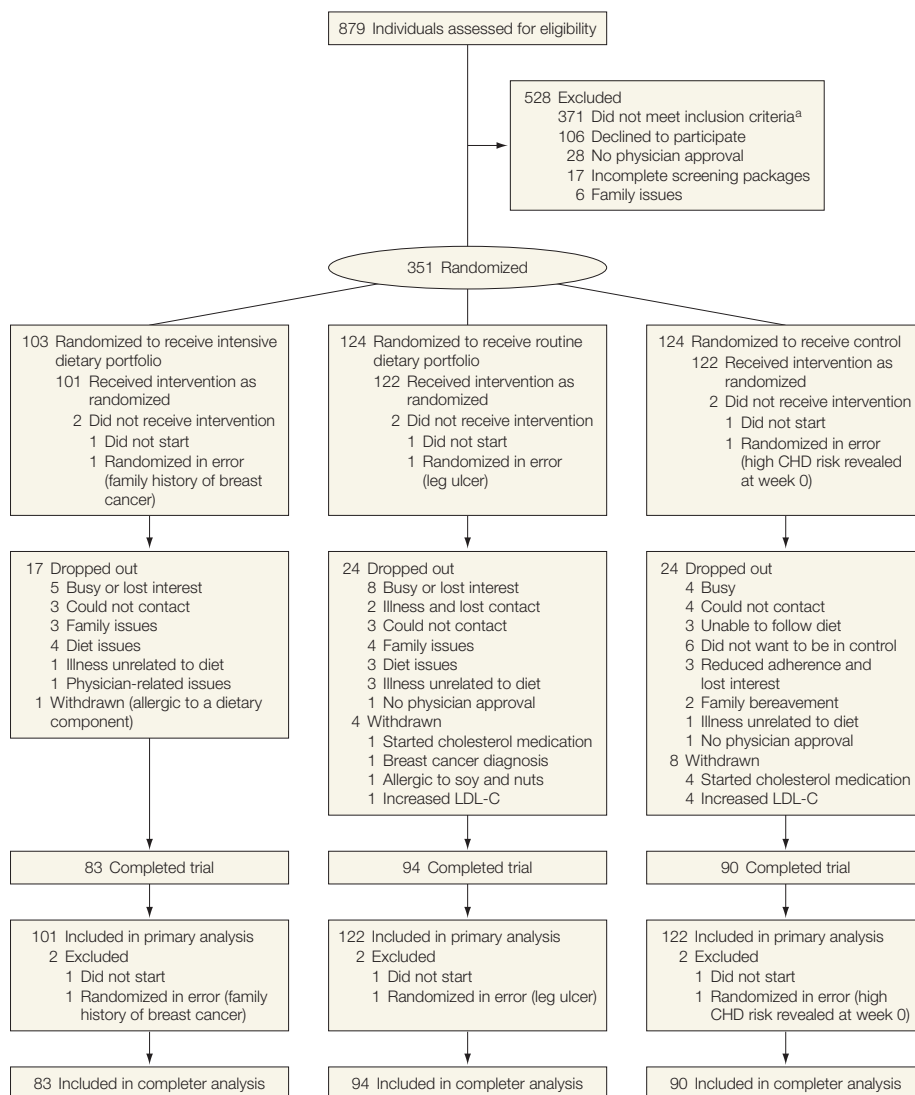
All samples from a given individual were labeled by code and analyzed in the routine laboratory of the hospital

for the Toronto and Vancouver centers (Beckman SYNCHRON LX Systems, Mississauga, Ontario, Canada, and Advia 1650, Siemens, Deerfield, Illinois, respectively) and the research laboratories of the Quebec and Winnipeg centers (Roche Hitachi 917 Chemistry Analyzer, Roche Diagnostics GmbH, Mannheim, Germany, and Vitros 350, Orthogonal Diagnostics, Johnson & Johnson, Markham, Ontario, Canada). Serum lipid standards (Solo-

mon Park Research Laboratories, Kirkland, Washington) were used to quality control the lipid analyses at the 4 collaborating sites. The mean interbatch coefficients of variation at each site were all less than 3.9% for total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels. LDL-C level was calculated using the Friedewald equation¹² unless triglyceride levels were higher than 398 mg/dL, in which case

the prebaseline LDL-C value was used for baseline but no LDL-C value was ascribed for the 2 participants with increased triglyceride levels at week 24. Serum samples, stored at -70°C, were analyzed in the J. Alick Little Lipid Laboratory at St Michael's Hospital, Toronto, Ontario, Canada, for apolipoprotein A-I and B by nephelometry (intra-assay coefficients of variation, 2.2% and 1.9%, respectively)¹³ and C-reactive protein (CRP) by end point

Figure 1. Flow of Study Participants Through the Trial



CHD indicates coronary heart disease; LDL-C, low-density lipoprotein cholesterol.

