

Portfolio Dietary Pattern and Cardiovascular Disease: A Systematic Review and Meta-analysis of Controlled Trials^{☆,☆☆}



Laura Chiavaroli^{a,b}, Stephanie K. Nishi^{a,b}, Tauseef A. Khan^{a,b}, Catherine R. Braunstein^{a,b}, Andrea J. Glenn^{a,b}, Sonia Blanco Mejia^{a,b}, Dario Rahelić^f, Hana Kahleová^{g,h}, Jordi Salas-Salvadó^{i,j}, David J.A. Jenkins^{a,b,c,d,e}, Cyril W.C. Kendall^{a,b,k,*}, John L. Sievenpiper^{a,b,d,e,*}

^a Toronto 3D Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, ON, Canada

^b Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

^c Department of Medicine, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

^d Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada

^e Division of Endocrinology and Metabolism, St. Michael's Hospital, Toronto, ON, Canada

^f Department of Endocrinology, Diabetes and Clinical Pharmacology, Dubrava University Hospital, Zagreb, Croatia

^g Institute for Clinical and Experimental Medicine, Diabetes Centre, Prague, Czech Republic

^h Physicians Committee for Responsible Medicine, Washington, DC, USA

ⁱ CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain

^j Human Nutrition Department, IISPV, Universitat Rovira i Virgili, Reus, Spain

^k College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, SK, Canada

ARTICLE INFO

Article history:

24 May 2018

24 May 2018

Keywords:

Portfolio diet

Dietary Portfolio

Dietary pattern

Plant sterols

Plant protein

Viscous fibre

Nuts

LDL-cholesterol

Cardiovascular risk

Cardiometabolic risk

Systematic review and meta-analysis

ABSTRACT

Background: The evidence for the Portfolio dietary pattern, a plant-based dietary pattern that combines recognized cholesterol-lowering foods (nuts, plant protein, viscous fibre, plant sterols), has not been summarized.

Objective: To update the European Association for the Study of Diabetes clinical practice guidelines for nutrition therapy, we conducted a systematic review and meta-analysis of controlled trials using GRADE of the effect of the Portfolio dietary pattern on the primary therapeutic lipid target for cardiovascular disease prevention, low-density lipoprotein cholesterol (LDL-C), and other established cardiometabolic risk factors.

Methods: We searched MEDLINE, EMBASE, and The Cochrane Library through April 19, 2018. We included controlled trials ≥ 3 -weeks assessing the effect of the Portfolio dietary pattern on cardiometabolic risk factors compared with an energy-matched control diet free of Portfolio dietary pattern components. Two independent reviewers extracted data and assessed risk of bias. The primary outcome was LDL-C. Data were pooled using the generic inverse-variance method and expressed as mean differences (MDs) with 95% confidence intervals (CIs). Heterogeneity was assessed (Cochran Q statistic) and quantified (I^2 -statistic). GRADE assessed the certainty of the evidence. **Results:** Eligibility criteria were met by 7 trial comparisons in 439 participants with hyperlipidemia, in which the Portfolio dietary pattern was given on a background of a National Cholesterol Education Program (NCEP) Step II diet. The combination of a portfolio dietary pattern and NCEP Step II diet significantly reduced the primary outcome LDL-C by $\sim 17\%$ (MD, -0.73 mmol/L, [95% CI, -0.89 to -0.56 mmol/L]) as well as non-high-density lipoprotein cholesterol, apolipoprotein B, total cholesterol, triglycerides, systolic and diastolic blood pressure, C-reactive protein, and estimated 10-year coronary heart disease (CHD) risk, compared with an NCEP Step 2 diet alone ($p < 0.05$). There was no effect on high-density lipoprotein cholesterol or body weight. The certainty of the evidence was high for LDL-cholesterol and most lipid outcomes and moderate for all others outcomes.

Abbreviations and Acronyms: ApoB, Apolipoprotein B; BMI, Body mass index; CRP, C-reactive protein; CCS, Canadian Cardiovascular Society; CV, Cardiovascular; CVD, Cardiovascular disease; CTT Collaboration, Cholesterol Treatment Trialists'; CIs, Confidence intervals; CHD, Coronary heart disease; DNSG, Diabetes and Nutrition Study Group; DBP, Diastolic blood pressure; DASH, Dietary Approaches to Stop Hypertension; EAS, European Atherosclerosis Society; EFSA, European Food Safety Authority; ESC, European Society of Cardiology; EASD, European Association for the Study of Diabetes; FDA, Food and Drug Administration; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; non-HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein; MID, Minimally important difference; MUFAs, Monounsaturated fatty acids; NCEP, National Cholesterol Education Program; non-HDL-C, Non-high density lipoprotein cholesterol; PREDIMED, Prevención con Dieta Mediterránea; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RevMan, Review Manager; SBP, Systolic blood pressure; TC, Total cholesterol; TG, Triglycerides.

[☆] Statement of Conflict of Interest: see page 51.

^{☆☆} Protocol registration: ClinicalTrials.gov identifier, NCT03534414.

* Address reprint requests to Dr. Cyril WC Kendall, PhD and Dr. John L Sievenpiper, MD, PhD, FRCPC, Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, The Fitzgerald Building, 150 College Street East, Room 432, Toronto, ON M5S 3E2, Canada.

E-mail addresses: cyril.kendall@utoronto.ca, (C.W.C. Kendall), john.sievenpiper@utoronto.ca (J.L. Sievenpiper).

Conclusions: Current evidence demonstrates that the Portfolio dietary pattern leads to clinically meaningful improvements in LDL-C as well as other established cardiometabolic risk factors and estimated 10-year CHD risk.

© 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Contents

Introduction	44
Methods	44
Design	44
Data search	45
Study selection	45
Data extraction	45
Risk of bias assessment	45
Outcomes	45
Statistical analysis	45
Grading of the evidence	45
Results	45
Search results	45
Trial characteristics	45
Risk of bias	48
Effect on LDL-C	48
Effect on blood lipids and apolipoproteins	48
Effect on blood pressure	48
Effect on inflammation	48
Effect on estimated 10-year risk of CHD	48
The effect of the Portfolio dietary pattern on body weight	48
Sensitivity analysis	49
GRADE assessment	49
Discussion	49
Findings in the context of the literature	49
Strengths and limitations	50
Implications	50
Conclusions	50
Funding statement	50
Conflicts of interest	51
Appendix A. Supplementary data	52
References	52

Introduction

The portfolio dietary pattern (also known as the “Dietary Portfolio” or “Portfolio Diet”) is a plant-based dietary pattern that was first devised in the early 2000s as a “portfolio” of 4 cholesterol-lowering foods, each of which has a Food and Drug Administration (FDA), Health Canada, and/or European Food Safety Authority (EFSA) approved health claim for cholesterol-lowering or cardiovascular (CV) disease (CVD) risk reduction.^{1–7} The 4 core food components of the Portfolio dietary pattern include (based on a 2000 kcal diet): 42 g nuts (tree nuts or peanuts); 50 g plant protein from soy products or dietary pulses such as beans, peas, chickpeas, and lentils; 20 g viscous soluble fibre from oats, barley, psyllium, eggplant, okra, apples, oranges, or berries; and 2 g plant sterols initially provided in a plant sterol-enriched margarine.^{8–13} An enhanced Portfolio dietary pattern has also been studied in which monounsaturated fat (MUFA) replaces carbohydrate (13% replacement providing 26% energy from MUFA) and is added to the other 4 components.¹² Controlled feeding trials of the portfolio dietary pattern demonstrated that each of the components had a low-density lipoprotein cholesterol (LDL-C) lowering effect of 5–10%^{14–18} and that the effect was additive when combined as part of this dietary pattern.^{8–13} An early randomized controlled trial showed the maximal LDL-C lowering efficacy was similar to that of 20 mg lovastatin (–28.6% versus –30.9%) in a “head-to-head” comparison when all foods were provided under metabolically-controlled conditions¹⁰ with a subsequent longer term multi-centre randomized controlled trial of effectiveness showing smaller reductions of 10–15% under free living conditions in which adherence was only

43% of the earlier metabolic trial since the participants received only dietary advice.¹³

The benefits of the Portfolio dietary pattern have been recognized by major international CVD and diabetes clinical practice guidelines including those of the Canadian Cardiovascular Society (CCS),^{19,20} Diabetes Canada,²¹ European Atherosclerosis Society (EAS),²² and Heart UK^{23,24} while each of the food components have been recognized for their LDL-C cholesterol lowering by the joint task force of the European Society of Cardiology (ESC) and EAS. Despite this recognition, the European Association for the Study of Diabetes (EASD) clinical practice guidelines for nutrition therapy have not made any specific recommendations regarding the Portfolio dietary pattern. To update the recommendations, the Diabetes and Nutrition Study Group (DNSG) of the EASD commissioned a systematic review and meta-analysis using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to summarize the available evidence from controlled trials of the effect of the Portfolio dietary pattern on the primary therapeutic blood lipid target for CVD prevention, LDL-C, and other established cardiometabolic risk factors.

Methods

Design

This systematic review and meta-analysis was conducted according to the Cochrane Handbook for Systematic Reviews and interventions²⁵ with all results reported according to the Preferred Reporting Items

for Systematic Reviews and Meta-Analyses (PRISMA) guidelines²⁶ (Supplementary Table S1). The study protocol was registered at ClinicalTrials.gov (identifier, NCT03534414).

Data search

We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Studies databases using OVID from inception through April 19, 2018. Search terms used were “Portfolio diet” and “dietary Portfolio” (Supplementary Table S2), limited to human studies with no language restrictions. Reference lists of selected studies and reviews were also searched to identify additional articles.

Study selection

We included randomized and non-randomized controlled trials that investigated the effect of a Portfolio dietary pattern in comparison to any energy-matched diet that did not provide components of the Portfolio dietary pattern. The Portfolio dietary pattern was defined as including the following components as the intended intervention: 1–3 g/day plant sterols (plant-sterol containing margarines, supplements), 15–25 g/day viscous fibres (gel-forming fibres, such as from oats, barley, psyllium, legumes, eggplants, okra), 35–50 g/day plant protein (such as from soy and pulses) and 25–50 g/day nuts (including tree nuts and peanuts).

Data extraction

Three reviewers (LC, CRB, TAK) assessed titles and abstracts of all identified studies and independently reviewed and extracted relevant data from each report, including study design, setting, underlying disease status of participants, level of feeding control, randomization, sample size, follow-up duration, Portfolio dietary intervention, comparator diet, macronutrient profile, funding sources and outcome data. Additional information was requested from authors of all included trials. Disagreements were resolved by consensus or where necessary by the senior author (JLS).

Risk of bias assessment

Risk of bias was assessed independently for each study using the Cochrane Collaboration's tool for assessing Risk of Bias²⁶ by two reviewers (LC, CRB). Assessment was done across 5 domains of bias (sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting). Risk of bias was assessed as either low (proper methods taken to reduce bias), high (improper methods creating bias) or unclear (insufficient information provided to determine the bias level).

Outcomes

The primary outcome was the primary blood lipid target for CVD prevention, LDL-C.¹⁹ Secondary outcomes included established alternate blood lipid targets [non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (apoB)¹⁹], other blood lipids [(total cholesterol (TC), HDL-C, triglycerides (TG)], adiposity (body weight), inflammation[(C-reactive protein (CRP)], systolic blood pressure (SBP) and diastolic blood pressure (DBP), glycemic outcomes (fasting blood glucose, fasting insulin and HbA1c) and 10-year coronary heart disease (CHD) risk estimated by the Framingham risk score.²⁷ Change-from-baseline differences were used and expressed as mean \pm standard deviations (SDs). When not provided, between-treatment differences in change-from-baseline or end differences were calculated by subtracting means and SDs were calculated from the available data and statistics using published formulas.²⁶ Paired analyses were applied to all cross-over trials with the use of a within-individual correlation coefficient between treatments of 0.5 as described by Elbourne et al.²⁸ End-differences were

preferred if cross-over studies had the entire trial population following the same sequence without a wash-out between treatments to avoid bias due to period effects. Study authors were contacted for missing data.

Statistical analysis

Review Manager (RevMan) 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark, 2014) was used for all analyses. Data were pooled by the generic inverse-variance method with DerSimonian and Laird random-effects models and expressed as mean differences (MDs) with 95% confidence intervals (95% CIs). Random-effects models were used as they account for residual heterogeneity and yield more conservative estimates.^{26,29} To improve clinical translation of the pooled estimates, we also calculated the percentage change for each pooled outcome by dividing the MD by the median baseline value from the included studies (based on the baseline of both the test and control diets in parallel trials and the baseline of the first arm in crossover trials). Heterogeneity was assessed with the Cochran I^2 statistic and quantified by the I^2 statistic, where $I^2 \geq 50\%$ at $p < 0.10$ was considered evidence of substantial heterogeneity.²⁶ Sources of heterogeneity were explored by a priori sensitivity analyses. One sensitivity analysis was done to assess the influence of individual trials on the summary estimates by the systematic removal of each trial comparison with the recalculation of the summary estimates. A second sensitivity analyses was done to assess the influence of the level of experimental control by restricting analyses to either “effectiveness” trials (that is, trials in which the Portfolio dietary pattern intervention was delivered as dietary advice without the provision of foods) or “efficacy” trials (that is, trials in which the Portfolio dietary pattern intervention was delivered under metabolically controlled feeding conditions with the provision of all foods including the key components of the Portfolio dietary pattern). The removal of a single trial comparison or restriction to a single trial type was considered influential if it changed the significance, direction, or magnitude ($>10\%$) of the pooled estimates or changed the significance of the evidence for heterogeneity. We did not perform a-priori subgroup analyses or assess publication bias analyses, as all of the outcomes had <10 trial comparisons available for analyses.^{26,30,31}

Grading of the evidence

The certainty of the evidence was assessed using the GRADE approach.³² The quality of the evidence can be graded as very low, low, moderate, or high. Controlled trials receive an initial grade of high and are then downgraded based on pre-specified criteria. These criteria include risk of bias (as assessed by the Cochrane Collaboration's tool for assessing risk of bias²⁶), inconsistency (substantial unexplained inter-study heterogeneity, $I^2 \geq 50\%$, $p < 0.10$), indirectness (presence of factors that limit the generalizability of the results), imprecision (the 95% CI for risk estimates are wide or cross a minimally important difference (MID) for benefit or harm and publication bias (evidence of small-study effects)).³²

Results

Search results

Fig. 1 shows the flow of the literature search and study selection. Of the 103 reports identified, 5 met eligibility criteria. These included 7 trial comparisons with 439 participants for LDL-C, blood lipids, blood pressure, and body weight, 435 participants for CRP, and 5 trial comparisons with 415 participants for 10-year CHD risk. No trials were available that assessed fasting blood glucose, fasting insulin, or hemoglobin A1c.

Trial characteristics

Table 1 shows the characteristics of the included trials. Study sizes were relatively small, with a median of 25 participants (range 13–345).