^aThe number of individuals that did not meet inclusion criteria included 218 with lipids not in study range, 109 with concurrent disorders, 15 with food allergies, 7 with acute and chronic infections, 5 with excess alcohol intake, 5 with high BMI, 4 who were premenopausal, 3 who did not stop taking statins, 2 with weight not stable, 1 with high family risk for cancer, 1 with concern about adherence to study diet, and 1 with a hostile attitude.

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nephelometry (coefficient of variation, 3.5%) (N high sensitivity CRP reagent; Dade-Behring, Mississauga, Ontario, Canada). Plant sterols in serum were measured in the sterol laboratory of the Richardson Center by gas chromatography with flame ionization detectors (6890 GC, Agilent Technologies, Palo Alto, California).¹⁴

Diets were analyzed using a program based on US Department of Agriculture data (ESHA Food Processor SQL version 10.1.1; ESHA, Salem, Oregon) with addition of data on foods relevant to ongoing studies.

Adherence with the 4 portfolio components was estimated from the 7-day food records by expressing the recorded intake for each of the 4 main components as 25%. The sum of the 4 components if consumed as prescribed would equal 100% adherence.

Statistical Analysis

A modified intention-to-treat analysis was undertaken on the 345 participants to whom randomization had been

revealed. Missing data were multiple imputed using PROC MIXED and MIANALYZE in SAS version 9.2 (SAS Institute Inc, Cary, North Carolina). Multiple imputation assumes the values imputed are randomly sampled from the distribution of true (unobserved) missing values. This process results in valid statistical inferences that properly reflect the uncertainty due to missing values, producing valid standard errors (and 95% confidence interval [CI]) for parameters. For example, using LDL-C at 24 weeks, the strongest predictors of missingness at 24 weeks were age ($\beta=0.0454$, $P=.01$) and sex (women vs men) ($\beta=-0.2807$, $P=.11$), and these, along with the observed values, were used to inform the imputations. Site and diet assignment did not predict missingness ($P\geq .16$). PROC MIXED was used to determine the significance of the change in outcome from week 0 to week 24 as the response variable with treatment, sex, and treatment \times sex as main effects and baseline as a covariate. A Tukey adjust-

ment was used for multiple comparisons.¹⁵ Percentage change in LDL-C adjusted for sex was the primary outcome. In addition, the 10-year Framingham CHD risk score was calculated¹⁶ for this predominantly white cohort. Pearson correlation was used to calculate the correlation coefficient between dietary adherence and percentage change in LDL-C. χ^2 Test was used to determine the differences in participants' categorical baseline characteristics.

One hundred ten participants were required per treatment group. Assuming a maximum effect size of 10% (17 mg/dL) for percentage LDL-C change, a 10% SD of effect with $\alpha=.05$ and $1-\beta=.80$, and a 20% attrition rate, we had sufficient power to detect a 5% change (9 mg/dL) in LDL-C between treatments.

RESULTS

The study was conducted between 2007 and 2009, and randomization took place between June 25, 2007, and February 19, 2009. The baseline characteristics of the participants were simi-

Table 1. Mean Daily Macronutrient Profiles of Portfolio and Control Diets at Weeks 0 and 24^a

Nutrients	Treatments					
	Intensive Dietary Portfolio (n = 101)		Routine Dietary Portfolio (n = 122)		Control (n = 122)	
	Week 0	Week 24	Week 0	Week 24	Week 0	Week 24
Energy, kcal/d	2042	1977	1883	1804	1901	1802
Total protein	88 (17)	88 (18)	79 (17)	79 (18)	84 (18)	80 (18)
Vegetable protein	34 (7)	54 (11)	29 (6)	46 (10)	31 (7)	32 (7)
Available carbohydrate	240 (47)	225 (45)	221 (47)	208 (46)	219 (46)	225 (50)
Total dietary fiber (g/1000 kcal)	29 (15)	42 (22)	26 (14)	36 (20)	27 (14)	31 (17)
Total fat	66 (29)	70 (32)	63 (30)	63 (31)	64 (30)	52 (26)
Saturated fatty acid	20 (9)	14 (7)	19 (9)	14 (7)	18 (9)	14 (7)
Monounsaturated fatty acid	23 (10)	27 (12)	22 (10)	24 (12)	23 (11)	19 (9)
Polyunsaturated fatty acid	13 (6)	18 (9)	12 (6)	16 (8)	12 (6)	11 (6)
Cholesterol (mg/1000 kcal) ^b	224 (112)	123 (66)	220 (119)	120 (68)	217 (117)	154 (86)
Alcohol	9 (3)	6 (2)	7 (3)	6 (2)	7 (3)	6 (2)
Portfolio components						
Viscous fiber (g/1000 kcal)	1.0 (0.5)	8.2 (4.2)	0.7 (0.4)	6.1 (3.5)	0.6 (0.3)	1.0 (0.6)
Soy protein	2.4 (1.2)	15.2 (7.6)	1.1 (0.6)	11.6 (6.6)	1.0 (0.5)	1.6 (0.9)
Plant sterols (g/1000 kcal)	0	0.8 (0)	0	0.6 (0.4)	0	0
Nuts (g/1000 kcal)	12 (6)	31 (16)	11 (6)	26 (15)	17 (9)	8 (4)
Adherence with dietary portfolio components, % ^c	9	46	8	41	11	8

^aData are expressed as mean grams per day (percentage of energy intake) unless otherwise noted.