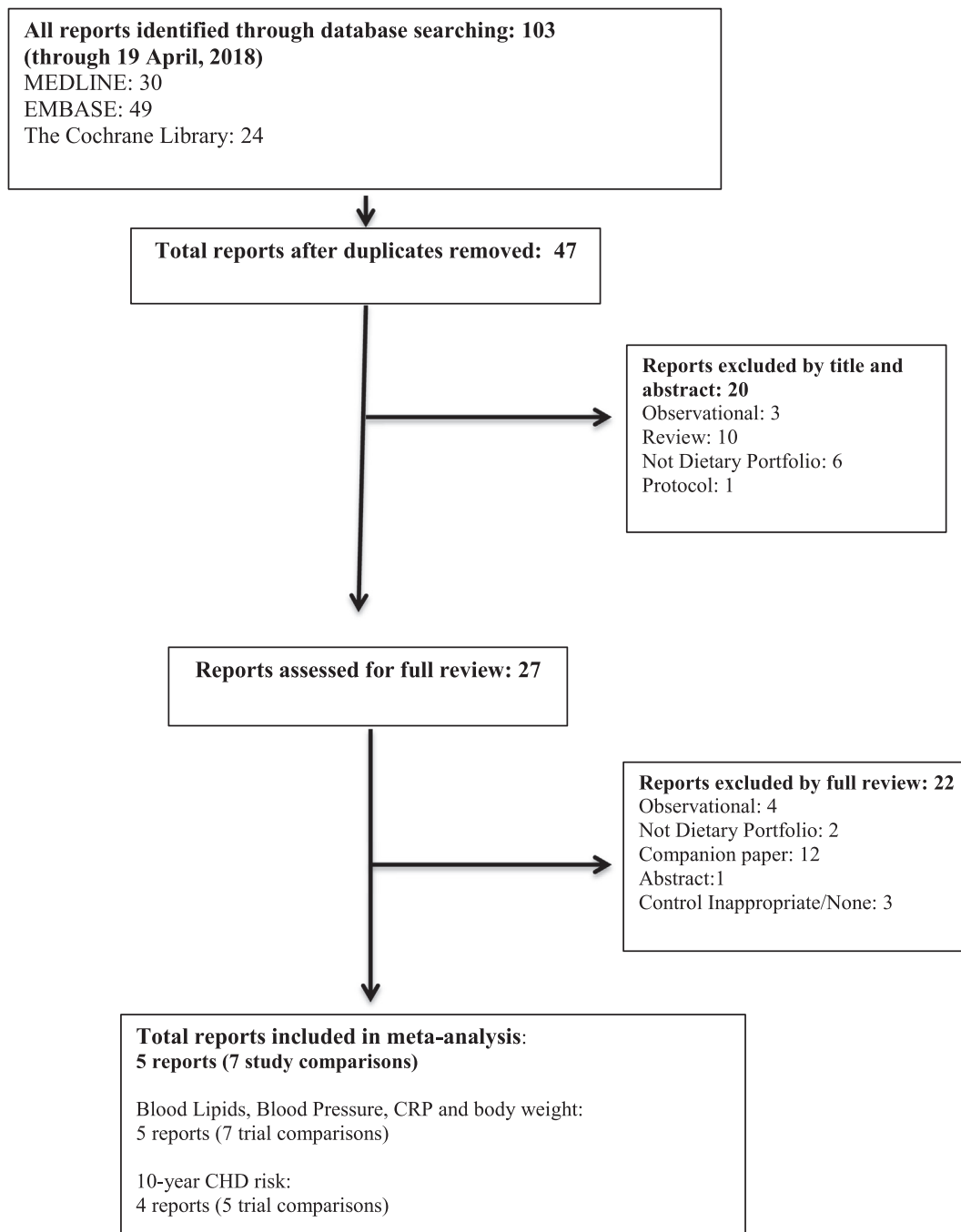


Fig. 1. Literature Search.

Participants were more likely to be middle-aged (median age, 57 years; range 54.7–65 years) and overweight [median body mass index (BMI) of 27 kg/m²; range 25.6–29.0 kg/m²] and ~44% men. All 7 trial comparisons included participants who had hyperlipidemia (median baseline LDL-C 4.4 mmol/L, range 4.2–4.6 mmol/L) but were otherwise healthy, no diabetes, no history of CVD. All trials included neutral energy balance diets designed for weight maintenance and all diets were isocaloric between test and control groups. Four of the 7 trials were parallel design and three were randomized. Five trial comparisons had a follow-up duration of 4 weeks and were performed in one centre, while the other two trial comparisons had a follow up of 24 weeks and performed in multiple

centers. Five trials were metabolically controlled with the provision of all study foods, 4 of which followed the Portfolio dietary pattern combining the 4 core food components (nuts, plant protein, viscous fibre, and plant sterols),^{8–10,13} while the other followed an enhanced Portfolio dietary pattern in which MUFA was added to the 4 for core food components.¹² Two trial comparisons used dietary advice, one based on routine advice (2 clinic visits of 40-to 60-minute sessions) and the other based on intensive advice (7 clinic visits of 40-to 60-minute sessions) over 24-weeks of follow-up.¹³ All 7 trials used a National Cholesterol Education Program (NCEP) Step II diet (≤30% energy total fat, <7% energy saturated fat, and <200 mg/day cholesterol) as the background diet to the Portfolio dietary

Table 1
Summary of trial characteristics.

Study	Participants	Disease status	Age (SD or range), y	BMI (SD or range), kg/m ²	LDL-C (SD or range), mmol/L	Setting	Design	Feeding control ^a	Randomization	Comparator	Energy balance ^b	Follow-up, wk	Diet ^c	Funding source
Jenkins et al. 2011 ^d	345 (134M:211F)	Hyper-lipidemia				OP, Canada	P	Dietary advice	Y	NCEP Step II diet	Neutral	24		A, I
Portfolio - routine	122		57 (8)	27 (6)	4.5 (0.9)								46:31:18	
Portfolio - intense	101		55 (10)	27 (3)	4.4 (0.9)								46:32:18	
NCEP Step II Diet	122		57 (11)	27 (3)	4.4 (1.5)								50:26:18	
Jenkins et al. 2010 ^e	24 (17M:7F)	Hyper-lipidemia				OP, Canada	C ^f	Metabolic	N	NCEP Step II diet	Neutral	4		A, I
Portfolio - high-MUFA	12		54.7 (8.0) (42–68)	29.0 (4.3) (25–36)	4.3 (0.7) (3.5–5.6)								33.9:45.6:20.5	
Portfolio - low-MUFA	12		55.5 (11.0) (38–69)	28.8 (1.8) (26–32)	4.2 (0.8) (3.3–5.2)								49.1:29.3:21.7	
NCEP Step II diet	24												51.9:27.5:20.4	
Jenkins et al. 2003a ^g	32 (18 M:14F)	Hyper-lipidemia	~59 (7) ^h (36–85)	~27.6 (3.4) ^h (20.5–35.5)		OP, Canada	P	Metabolic	Y	NCEP Step II diet	Neutral	4		A, I
Portfolio	16				4.62 (3.6)								48.0:30.2:21.5	
NCEP Step II diet	16				4.29 (3.4)								52.3:24.9:22.1	
Jenkins et al. 2003b	25 (16 M:9F)	Hyper-lipidemia	60.0 (9.9) (36–85)	26.6 (2.9) (20.2–33.2)		OP, Canada	P	Metabolic	Y	NCEP Step II diet	Neutral	4		A, I
Portfolio	13				4.4 (0.97)								56.6:23.2:20.0 ⁱ	
NCEP Step II diet	12				4.64 (0.55)								58.8:21.6:19.6 ⁱ	
Jenkins et al. 2002	13 (7 M:6F)	Hyper-lipidemia	65 (11)	25.6 (3.2) (20.6–30.7)	4.22 (0.40)	OP, Canada	C		N	NCEP Step II diet	Neutral			A, I
Portfolio								Metabolic				4	50.6:27.0:22.4 ⁱ	
NCEP Step II diet								Ad libitum				2	58.2:22.7:18.1 ⁱ	

Abbreviations: A, agency; BMI, Body Mass Index; C, crossover; F, female; I, industry; M, male; MUFA, monounsaturated fatty acids; N, no; NCEP ATP III, National Cholesterol Education Program (NCEP); OP, outpatient; P, parallel; SD, standard deviation; SFA, saturated fatty acids; wks, weeks; Y, yes; y, years.

^a Metabolic feeding control included provision of all study foods, supplement feeding control included provision of study supplements only, and dietary advice included dietary counseling without the provision of any dietary foods or supplements.

^b Neutral energy balance diets were designed for weight maintenance, where all diets are isocaloric between test and control groups.

^c Total energy intake in the form of carbohydrate:fat:protein expressed as a percentage of total calories.

^d Raw data for C-reactive protein was obtained from the study authors.

^e All mean differences and their standard deviations were calculated using raw data provided by the original publication's authors. Thus, some values may appear different in this publication since there were multiple adjustments to the means presented in the original publication.

^f The trial as published consisted of a low-saturated fat run-in diet after which participants were randomized to either a high or low MUFA Portfolio diet. For the purpose of our statistical analysis, each Portfolio diet arm (high and low MUFA) was treated as a crossover study.

^g Raw data for C-reactive protein was obtained from the study authors, as well as for all other outcomes to calculate variance.

^h Based on 46 participants who completed the 3 arms of the study, the third not included here was a low saturated fat diet plus statin.

ⁱ Approximate values based on available carbohydrate as reported.

pattern in the intervention arm and the comparator diet in the control arm. The funding source for all trials was a combination of agency and industry.

Risk of bias

Supplementary Figs. S1–S2 show the individual Cochrane Risk of Bias assessments for each of the included trials on the effect of the Portfolio dietary pattern on cardiometabolic outcomes. Overall, no evidence of serious risk of bias was detected among the trials.

Effect on LDL-C

Fig. 2 and Supplementary Fig. S3 show the effect of the Portfolio dietary pattern on a background of an NCEP Step II diet compared with an NCEP Step II diet alone on the primary outcome, LDL-C. The Portfolio dietary pattern lowered LDL-C by 17% (7 trial comparisons, MD = -0.73 mmol/L [95% CI: -0.89 to -0.56 mmol/L], $p < 0.0001$) with evidence of substantial heterogeneity ($I^2 = 67%$, P-heterogeneity = 0.006).