^bExpressed in milligrams.

^cAdherence represents the actual intake of the 4 dietary portfolio components at baseline (week 0) and week 24 expressed as a percentage of those components prescribed in the 2 portfolio groups.

lar for all 3 treatments, with the exception of the ratio of men to women, which was higher on the intensive portfolio than on the other 2 treatments (TABLE 2). No participants were taking medications known to influence serum lipids, except 31 women and 4 men who were all receiving stable doses of thyroxine and 12 women who were receiving estrogen therapy. Fifty-one participants (14%) had been taking statins before the study commenced and had discontinued taking the medications at least 2 weeks before the study (Table 2).

The mean overall adherence for all participants to the intensive dietary portfolio was 46.4% (95% CI, 40.4%-52.4%) and to the routine dietary portfolio was 40.6% (95% CI, 34.6%-46.6%). Participants lost a similar amount of weight while taking part in all 3 treatments (intensive dietary portfolio, -1.2 kg; 95% CI, -1.9 to -0.6 kg; $P < .001$; routine dietary portfolio, -1.7 kg; 95% CI, -2.4 to -1.0 kg; $P < .001$; and control, -1.5 kg; 95% CI, -2.1 to -0.8 kg; $P < .001$) (TABLE 3).

Blood Lipids, Apolipoproteins, and CRP

No differences were observed between the 3 treatment groups in baseline blood measurements. In the modified intention-to-treat analysis, the percentage changes from baseline to week 24 in the control diet were -3.0% (95% CI, -6.1% to 0.1%; $P = .06$) or -8 mg/dL (95% CI, -13 to -3 mg/dL; $P = .002$) for LDL-C and -1.4% (95% CI, -4.3% to 1.6%; $P = .37$) or -0.09 (95% CI, -0.24 to 0.05; $P = .18$) for TC:HDL-C ratio. In the routine and intensive dietary portfolio interventions, the respective percentage changes were -13.1% (95% CI, -16.7% to -9.5%; $P < .001$) or -24 mg/dL (95% CI, -30 to -19 mg/dL; $P < .001$) and -13.8% (95% CI, -17.2% to -10.3%; $P < .001$) or -26 mg/dL (95% CI, -31 to -21 mg/dL; $P < .001$) for LDL-C; and -8.2% (95% CI, -11.2% to -5.3%; $P < .001$) or -0.37 (95% CI, -0.52 to -0.23; $P < .001$) and -6.6% (95% CI, -9.8% to -3.4%; $P < .001$) or -0.39 (95% CI,

-0.56 to -0.24; $P < .001$) for TC:HDL-C ratio, respectively (FIGURE 2). The percentage change and absolute treatment differences between the control and both the dietary portfolio interventions were significant for LDL-C ($P < .001$) and in absolute units for the TC:HDL-C ratio ($P = .004$ for intensive dietary portfolio and $P = .006$ for routine dietary portfolio), with no significant differences between the dietary portfolios ($P = .66$) (Table 3). The apolipoproteins reflected the lipid and lipoprotein changes (Table 3). No significant differences were observed between treatments in CRP. No treat-

ment differences in response were observed between men and women.

Blood Pressure

The intensive dietary portfolio led to a nonsignificant reduction in systolic blood pressure of 2.6 mm Hg (95% CI, -5.4 to -0.2 mm Hg; $P = .07$) and a significant reduction in diastolic blood pressure of 2.1 mm Hg (95% CI, -3.7 to -0.4 mm Hg; $P = .01$) compared with the control diet (Table 3).

Calculated CHD Risk

The routine dietary portfolio reduced the calculated 10-year CHD risk by

Table 2. Baseline Characteristics of Participants

Characteristics	Treatments			P Value ^a
	Intensive Dietary Portfolio (n = 101)	Routine Dietary Portfolio (n = 122)	Control (n = 122)	
Age, mean (95% CI), y	55 (53-57)	57 (56-59)	57 (55-59)	.08
Sex, No. (%)				.01
Male	50 (50)	37 (30)	47 (39)	
Female	51 (51)	85 (70)	75 (62)	
Race/ethnicity, No. (%)				.45
White	78 (77)	98 (80)	98 (80)	
Asian	12 (12)	15 (12)	15 (12)	
Black	4 (4)	3 (3)	5 (4)	
Hispanic	4 (4)	0 (0)	0 (0)	
Aboriginal	0 (0)	1 (1)	0 (0)	
Other ^b	3 (3)	5 (4)	4 (3)	
Body weight, mean (95% CI), kg	76 (73-78)	74 (71-76)	77 (74-79)	.19
BMI, mean (95% CI)	27 (26-27)	27 (26-28)	27 (27-28)	.24
Blood pressure, mean (95% CI), mm Hg				
Systolic	121 (118-123)	119 (117-122)	120 (118-122)	.68
Diastolic	73 (71-75)	74 (72-75)	73 (72-74)	.73
Lipids, mean (95% CI), mg/dL				
TC	252 (244-260)	256 (249-263)	249 (243-255)	.83
LDL-C	171 (164-178)	173 (168-180)	168 (163-184)	.38
HDL-C	55 (53-57)	54 (51-57)	54 (51-56)	.84
Triglycerides	135 (122-148)	142 (129-156)	147 (130-162)	.57
Medication use, No. (%)				
Lipid-lowering medication ^c	13 (13)	20 (16)	18 (15)	.75
Antihypertensive medication	18 (18)	17 (14)	28 (23)	.19
Hormone therapy medication	2 (2)	7 (6) ^d	2 (2)	.20
Thyroxine	9 (9)	11 (9)	15 (12)	.63

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.
 SI conversions: To convert TC, HDL-C, and LDL-C to mmol/L, multiply by 0.0259; and triglycerides to mmol/L, multiply by 0.0113.
^aP values for between-group differences used generalized linear model analysis of variance for continuous variables and Fisher exact test for categorical variables, in which the null hypothesis is that the portion of participants receiving each medication was the same across all treatments.
^bIncluded those participants of mixed race and those whose race/ethnicity could not be self-determined.
^cParticipants who entered the study taking lipid-lowering drugs were required to discontinue them at least 2 weeks before randomization.
^dAn additional participant started estrogen at week 12.

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10.8% (95% CI, -16.8% to -5.0%; $P < .001$; absolute risk change, -0.9%; 95% CI, -1.4% to -0.5%), with a comparable reduction in the intensive dietary portfolio of -11.3% (95% CI, -17.1% to -5.4%; $P < .001$; absolute risk change, -1.2%; 95% CI, -1.5% to -0.8%). These percentage reductions were significantly different ($P = .02$ and $P = .01$, respectively) from the nonsig-

nificant decrease in the control diet (-0.5%; 95% CI, -6.0% to 5.0%; $P = .87$; absolute risk change, -0.3%; 95% CI, -0.7% to 0.1%; $P = .12$) (Table 3).

Completer Analysis

The mean percentage reductions in LDL-C were significant at -15.0% (95% CI, -18.6% to -11.4%; $P < .001$) or -27 mg/dL (95% CI, -32 to -22 mg/dL) for

routine dietary portfolio and -15.5% (95% CI, -19.0% to -12.0%; $P < .001$) or -28 mg/dL (95% CI, -32 to -22 mg/dL) for intensive dietary portfolio, but not for the control diet (-2.5%; 95% CI, -6.0% to 1.0%; $P = .16$; or -9 mg/dL; 95% CI, -14 to -4 mg/dL). Both portfolio treatments were different from the control ($P < .001$) but were similar to each other.

Table 3. Blood Lipids, Blood Pressure, and Plant Sterols in the Control and Portfolio Diets at Weeks 0 and 24 and the Between-Treatment Differences