Effect on blood lipids and apolipoproteins

Fig. 2 and Supplementary Figs. S4–S8 show the effect of the Portfolio dietary pattern on a background of an NCEP Step II diet compared with an NCEP Step II diet alone on other blood lipids and apolipoproteins. The Portfolio dietary pattern lowered TC by 12% (7 trial comparisons, MD = -0.81 mmol/L [95% CI: -0.98 to -0.64 mmol/L], $p < 0.001$), TG by 16% (7 trial comparisons, MD = -0.28 mmol/L [95% CI: -0.42 to -0.14 mmol/L], $p < 0.001$) and non-HDL by 14% (7 trial comparisons, MD = -0.83 mmol/L [95% CI: -1.03 to -0.64 mmol/L], $p < 0.001$), and apoB by 15% (7 trial comparisons, MD = -0.19 g/L [95% CI: -0.23 to -0.15 mmol/L], $p < 0.0001$) with evidence of substantial heterogeneity for all outcomes ($I^2 > 50%$, P-heterogeneity < 0.1). There was no effect on HDL-C (7 trial comparisons, MD = 0.01 mmol/L [95% CI: -0.03 to 0.05 mmol/L], $p = 0.56$) with no evidence of heterogeneity ($I^2 > 22%$, P-heterogeneity = 0.26).

Effect on blood pressure

Fig. 2 and Supplementary Figs. S9–S10 show the effect of the Portfolio dietary pattern on a background of an NCEP Step II diet compared with an NCEP Step II diet alone on blood pressure. The Portfolio dietary pattern lowered SBP by 1% (7 trial comparisons, MD = -1.75 mmHg [95% CI: -3.23 to -0.26 mmHg], $p = 0.02$) and DBP by 2% (7 trial comparisons, MD = -1.36 mmHg [95% CI: -2.33 to -0.38 mmHg], $p = 0.006$) with no evidence of heterogeneity ($I^2 = 0%$, P-heterogeneity > 0.1).

Effect on inflammation

Fig. 2 and Supplementary Fig. S11 show the effect of the Portfolio dietary pattern on a background of an NCEP Step II diet compared with an NCEP Step II diet alone on CRP. The Portfolio dietary pattern lowered CRP by 32% (7 trial comparisons, MD = -0.53 mg/L [95% CI: -1.01 to -0.15 mg/L], $p = 0.008$) with no evidence of heterogeneity ($I^2 = 33%$, P-heterogeneity = 0.18).

Effect on estimated 10-year risk of CHD

Fig. 2 and Supplementary Fig. S12 shows the effect of the Portfolio dietary pattern on a background of an NCEP Step II diet compared with an NCEP Step II diet alone on estimated 10-year risk of CHD. The Portfolio dietary pattern lowered the estimated 10-year risk of CHD by 13% (7 trial comparisons, MD = $-1.34%$ [95% CI: -2.19 to $-0.49%$], $p = 0.002$) with evidence of substantial heterogeneity ($I^2 = 54%$, P-heterogeneity = 0.07).

The effect of the Portfolio dietary pattern on body weight

Fig. 2 and Supplementary Fig. S13 shows the effect of the Portfolio dietary pattern on a background of an NCEP Step II diet compared with an NCEP Step II diet alone on body weight. The Portfolio dietary pattern showed a non-significant decreasing effect on body weight (7 trial comparisons, MD = -0.10 kg [95% CI: -0.48 to 0.27 kg], $p = 0.59$) with no evidence of heterogeneity ($I^2 = 0%$, P-heterogeneity = 0.99).

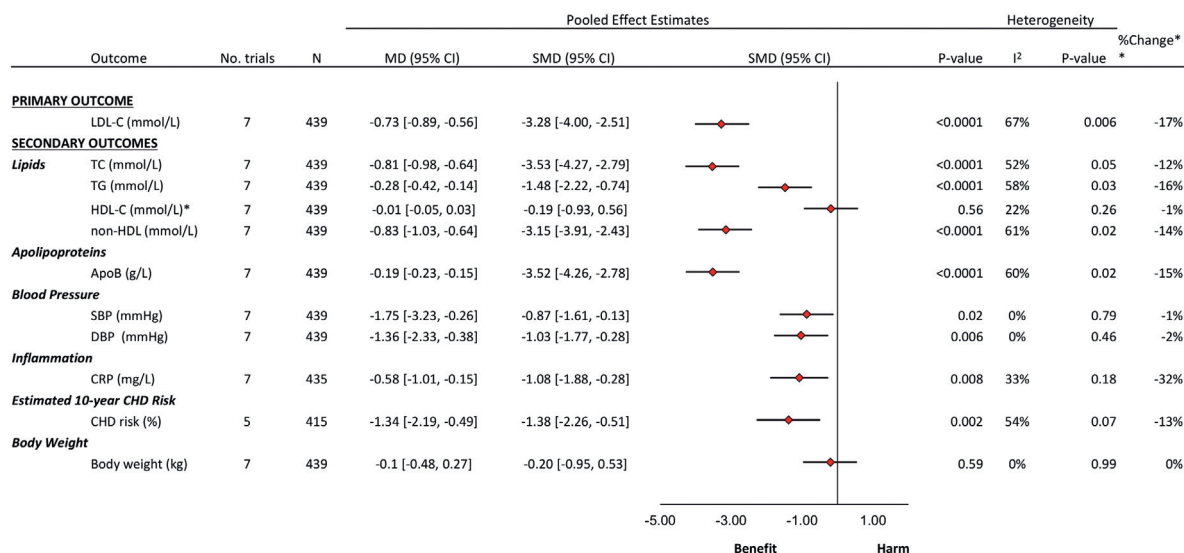


Fig. 2. Summary plot of pooled effect estimates from randomized controlled trials investigating the effects of the Portfolio dietary pattern on cardiometabolic outcomes. Pooled effect estimates are expressed as standardized mean differences, represented by diamonds and 95% CIs by the line through the diamond, and were estimated with the use of generic inverse variance random effects models. Between-study heterogeneity was detected with the use of the Cochran's Q statistic at a significance level of $p < 0.10$ and quantified with the use of the I^2 statistic where $I^2 \geq 50%$ is considered to be evidence of substantial heterogeneity and $\geq 75%$ considerable heterogeneity. *The reciprocal of the actual pooled MD (0.01 [–0.03, 0.05]) for HDL-cholesterol was provided so that it could be presented on the same scale (benefit vs. harm) as the other endpoints. ** % change was calculated by dividing the median baseline level by the MD *100. For parallel studies, the baseline of both the control and test diets was used. For crossover studies, the baseline of the first arm was used. ApoB, apolipoprotein B; CHD, coronary heart disease; CI, confidence interval; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-cholesterol, high density lipoprotein; kg, kilogram; LDL-cholesterol, low density lipoprotein cholesterol; MD, mean difference; non-HDL, non-high density lipoprotein cholesterol; SBP, systolic blood pressure; SMD, standardized mean difference; TG, triglycerides; TC, total cholesterol.

Sensitivity analysis

Supplementary Table S3 shows the sensitivity analyses by the systematic removal of each trial. No one trial modified the significance, direction, or magnitude of the pooled estimates or changed the significance for heterogeneity for LDL-C, TC, HDL-C, non-HDL-C, apoB, CRP or body weight. Removal of Jenkins et al. 2011 (routine) did explain all of the heterogeneity ($I^2 = 0\%$, P-heterogeneity = 0.71) without changing the direction or significance of the effect for TG and changed the reduction in DBP from significant to non-significant. Removal of Jenkins et al. 2011 (intensive) also changed the reduction in SBP and DBP from significant to non-significant. Finally, removal of Jenkins et al. 2003a explained all of the heterogeneity ($I^2 = 0\%$, P-heterogeneity = 0.67) but did not change the direction or significance of the effect for estimated 10-year CHD risk.

Supplementary Table S4 shows the sensitivity analysis by restricting analyses to efficacy trials. Removal of the effectiveness trials (2 trial comparisons, Jenkins et al. 2011 [routine] and Jenkins et al. 2011 [intensive])¹³ resulted in a 21% reduction (MD = -0.87 mmol/L [95% CI, -1.02 to -0.73 mmol/L], $p < 0.00001$) and explained all of the heterogeneity ($I^2 = 0\%$, P-heterogeneity = 0.67) in the primary outcome, LDL-C. The evidence for heterogeneity was also explained for TC, TG, non-HDL-C, apoB, and estimated 10-year CHD risk ($I^2 = 0\%$, P-heterogeneity > 0.42) without changing the direction or significance of the effect. The reductions in SBP, DBP and CRP lost their significance.