Variable	Treatments, Mean (95% CI)					
	Intensive Dietary Portfolio (n = 101)		Routine Dietary Portfolio (n = 122)		Control (n = 122)	
	Week 0	Week 24	Week 0	Week 24	Week 0	Week 24
Body weight, kg	75.5 (72.9 to 78.0)	74.3 (71.7 to 76.8) ^a	73.7 (71.3 to 76.1)	71.8 (69.6 to 74.1) ^a	76.9 (74.5 to 79.3)	75.2 (72.8 to 77.7) ^a
Blood pressure, mm Hg						
Systolic	120.9 (118.4 to 123.4)	117.7 (115.1 to 120.3) ^a	119.5 (117.0 to 121.8)	118.0 (114.9 to 121.0)	119.9 (117.7 to 122.1)	119.5 (116.9 to 122.0)
Diastolic	73.1 (71.3 to 74.9)	70.9 (69.2 to 72.6) ^a	73.8 (72.2 to 75.4)	72.3 (70.5 to 74.1)	73.0 (71.6 to 74.4)	72.9 (71.4 to 74.4)
Lipids, mg/dL						
TC	252 (244 to 260)	225 (217 to 232) ^a	256 (249 to 263)	230 (223 to 238) ^a	249 (243 to 255)	246 (240 to 252)
LDL-C	171 (164 to 178)	145 (139 to 151) ^a	173 (167 to 179)	148 (142 to 154) ^a	167 (163 to 172)	161 (156 to 166) ^a
HDL-C	55 (53 to 57)	53 (50 to 56)	54 (51 to 57)	54 (51 to 57)	54 (51 to 56)	54 (52 to 57)
Triglycerides	135 (122 to 148)	133 (120 to 146)	142 (129 to 156)	141 (127 to 155)	147 (130 to 162)	153 (137 to 169)
TC:HDL-C ratio	4.81 (4.59 to 5.03)	4.44 (4.21 to 4.67) ^a	5.01 (4.77 to 5.25) ^a	4.53 (4.31 to 4.75)	4.93 (4.71 to 5.15)	4.82 (4.59 to 5.05)
Apolipoproteins, mg/dL						
A-1	160 (155 to 164)	159 (155 to 164)	160 (156 to 164)	159 (155 to 164)	160 (156 to 164)	160 (156 to 164)
B	122 (119 to 127)	109 (105 to 114) ^a	126 (122 to 130)	112 (108 to 116) ^a	120 (117 to 124)	120 (116 to 123)
CRP, mg/L	1.37 (1.09 to 1.66)	1.54 (0.56 to 2.52)	1.72 (1.39 to 2.05)	1.49 (0.22 to 2.75)	2.14 (1.36 to 2.92)	2.85 (0.63 to 5.08)
Phytosterols, μmol/L	10.7 (9.5 to 11.9)	13.3 (12.0 to 14.6) ^a	10.1 (9.3 to 10.9)	12.8 (11.5 to 14.1) ^a	10.6 (9.7 to 11.5)	11.4 (10.2 to 12.5)
10-y CHD risk,% ^b	7.5 (6.7 to 8.3)	6.4 (5.7 to 7.1) ^a	7.9 (7.0 to 8.6)	6.8 (6.1 to 7.5) ^a	8.1 (7.0 to 9.0)	7.7 (6.9 to 8.5)
	Between-Treatment Differences^c					
	Intensive vs Routine		Intensive vs Control		Routine vs Control	
	Mean (95% CI)	P Value	Mean (95% CI)	P Value	Mean (95% CI)	P Value
Body weight, kg	0.5 (-0.5 to 1.4)	.35	0.2 (-0.7 to 1.1)	.65	-0.2 (-1.1 to 0.6)	.58
Blood pressure, mm Hg						
Systolic	-1.3 (-4.4 to 1.8)	.40	-2.6 (-5.4 to 0.20)	.07	-1.3 (-4.3 to 1.8)	.40
Diastolic	-0.9 (-2.7 to 0.8)	.30	-2.1 (-3.7 to -0.4)	.01	-1.1 (-2.9 to 0.6)	.19
Lipids, mg/dL						
TC	-2 (-10 to 6)	.62	-22 (-31 to -13)	<.001	-20 (-28 to -12)	<.001
LDL-C	-2 (-9 to 6)	.66	-18 (-25 to -10)	<.001	-16 (-23 to -9)	<.001
HDL-C	0 (-2 to 3)	.95	-1 (-4 to 1)	.25	-2 (-4 to 1)	.23
Triglycerides	-4 (-19 to 11)	.57	-10 (-25 to 5)	.18	-6 (-21 to 10)	.47
TC:HDL-C ratio	-0.02 (-0.22 to 0.19)	.86	-0.30 (-0.50 to -0.09)	.004	-0.28 (-0.48 to -0.08)	.006
Apolipoproteins, mg/dL						
A-1	2 (-2 to 6)	.31	0.2 (-4 to 4)	.94	-2 (-6 to 2)	.33
B	-1 (-5 to 2)	.68	-11 (-16 to -7)	<.001	-11 (-15 to -7)	<.001
CRP, mg/L	0.17 (-2.08 to 2.42)	.88	-1.22 (-3.34 to 0.91)	.26	-1.38 (-3.53 to 0.75)	.20
Phytosterols, μmol/L	0.6 (-1.1 to 2.3)	.50	1.8 (0.3 to 3.4)	.02	1.2 (-0.4 to 2.9)	.14
10-y CHD risk,% ^b	-1.2 (-9.8 to 7.4)	.78	-10.7 (-18.9 to -2.6)	.01	-9.5 (-17.8 to -1.2)	.02

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

SI conversions: To convert TC, HDL-C, and LDL-C to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; CRP to nmol/L, multiply by 9.524; apolipoproteins A-1 and B to g/L, multiply by 0.01; and phytosterols to mg/dL, multiply by 0.04.

^aSignificant change from baseline by *t* test, $P \leq .05$.

^bUsing algorithm of Anderson et al.¹⁶ means, 95% CIs, and *P* values for between-treatment differences were based on comparisons between percentage changes in CHD risk.

^cUsing analysis of covariance with sex, treatment, and sex × treatment interaction as main effects and baseline as a covariate. A Tukey adjustment was made for multiple comparisons.

Factors Associated With the Percentage Reduction in LDL-C

Overall adherence with the 4 principal portfolio components (nuts, soy, viscous fiber, and plant sterol) was significantly associated with the percentage reduction in LDL-C in participants who completed the study ($r = -0.34$, $n = 157$, $P < .001$).

Center Differences

The mean percentage LDL-C response of the 2 portfolio treatments for Vancouver (-19.9%; 95% CI, -25.0% to -14.8%; or -33 mg/dL; 95% CI, -41 to -25 mg/dL) differed significantly from both Toronto (-11.6%; 95% CI, -15.6% to -7.6%; or -23 mg/dL; 95% CI, -30 to -17 mg/dL) and Winnipeg (-11.1%; 95% CI, -16.4% to -5.8%; or -22 mg/dL; 95% CI, -30 to -14 mg/dL) for the difference in percentage reduction between centers ($P = .01$ and $P = .02$, respectively), and the difference between Vancouver and Quebec (-12.7%; 95% CI, -18.2% to -7.2%; or -26 mg/dL; 95% CI, -35 to -17 mg/dL) was of borderline significance for the percentage reduction in LDL-C ($P = .06$). Vancouver (48.3%) differed from Winnipeg (34.0%) in terms of adherence ($P = .001$).

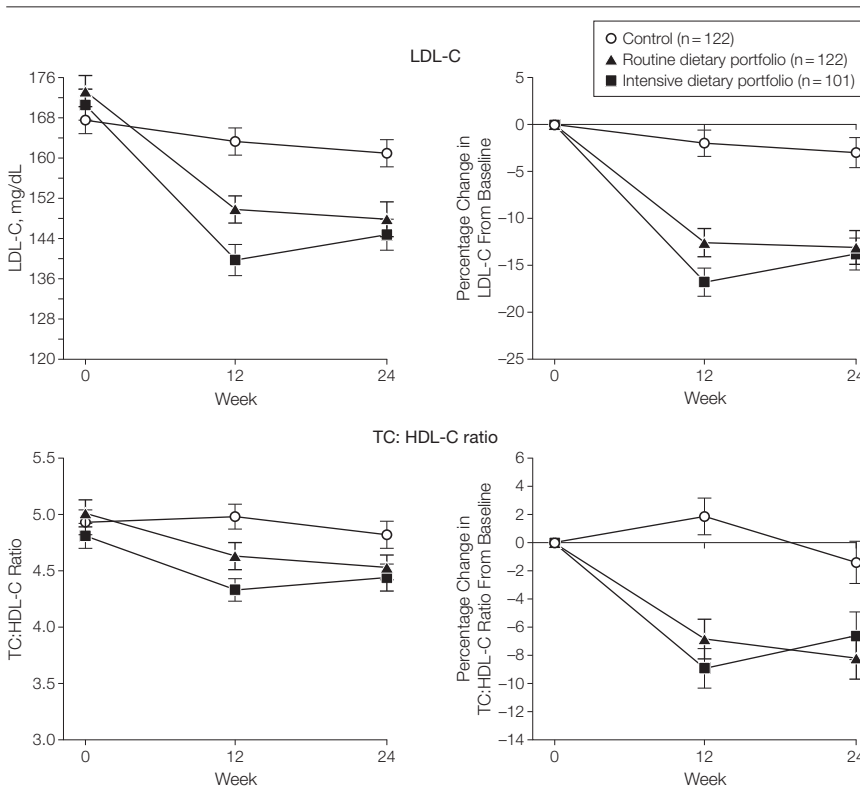
Adverse Clinical Events

There were no serious adverse events or events that required hospitalization (eTable 2). However, 36 minor events were reported during the study (15 in the intensive dietary portfolio, 12 in the routine dietary portfolio, and 9 in the control diet), with no treatment difference in event number ($P = .20$). None of the events were directly linked to the study intervention, except for 1 man who had recurrent facial flushing and itching at the back of the neck and was found to have positive skin test for soy in the routine dietary portfolio, and 1 woman with a rash and positive skin test for soy and almonds in the intensive dietary portfolio.