Supplementary Table S5 shows the sensitivity analysis by restricting analyses to effectiveness trials. Removal of the efficacy trials (5 trial comparisons, Jenkins et al. 2002, Jenkins et al. 2003 a and b, and Jenkins et al. 2010 Low and High MUFA)^{8–10,12} resulted in an 11% reduction (MD = -0.50 mmol/L [95% CI, -0.61 to -0.40 mmol/L], $p < 0.00001$) and explained all of the heterogeneity ($I^2 = 0\%$, P-heterogeneity = 0.81) in the primary outcome, LDL-C. The magnitude of the effect was also changed by >10% for all outcomes except SBP and DBP with the heterogeneity explained for TC, non-HDL-C, apoB and estimated 10-year CHD risk. The reductions in TG and CRP lost their significance.

GRADE assessment

A summary of the overall quality of evidence assessment for the effect of the Portfolio dietary pattern on the outcome measures is shown in Supplemental Table S6. The certainty in the evidence was high for LDL-C, TC, TG, non-HDL-C, apoB and body weight and moderate for HDL-C, SBP, DBP, CRP and 10-year CHD risk owing to downgrades for serious imprecision.

Discussion

Our systematic review and meta-analysis included 7 controlled trial comparisons of the effect of a Portfolio dietary pattern including nuts, plant protein, viscous fibre, and plant sterols with or without MUFA on a background of an NCEP Step II diet compared with an NCEP Step II diet alone in 439 participants with hyperlipidemia over a median follow-up of 4 weeks. The combination of a Portfolio dietary pattern and NCEP Step II diet significantly lowered the primary outcome LDL-C by 17% (21% in efficacy and 12% in effectiveness trials) which is beyond that which was seen with the NCEP Step II diet alone of 10% (11% in efficacy and 3% in effectiveness trials), suggesting that the benefit of the intended combination is additive and would result in LDL-C reductions of ~27% (32% in efficacy and 15% in effectiveness trials) in clinical practice. Meaningful reductions were also seen in most of the secondary outcomes including the established alternate blood lipid targets (non-HDL-C and apoB), TC, TG, SBP/DBP, and CRP, without a change in body weight. The combined effect of the Portfolio dietary pattern on these cardiometabolic risk factors translated into a reduction in estimated 10-year CHD risk of ~13% (20% in efficacy and 9% in effectiveness trials).

Findings in the context of the literature

Our findings are supported by evidence of similar benefits for each of the 4 individual food components of the Portfolio dietary pattern. Systematic reviews and meta-analyses of randomized controlled trials have shown reductions in LDL-C of 7% for nuts at a median dose of 67 g/d,³³ 4–5% for plant proteins at median doses from ~30 g/day,^{34–36} 7% for viscous fibres at a median dose of 5–10 g/day,³⁷ and 7% for plant sterols at a dose of 2 g/day plant sterols/stanols.³⁸ The evidence for their LDL-C lowering efficacy is considered sufficiently strong that all have related FDA, Health Canada, and/or EFSA approved health claims.^{1–7} The combined effect of these 4 food components as part of the Portfolio dietary pattern resulted in the predicted additive effect on LDL-C with a 21% reduction seen in our pooled analyses of the efficacy trials.

The 4 individual food components of the Portfolio dietary pattern have also shown reductions in other blood lipids. Systematic reviews and meta-analyses of randomized controlled trials have shown beneficial effects of plant sterols,^{38,39} viscous fibres,^{37,40,41} plant proteins,³⁴ and nuts^{33,42,43} on the established alternate lipid targets, non-HDL-C and apoB, and other blood lipids including TC and TG.

Two of the components of the Portfolio dietary pattern have shown advantages for inflammation. Systematic reviews and meta-analyses of randomized controlled trials have shown that fibre inclusive of viscous fibres and plant protein reduce CRP by -0.37 mg/L and from -0.32 to -0.53 mg/L (in specific sensitivity and subgroup analyses), respectively,^{42,44–47} while nuts and plant sterols have demonstrated only a non-significant tendency for CRP reductions.⁴⁴ The combined effect of these food components as part of the Portfolio dietary pattern again resulted in the predicted additive effect on CRP with a -0.74 mg/L (-32%) reduction seen in our overall pooled analyses.

Three of the components of the Portfolio dietary pattern have shown a blood pressure lowering effect. Systematic reviews and meta-analyses of randomized controlled trials of viscous fibre^{48,49} as well as total dietary fibre (inclusive of viscous fibre)⁵⁰ and sources of plant protein including dietary pulses and soy protein, have shown reductions in SBP/DBP^{51,52}. Individual randomized controlled trials of nuts have also demonstrated significant reductions in blood pressure^{42,53}; however, systematic reviews and meta-analyses of the available randomized controlled trials have only shown non-significant reductions.⁴³ Although the combined blood pressure lowering effects of these foods as part of the Portfolio dietary pattern were found to decrease SBP/DBP by only as much as any one of these components in our pooled analyses ($-1.75/-1.36$ mm Hg), the Portfolio dietary pattern has been shown to produce similar SBP/DBP reductions to that of a Dietary Approaches to Stop Hypertension (DASH)-type diet in a direct comparison.⁵⁴

These reductions in the primary lipid target, LDL-C, and other established cardiometabolic risk factors appear to confer the expected cardiovascular benefit. Two of the components of the Portfolio dietary pattern have been shown to reduce incident CV events. Systematic reviews and meta-analyses of prospective cohort studies have shown that legumes inclusive of soy and dietary pulses are associated with reductions in incident CHD and CVD with evidence of a dose response gradient, where ≥ 4 servings (100 g) per week is associated with a ~17–22% risk reduction.^{55–57} Evidence from systematic reviews and meta-analyses of prospective cohort studies of dietary fibre inclusive of viscous fibre and nuts have also shown associations with reductions in CVD events.^{58,59} Consumption of 5 servings per week of nuts, a level similar to that recommended as part of the Portfolio dietary pattern, is associated with reductions in CHD events of 40% to 60%.^{60,61} These findings are further supported by findings from observational studies of vegetarian diets⁶² and the PREDIMED (Prevención con Dieta Mediterránea) trial which showed that a predominantly plant-based Mediterranean diet supplemented with nuts decreased major CV events by 28%.⁶³ While there is limited data on plant sterols and CHD risk, a systematic review and meta-analysis of prospective cohort studies of

the relationship between serum concentrations of two common plant sterols (sitosterol, campesterol) and CVD risk failed to show evidence of a protective association.⁶⁴

Strengths and limitations

Our systematic review and meta-analysis has several strengths. First, we employed a comprehensive and reproducible search and selection process of the literature examining the effect of the Portfolio dietary pattern on cardiometabolic risk factors. Second, we collated and synthesized the totality of the available evidence from controlled trials which provide the greatest protection against bias and start as high certainty of evidence by GRADE.³² Finally, we used the GRADE approach to assess the overall certainty of the evidence.

Several limitations also need to be considered. There was evidence of serious imprecision for HDL-C, SBP, DBP, CRP and 10-year CHD risk. As the 95% CIs of the pooled risk estimates contained the pre-specified MIDs, we could not rule out unimportant effects of the Portfolio dietary pattern on these outcomes and so downgraded the evidence for imprecision. Although we did not downgrade the evidence for serious indirectness, the concern might be raised that the trials were conducted by a single investigator group and did not include participants with diabetes. We felt that this concern was mitigated by the inclusion of a large ($n = 351$), multi-centre randomized trial that showed similar results across 4 different centres (Quebec City, Toronto, Winnipeg, and Vancouver) when the Portfolio dietary pattern was administered as dietary advice regardless of the intensity of the advice under free-living conditions.¹³ We also did not feel that there was any biological reason to believe that the dietary pattern would behave differently in people with diabetes, as each component of the Portfolio dietary pattern has been shown individually to lower LDL-C in systematic reviews and meta-analyses of randomized controlled trials inclusive of people with diabetes without any evidence of a subgroup effect by diabetes status.^{34,43,65–68} Another potential limitation was inconsistency in the treatment effects among the trials for LDL-C, TC, TG, non-HDL-C, apoB, and 10-year CHD risk. We did not downgrade the evidence for serious inconsistency, as the evidence of heterogeneity was explained in each case by our a priori sensitivity analyses in which we restricted analyses to the efficacy trials, suggesting that adherence to the components of the Portfolio dietary pattern is an important determinant of its intended benefit.