COMMENT

Our data demonstrate the cholesterol-lowering potential of a dietary portfolio

Figure 2. Absolute Values of LDL-C and TC:HDL-C Ratio and Percentage Changes in LDL-C and TC:HDL-C Ratio From Baseline in the Control, Intensive Dietary, and Routine Dietary Portfolios



LDL-C indicates low-density lipoprotein cholesterol; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol. To convert LDL-C to mmol/L, multiply by 0.0259. Error bars indicate SE.

intervention that counsels participants to increase consumption of cholesterol-lowering foods denoted by the US FDA to have a heart health benefit and that have also been recommended in national guidelines to enhance the effectiveness of cholesterol-lowering therapeutic diets.^{1,10} Our study also represents the first randomized trial to our knowledge to assess the ability of an intervention that counsels for consumption of these cholesterol-lowering foods to reduce LDL-C at 6-month follow-up in real-world conditions. The reductions in LDL-C in the dietary portfolio intervention were approximately half those observed with early statin trials that were associated with 20% reductions in CHD mortality.¹⁷

Although there are no data on plant sterol consumption and reduction in CHD risk, cohort studies have consistently

shown that consumption of 5 servings of nuts a week, similar to the 26 to 31 g/d consumed in our study, is associated with a decrease in CHD events by 40% to 60%.^{18,19} Fiber intake has been negatively associated with CHD risk.^{20,21} Increased consumption of vegetable sources of protein and fat is associated with reductions in CHD risk.²² Similar associations were identified for soy protein consumption in the Shanghai cohort.²³ Further study is needed to determine whether cholesterol reduction using these portfolio components is associated with lower rates of CHD events.

The specific food components used in the portfolio have well-established cholesterol-lowering properties and are recognized by the US FDA as justifying a heart health claim.¹⁰ Review articles and meta-analyses have con-

firmed LDL-C benefits for viscous fibers,^{24,25} plant sterols,^{26,27} soy protein,²⁸⁻³⁰ and nuts.³¹

On the basis of the reported intake of portfolio components, one might expect a 4% LDL-C reduction from viscous fiber, 2% each from nuts and soy, and 5% from plant sterols, resulting in 13% LDL-C reduction. A reduction of a similar magnitude (13%-14%) was observed in our study.

This is the first study to our knowledge to assess the effect of frequency of visit on dropout rate, adherence, and outcome. Although a small reduction was observed in the dropout rate by increasing the frequency of visits from 2 to 7 during the 6-month period, no advantage was observed in terms of dietary adherence or the percentage LDL-C reduction at 24 weeks. More frequent clinic attendance therefore appears to be unnecessary in achieving a significant percentage reduction in LDL-C. The near maximal effectiveness of only 2 clinic visits enhances the suitability of this dietary approach for clinical application.

The study had limitations. First, the intervention was complex. Second, colinearity between the different dietary components did not permit attribution of the lipid-lowering effect to specific components of the intervention. Third, the study was not metabolically controlled in terms of providing all food to the participants. However, our goal was to assess the effect of dietary advice in real-world conditions. Studies of longer duration in which provision of specific diets was possible have relied on workplace or institutional environments.^{7,32-34} Fourth, the study had a high overall dropout rate of 22.6%. This attrition rate is common to dietary studies provided at these levels of intensity.³⁵⁻³⁷ In addition, participants were predominantly white with low to intermediate risk of cardiovascular disease and relatively low mean body mass index levels. The generalizability of this clinical trial to higher-risk, more overweight, or obese patient populations is unknown.

The study advantages include its multicenter nature with centers from across the continent. Participants who joined the study were already consuming an acceptable background diet low in saturated fat and cholesterol to provide a fairer illustration of the type of patients for whom standard dietary advice has failed to achieve therapeutic targets. This approach may underestimate the effectiveness of the diet when applied to those individuals who are not already following therapeutic diets. However, it is also possible that participants in this study are better able to adhere to healthy diets than those who chose not to participate. Many of the foods have other attributes, including lowering the glycemic index, which may aid in reducing disease risk for CHD, diabetes, and obesity.³⁸ In addition, the dietary portfolio treatments lowered LDL-C without also lowering HDL-C.

In conclusion, this study indicated the potential value of using recognized cholesterol-lowering foods in combination. We believe this approach has clinical application. A meaningful 13% LDL-C reduction can be obtained after only 2 clinic visits of approximately 60- and 40-minute sessions. The limited 3% LDL-C reduction observed in the conventional diet is likely to reflect the adequacy of the baseline diet and therefore suggests that larger absolute reductions in LDL-C may be observed when the dietary portfolio is prescribed to patients with diets more reflective of the general population.

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Author Contributions: Dr Jenkins 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. *Study concept and design:* Jenkins, Jones, Lamarche, Kendall, Cermakova.

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Statistical analysis: de Souza, Abdulnour.

Obtained funding: Jenkins, Jones, Lamarche, Kendall, Frohlich.

Administrative, technical, or material support: Jones, Kendall, Faulkner, Cermakova, Giguere, Ramprasath, Ireland, Patel, Srichaikul, Abdulnour, Bashyam, Collier, Hoshizaki, Josse, Leiter, Connelly, Frohlich.