Balancing these strengths and limitations, the certainty in the evidence based on the GRADE approach was rated as high for LDL-C, TC, TG, non-HDL-C, apoB and body weight and moderate for HDL-C, SBP, DBP, CRP, and 10-year CHD risk.

Implications

Diet and lifestyle therapy remain the cornerstone of the management of dyslipidemia and CVD risk in people with and without diabetes. Our pooled analyses showed that the Portfolio dietary pattern can produce meaningful reductions in the primary lipid target for CVD prevention, LDL-C, as well the established alternate lipid targets, non-HDL-C and apoB, in people with dyslipidemia. The expected reductions of the intended combination of a Portfolio dietary pattern and NCEP Step II diet of ~27% (32% in efficacy and 15% in effectiveness trials) are similar to those seen with the starting doses of low intensity statins (18 to 28%)⁶⁷ or 10 mg of ezetimibe (15–20%).⁶⁹ These reductions would be expected to translate into meaningful reductions in CVD risk. The ~20% reduction in major cardiovascular events for every 1.0 mmol/L reduction in LDL-C seen for statin and ezetimibe therapy in individual patient level pooled analyses by the Cholesterol Treatment Trialists' (CTT) Collaboration^{70–72} are consistent with the ~13% reduction in estimated 10-year CHD risk that we saw in relation to a 0.73 mmol/L reduction in LDL-C in our overall pooled analyses. In clinical practice, the current pharmacological approach to dyslipidemia includes the use

of high intensity statins alone or in combination with ezetimibe as 1st-line therapy.¹⁹ Our data suggest that the Portfolio dietary pattern may be a useful add-on to statin therapy or statin plus ezetimibe therapy to help people achieve their lipid targets.

There may be an important opportunity for people to realize the CV benefits of a Portfolio dietary pattern. Dietary intake patterns in Canada, the United States, and Europe do not currently meet the targets for the food components of the Portfolio dietary pattern: ≥ 45 g/day nuts, ≥ 50 g/day plant protein, ≥ 20 g/day viscous fibre, and 2 g/day plant sterols.^{66,73–76} Adherence has also been directly associated with reductions in LDL-C in the available trials^{11,13} with the efficacy trials, in which adherence is $>90\%$ ^{8–10,12}, showing nearly double the reductions in LDL-C (21% versus 12%) than the effectiveness trials, in which reported adherence is $<50\%$.¹³ These data provide confirmation that the LDL-C lowering effect of 5–10%^{14–18} of each of the 4 core food components can be considered additive,^{8–13} suggesting strategies to improve the availability, accessibility, and palatability of any one or more of the different food components of the Portfolio dietary pattern may lead to important metabolic advantages and CVD risk reduction. With the continued development and marketing of plant-based foods, greater benefits are anticipated. The use of plant food components further fits with recommendations to the general public to consume more plant-based diets.

Conclusions

In conclusion, our syntheses of the available evidence from controlled trials demonstrates that the portfolio dietary pattern results in clinically meaningful reductions in the primary therapeutic lipid target for CVD prevention, LDL-C, the established alternate lipid targets, non-HDL-C and apoB, as well as other established cardiometabolic risk factors, including TG, SBP/DBP, and CRP, culminating in an improvement in estimated 10-year CHD risk. Our certainty in the evidence was generally high for the blood lipid benefits and moderate for the benefits related to other cardiometabolic risk factors and estimated 10-year CHD risk. More research is needed to improve our estimates and confirm that these benefits do translate into reductions in clinical outcomes of clinical practice and public health importance. In this regard, there remains a need for large randomized trials of the effect of the portfolio dietary pattern on hard CV outcomes or surrogate endpoints of atherosclerosis. We await the results of the enhanced Portfolio and exercise (PortfolioEx) trial, a multi-centre randomized trial of the effect of an enhanced Portfolio diet (nuts, plant protein, viscous fibre, plant sterols, heart healthy unsaturated plant oils, and low glycemic index) on the primary outcome of vascular magnetic resonance imaging of atherosclerosis (plaque volume) over 3 years in participants at high CVD risk of which ~50% will have type 2 diabetes ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02481466) identifier, NCT02481466). If the findings are positive, then the data will provide further evidence to support current recommendations to consume more plant-based dietary patterns for health benefits.

Funding statement

The Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD) commissioned this systematic review and meta-analysis and provided funding and logistical support for meetings as part of the development of the EASD Clinical Practice Guidelines for Nutrition Therapy. This work was also supported by the Canadian Institutes of Health Research (funding reference number, 129920) through the Canada-wide Human Nutrition Trialists' Network (NTN). The Diet, Digestive tract, and Disease (3-D) Centre, funded through the Canada Foundation for Innovation (CFI) and the Ministry of Research and Innovation's Ontario Research Fund (ORF), provided the infrastructure for the conduct of this project. Laura Chiavaroli was funded by a Toronto 3D Knowledge Synthesis and Clinical Trials foundation Postdoctoral Fellowship Award. David JA Jenkins was funded by the

Government of Canada through the Canada Research Chair Endowment. John L Sievenpiper was funded by a PSI Graham Farquharson Knowledge Translation Fellowship, Diabetes Canada Clinician Scientist award, CIHR INMD/CNS New Investigator Partnership Prize, and Banting & Best Diabetes Centre Sun Life Financial New Investigator Award. With the exception of the Clinical Practice Guidelines Committee of the DNSG of the EASD, none of the sponsors had a role in any aspect of the present study, including design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, approval of the manuscript or decision to publish.

Conflicts of interest

LC has worked as a clinical research coordinator at Glycaemic Index Laboratories, Toronto, Ontario, Canada. **DR** has served as principal investigator or co-investigator in clinical trials of AstraZeneca, Eli Lilly, MSD, Novo Nordisk, Sanofi Aventis, Solvay and Trophos. He received honoraria for speaking or advisory board engagements and consulting fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Lifescan – Johnson & Johnson, Novartis, Novo Nordisk, MSD, Merck Sharp & Dohme, Pfizer, Pliva, Roche, Salvus, Sanofi Aventis and Takeda. He served as a Board member and Secretary of IDF Europe in biennium 2015–2017. He is a president of Croatian Society for Diabetes and Metabolic Disorders of Croatian Medical Association, chair of IDF Young Leaders in Diabetes Programme, Executive committee member of Diabetes and Cardiovascular Disease Study Group of EASD, Croatian Endocrine Society, Croatian Society for Obesity and Croatian Society for Endocrine Oncology. **JSS** reports serving on the board of and receiving grant support through his institution from the International Nut and Dried Fruit Council, and Eroski Foundation. Reports serving in the Executive Committee of the Instituto Danone Spain. Has received research support from the Instituto de Salud Carlos III, Spain; Ministerio de Educación y Ciencia, Spain; Departament de Salut Pública de la Generalitat de Catalunya, Catalonia, Spain; European Commission. Has received research support from California Walnut Commission, Sacramento CA, USA; Patrimonio Comunal Olivarero, Spain; La Morella Nuts, Spain; and Borges S.A., Spain. Reports receiving consulting fees or travel expenses from Danone; California Walnut Commission, Eroski Foundation, Instituto Danone - Spain, Nuts for Life, Australian Nut Industry Council, Nestlé, Abbot Laboratories, and Font Vella Lanjarón. He is on the Clinical Practice Guidelines Expert Committee of the European Association for the study of Diabetes (EASD), and served in the Scientific Committee of the Spanish Food and Safety Agency, and the Spanish Federation of the Scientific Societies of Food, Nutrition and Dietetics. He is a member of the International Carbohydrate Quality Consortium (ICQC), and Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD. **DJAJ** has received research grants from Saskatchewan Pulse Growers, the Agricultural Bioproducts Innovation Program through the Pulse Research Network, the Advanced Foods and Material Network, Loblaw Companies Ltd., Unilever, Barilla, the Almond Board of California, Agriculture and Agri-food Canada, Pulse Canada, Kellogg's Company, Canada, Quaker Oats, Canada, Procter & Gamble Technical Centre Ltd., Bayer Consumer Care, Springfield, NJ, Pepsi/Quaker, International Nut & Dried Fruit (INC), Soy Foods Association of North America, the Coca-cholesterolola Company (investigator initiated, unrestricted grant), Solae, Haine Celestial, the Sanitarium Company, Orafiti, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, the Canola and Flax Councils of Canada, the Calorie Control Council (CCC), the CIHR, the Canada Foundation for Innovation and the Ontario Research Fund. He has received in-kind supplies for trial as a research support from the Almond board of California, Walnut Council of California, American Peanut Council, Barilla, Unilever, Unico, Primo, Loblaw Companies, Quaker (Pepsico), Pristine Gourmet, Bunge Limited, Kellogg Canada, WhiteWave Foods. He has been on the speaker's panel, served on the scientific advisory board and/or received travel support and/or

honoraria from the Almond Board of California, Canadian Agriculture Policy Institute, Loblaw Companies Ltd., the Griffin Hospital (for the development of the NuVal scoring system, the Coca-cholesterolola Company, EPICURE, Danone, Diet Quality Photo Navigation (DQPN), Better Therapeutics (FareWell), Verywell, True Health Initiative, Institute of Food Technologists (IFT), Saskatchewan Pulse Growers, Sanitarium Company, Orafiti, the Almond Board of California, the American Peanut Council, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, Herbalife International, Pacific Health Laboratories, Nutritional Fundamentals for Health, Barilla, Metagenics, Bayer Consumer Care, Unilever Canada and Netherlands, Solae, Kellogg, Quaker Oats, Procter & Gamble, the Coca-cholesterolola Company, the Griffin Hospital, Abbott Laboratories, the Canola Council of Canada, Dean Foods, the California Strawberry Commission, Haine Celestial, PepsiCo, the Alpro Foundation, Pioneer Hi-Bred International, DuPont Nutrition and Health, Spherix Consulting and WhiteWave Foods, the Advanced Foods and Material Network, the Canola and Flax Councils of Canada, the Nutritional Fundamentals for Health, Agri-cholesterolulture and Agri-Food Canada, the Canadian Agri-Food Policy Institute, Pulse Canada, the Saskatchewan Pulse Growers, the Soy Foods Association of North America, the Nutrition Foundation of Italy (NFI), Nutra-Source Diagnostics, the McDougall Program, the Toronto Knowledge Translation Group (St. Michael's Hospital), the Canadian College of Naturopathic Medicine, The Hospital for Sick Children, the Canadian Nutrition Society (CNS), the American Society of Nutrition (ASN), Arizona State University, Paolo Sorbini Foundation and the Institute of Nutrition, Metabolism and Diabetes. He received an honorarium from the United States Department of Agriculture to present the 2013 W.O. Atwater Memorial Lecture. He received the 2013 Award for Excellence in Research from the International Nut and Dried Fruit Council. He received funding and travel support from the Canadian Society of Endocrinology and Metabolism to produce mini cases for the Canadian Diabetes Association (CDA). He is a member of the International Carbohydrate Quality Consortium (ICQC). His wife, ALJ, is a director and partner of Glycemic Index Laboratories, Inc., and his sister received funding through a grant from the St. Michael's Hospital Foundation to develop a cookbook for one of his studies. **CWC** has received grant grants or research support from the Advanced Food Materials Network, Agriculture and Agri-Foods Canada (AAFC), Almond Board of California, American Pistachio Growers, Barilla, California Strawberry Commission, Calorie Control Council, Canadian Institutes of Health Research (CIHR), Canola Council of Canada, International Nut and Dried Fruit Council, International Tree Nut Council Research and Education Foundation, Loblaw Brands Ltd., Pulse Canada, Saskatchewan Pulse Growers and Unilever. He has received in-kind research support from the Almond Board of California, California Walnut Council, American Peanut Council, Barilla, Unilever, Unico, Primo, Loblaw Companies, Quaker (Pepsico), Pristine Gourmet, Kellogg Canada, WhiteWave Foods. He has received travel support and/or honoraria from the American Peanut Council, American Pistachio Growers, Barilla, Bayer, California Walnut Commission, Canola Council of Canada, General Mills, International Tree Nut Council, Loblaw Brands Ltd., Nutrition Foundation of Italy, Oldways Preservation Trust, Orafiti, Paramount Farms, Peanut Institute, Pulse Canada, Sabra Dipping Co., Saskatchewan Pulse Growers, Sun-Maid, Tate & Lyle, Unilever and White Wave Foods. He has served on the scientific advisory board for the International Tree Nut Council, McCormick Science Institute, Oldways Preservation Trust, Paramount Farms and Pulse Canada. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD), is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the EASD and is a Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. **JLS** has received research support from the Canadian Institutes of health Research (CIHR), Diabetes Canada, PSI Foundation, Banting and Best Diabetes Centre (BBDC), Canadian Nutrition Society (CNS), American Society for

Nutrition (ASN), Calorie Control Council, INC International Nut and Dried Fruit Council Foundation, National Dried Fruit Trade Association, The Tate and Lyle Nutritional Research Fund at the University of Toronto, The Glycemic Control and Cardiovascular Disease in Type 2 Diabetes Fund at the University of Toronto (a fund established by the Alberta Pulse Growers) and the Nutrition Trialists Fund at the University of Toronto (a fund established by the Calorie Control Council). He has received in-kind research support from the Almond Board of California, California Walnut Commission, American Peanut Council, Barilla, Unilever, Unico, Primo, Loblaw Companies, Quaker (Pepsico), Kellogg Canada, WhiteWave Foods. He has received travel support, speaker fees and/or honoraria from Diabetes Canada, Canadian Nutrition Society (CNS), Mott's LLP, Dairy Farmers of Canada, Sprim Brasil, WhiteWave Foods, Rippe Lifestyle, mdBriefcase, Alberta Milk, FoodMinds LLC, Memac Ogilvy & Mather LLC, PepsiCo, The Ginger Network LLC, International Sweeteners Association, Nestlé Nutrition Institute, Pulse Canada, Canadian Society for Endocrinology and Metabolism (CSEM), Barilla Centre for Food and Nutrition (BCFN) Foundation, and GI Foundation. He has ad hoc consulting arrangements with Winston & Strawn LLP, Perkins Coie LLP, Tate & Lyle and Wirtschaftliche Vereinigung Zucker e.V. He is a member of the European Fruit Juice Association Scientific Expert Panel. He is on the Clinical Practice Guidelines Expert Committees of Diabetes Canada, European Association for the study of Diabetes (EASD), Canadian Cardiovascular Society (CCS), and Canadian Obesity Network. He serves as an unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and the Technical Committee on Carbohydrates of the International Life Science Institute (ILSI) North America. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD, and Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. His wife is an employee of Unilever Canada. No competing interests were declared by **TAK, CRB, SKN, AJG, SBM, and HK.**

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pcad.2018.05.004>.