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Jenkins reported serving on the Scientific Advisory Board of Unilever, Sanitarium Company, 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; receiving honoraria for scientific advice from the Almond Board of California, International Tree Nut Council Nutrition Research and Education Foundation, Barilla, Unilever Canada, Solae, Oldways, Kellogg's, Quaker Oats, Procter & Gamble, Coca-Cola, NuVal Griffin Hospital, Abbott, Canola Council of Canada, Dean Foods, California Strawberry Commission, Haine Celestial, and Alpro Foundation; being on the speakers panel for the Almond Board of California; receiving research grants from Loblaw Brands Ltd, Unilever, Barilla, Almond Board of California, Solae, Haine Celestial, Sanitarium Company, Orafit, International Tree Nut Council, and Peanut Institute; and receiving travel support to meetings from the Almond Board of California, Unilever, Alpro Foundation, and International Tree Nut Council. Dr Jenkins' wife is a director of Glycemic Index Laboratories, Toronto, Ontario, Canada, and his sister, Caroline Brydson, contributed to the diet booklet used in the study, which may in the future be expanded to book form for the general public. Dr Jones reported receiving grants from the Canadian Institutes of Health Research (CIHR), Canada Research Chair Endowment (CRCE) of the Federal Government of Canada, Advanced Foods and Materials Network (AFM Net), Danone, Enzymotec, and Unilever. Dr Jones also serves as president of Nutritional Fundamentals for Health Inc, which markets plant sterols among other nutraceuticals. Dr Lamarche reported receiving grants from CIHR and AFM Net, being a consultant and on speakers bureaus for Danone, and receiving royalties from Atrium Innovations. Dr Kendall reported being on speakers bureaus for Almond Board of California, Solae, and Unilever; and receiving research grants from CIHR, Unilever, Solae, Loblaw

Brands Ltd, International Tree Nut Council, and Almond Board of California. Dr Faulkner reported receiving grants from CRCE of the Federal Government of Canada, CIHR, AFM Net, Loblaw Brands Ltd, Unilever, and Solae. Ms Cermakova reported receiving grants from CRCE of the Federal Government of Canada, CIHR, AFM Net, Loblaw Brands Ltd, Unilever, Solae, and Viterra Food Processing-Oat and Specialty Grain Milling. Dr Ramprasath reported receiving grants from CRCE of the Federal Government of Canada, CIHR, AFM Net, Loblaw Brands Ltd, Solae, and Unilever. Dr de Souza reported receiving grants from Coca-Cola, Calorie Control Council, and CIHR. Mr Ireland reported receiving grants from CRCE of the Federal Government of Canada, CIHR, AFM Net, Loblaw Brands Ltd, Solae, and Unilever. Ms Patel reported receiving grants from CRCE of the Federal Government of Canada, CIHR, AFM Net, Loblaw Brands Ltd, Solae, and Unilever. Dr Bashyam reported receiving grants from CIHR, CRCE of the Federal Government of Canada, AFM Net, Loblaw Brands Ltd, Solae, and Unilever. Ms Hoshizaki reported receiving

grants from CRCE of the Federal Government of Canada, CIHR, AFM Net, Loblaw Brands Ltd, Unilever, and Solae. No other authors reported any financial disclosures.

Funding/Support: This work was supported by the CRCE of the Federal Government of Canada (Drs Jenkins, Jones, and Lamarche), CIHR, AFM Net, Loblaw Brands Ltd, Solae (St Louis, Missouri), and Unilever (Vlaardingen, the Netherlands, and Toronto, Ontario, Canada). Unilever Research and Development provided the donation of margarines used in the study and Can-Oat Milling, a division of Viterra Inc (Portage La Prairie, Manitoba, Canada), provided the generous donation of HiFi medium oat bran used for the study breads and funding for freezer acquisition. St Michael's Hospital Foundation provided funding for the production of the study booklet.

Role of the Sponsors: The primary funder of the study was the CIHR. AFM Net, a government-funded Center of Excellence, and the industrial sponsors, Loblaw Brands Ltd, Solae, and Unilever, provided supplementary funding but played no role

in the design and conduct of the study, in the collection, management, analysis, or interpretation of the data, or in the preparation, review, or approval of the manuscript.

Online-Only Material: eTables 1 and 2 and the eFigure are available at <http://www.jama.com>.

Additional Contributions: Edward Vidgen, BSc (BSH Group of Companies Canada LTD, Toronto, Ontario, Canada) was responsible for the power calculation in the original grant and for the generation of the randomization blocks. His work was funded by grants to the University of Toronto by Loblaw Brands Ltd and the Almond Board of California. Gail M. Eysen, PhD (Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada), provided help with the original grant, especially with the statistical section. No compensation was received for her contribution. We thank the academic and private family practice units at all participating centers for their help in participant recruitment and the participants for their attention to detail, which made this study possible.

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