References

- Food Directorate Health Products and Food Branch, Health Canada. Plant sterols and blood cholesterol lowering. Ottawa: Bureau of Nutritional Sciences. 21 May 2010. Available: <https://www.canada.ca/en/health-canada/services/food-nutrition/food-labelling/health-claims/assessments/plant-sterols-blood-cholesterol-lowering-nutrition-health-claims-food-labelling.html>.
- Food Directorate, Health Products and Food Branch, Health Canada. *Summary of Health Canada's assessment of a health claim about soy protein and cholesterol lowering*. Ottawa: Bureau of Nutritional Sciences. March 2015 Available: <https://www.canada.ca/en/health-canada/services/food-nutrition/food-labelling/health-claims/assessments/summary-assessment-health-claim-about-protein-cholesterol-lowering.html>.
- Food Directorate Health Products and Food Branch, Health Canada. *Oat products and blood cholesterol lowering*. Ottawa: Bureau of Nutritional Sciences. 2010.
- Food Directorate, Health Products and Food Branch, Health Canada. *List of dietary fibres reviewed and accepted by Health Canada's Food Directorate*. Ottawa: Bureau of Nutritional Sciences. May 2017. Available: <https://www.canada.ca/en/health-canada/services/publications/food-nutrition/list-reviewed-accepted-dietary-fibres.html>.
- U.S. Food & Drug Administration. Qualified Health Claims: letter of enforcement discretion - nuts and coronary heart disease (Docket No 02P-0505). Available: <http://wayback.archive-it.org/7993/20171114183724/https://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm072926.htm> 14 July 2003.
- EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific Opinion on the substantiation of a health claim related to 3 g/day plant sterols/stanols and lowering blood LDL-cholesterol and reduced risk of (coronary) heart disease pursuant to Article 19 of Regulation (EC) No 1924/2006. *EFSA J* 2012;10(5):2693. <https://doi.org/10.2903/j.efsa.2012.2693>. Available online: www.efsa.europa.eu/efsajournal. [13 pp.].
- EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific Opinion on the substantiation of a health claim related to oat beta-glucan and lowering blood cholesterol and reduced risk of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006. *EFSA J* 2010;8(12):1885. <https://doi.org/10.2903/j.efsa.2010.1885>. Available online: www.efsa.europa.eu/efsajournal.htm [15 pp.].
- Jenkins DJ, Kendall CW, Faulkner D, et al. A dietary portfolio approach to cholesterol reduction: combined effects of plant sterols, vegetable proteins, and viscous fibers in hypercholesterolemia. *Metab Clin Exp* 2002;51:1596-1604.
- Jenkins DJ, Kendall CW, Marchie A, et al. The effect of combining plant sterols, soy protein, viscous fibers, and almonds in treating hypercholesterolemia. *Metab Clin Exp* 2003;52:1478-1483.
- 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;290:502-510.
- Jenkins DJ, Kendall CW, Faulkner DA, et al. Assessment of the longer-term effects of a dietary portfolio of cholesterol-lowering foods in hypercholesterolemia. *Am J Clin Nutr* 2006;83:582-591.
- Jenkins DJ, Chiavaroli L, Wong JM, et al. Adding monounsaturated fatty acids to a dietary portfolio of cholesterol-lowering foods in hypercholesterolemia. *CMAJ* 2010;182:1961-1967.
- 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;306:831-839.
- Olson BH, Anderson SM, Becker MP, et al. Psyllium-enriched cereals lower blood total cholesterol and LDL cholesterol, but not HDL cholesterol, in hypercholesterolemic adults: results of a meta-analysis. *J Nutr* 1997;127:1973-1980.
- Anderson JW, Allgood LD, Lawrence A, et al. Cholesterol-lowering effects of psyllium intake adjunctive to diet therapy in men and women with hypercholesterolemia: meta-analysis of 8 controlled trials. *Am J Clin Nutr* 2000;71:472-479.
- Brown L, Rosner B, Willett WW, Sacks FM. Cholesterol-lowering effects of dietary fiber: a meta-analysis. *Am J Clin Nutr* 1999;69:30-42.
- Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med* 1995;333:276-282.
- Law M. Plant sterol and stanol margarines and health. *Br Med J (Clin Res Ed)* 2000;320:861-864.
- Anderson TJ, Gregoire J, Pearson GJ, et al. 2016 Canadian cardiovascular society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol* 2016;32:1263-1282.
- Jenkins DJA, Kendall CWC, Burris L, Sievenpiper JL, Evans MF, Angl EN. The Portfolio Diet: an evidence-based eating plan for lower cholesterol. Available: https://www.ccs.ca/images/Images_2017/Portfolio_Diet_Scroll_eng.pdf 2017.
- Sievenpiper JL, Chan CB, Dworatzek PD, Freeze C, Williams SL. Nutrition therapy. *Can J Diabetes* 2018;42(Suppl 1):S64-S79.
- Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J* 2015;36:1012-1022.
- Heart UK: The cholesterol charity. Portfolio diet. 2014 Available: <https://heartuk.org.uk/cholesterol-and-diet/six-super-foods-for-lower-cholesterol/portfolio-diet>.
- Heart UK: The cholesterol charity. The portfolio diet. 2014 Available: https://heartuk.org.uk/files/uploads/documents/huk_fs_d01_theportfoliodiet.pdf.
- Higgins JP, Green S. *Cochrane handbook for systematic reviews of interventions*. Wiley Online Library. 2008.
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264-269. [w64].
- Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. *Circulation* 1991;83:356-362.
- Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol* 2002;31:140-149.
- Dersimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-188.
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Br Med J (Clin Res Ed)* 1997;315:629-634.
- Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088-1101.
- Schünemann H, Brożek J, Oxman G. *Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach*. 2013.
- Sabate J, Oda K, Ros E. Nut consumption and blood lipid levels: a pooled analysis of 25 intervention trials. *Arch Intern Med* 2010;170:821-827.
- Li SS, Blanco Mejia S, Lytvyn L, et al. Effect of plant protein on blood lipids: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc* 2017;6.
- Jenkins DJ, Mirrahimi A, Srichaikul K, et al. Soy protein reduces serum cholesterol by both intrinsic and food displacement mechanisms. *J Nutr* 2010;140:2302s-2311s.
- Ha V, Sievenpiper JL, de Souza RJ, et al. Effect of dietary pulse intake on established therapeutic lipid targets for cardiovascular risk reduction: a systematic review and meta-analysis of randomized controlled trials. *CMAJ* 2014;186:E252-E262.
- Ho HVT, Jovanovski E, Zurbau A, et al. A systematic review and meta-analysis of randomized controlled trials of the effect of konjac glucomannan, a viscous soluble fiber, on LDL cholesterol and the new lipid targets non-HDL cholesterol and apolipoprotein B. *Am J Clin Nutr* 2017;105:1239-1247.
- Abumweis SS, Barake R, Jones PJ. Plant sterols/stanols as cholesterol lowering agents: a meta-analysis of randomized controlled trials. *Food Nutr Res* 2008;52.
- Amir Shaghghi M, Abumweis SS, Jones PJ. Cholesterol-lowering efficacy of plant sterols/stanols provided in capsule and tablet formats: results of a systematic review and meta-analysis. *J Acad Nutr Diet* 2013;113:1494-1503.
- Ho HV, Sievenpiper JL, Zurbau A, et al. The effect of oat beta-glucan on LDL-cholesterol, non-HDL-cholesterol and apoB for CVD risk reduction: a systematic review and meta-analysis of randomised-controlled trials. *Br J Nutr* 2016;116:1369-1382.

41. Ho HV, Sievenpiper JL, Zurbau A, et al. A systematic review and meta-analysis of randomized controlled trials of the effect of barley beta-glucan on LDL-C, non-HDL-C and apoB for cardiovascular disease risk reduction (i-iv). *Eur J Clin Nutr* 2016;70:1239–1245.
42. Del Gobbo LC, Falk MC, Feldman R, Lewis K, Mozaffarian D. Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. *Am J Clin Nutr* 2015;102:1347–1356.
43. Blanco Mejia S, Kendall CW, Viguiliouk E, et al. Effect of tree nuts on metabolic syndrome criteria: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open* 2014;4, e004660.
44. Jiao J, Xu JY, Zhang W, Han S, Qin LQ. Effect of dietary fiber on circulating C-reactive protein in overweight and obese adults: a meta-analysis of randomized controlled trials. *Int J Food Sci Nutr* 2015;66:114–119.
45. Rocha VZ, Ras RT, Gagliardi AC, Mangili LC, Trautwein EA, Santos RD. Effects of phytosterols on markers of inflammation: a systematic review and meta-analysis. *Atherosclerosis* 2016;248:76–83.
46. Mazidi M, Rezaie P, Ferns GA, Gao HK. Impact of different types of tree nut, peanut, and soy nut consumption on serum C-reactive protein (CRP): a systematic review and meta-analysis of randomized controlled clinical trials. *Medicine* 2016;95, e5165.
47. Salehi-Abargouei A, Saraf-Bank S, Bellissimo N, Azadbakht L. Effects of non-soy legume consumption on C-reactive protein: a systematic review and meta-analysis. *Nutrition* 2015;31:631–639. (Burbank, Los Angeles County, Calif).
48. Khan K, Jovanovski E, Ho HVT, et al. The effect of viscous soluble fiber on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis* 2018;28:3–13.
49. Evans CE, Greenwood DC, Threapleton DE, et al. Effects of dietary fibre type on blood pressure: a systematic review and meta-analysis of randomized controlled trials of healthy individuals. *J Hypertens* 2015;33:897–911.
50. Hartley L, May MD, Loveman E, Colquitt JL, Rees K. Dietary fibre for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2016;1:1–58. Cd011472.
51. Jayalath VH, de Souza RJ, Sievenpiper JL, et al. Effect of dietary pulses on blood pressure: a systematic review and meta-analysis of controlled feeding trials. *Am J Hypertens* 2014;27:56–64.
52. Kou T, Wang Q, Cai J, et al. Effect of soybean protein on blood pressure in postmenopausal women: a meta-analysis of randomized controlled trials. *Food Funct* 2017;8:2663–2671.
53. Mohammadifard N, Salehi-Abargouei A, Salas-Salvado J, Guasch-Ferre M, Humphries K, Sarrafzadegan N. The effect of tree nut, peanut, and soy nut consumption on blood pressure: a systematic review and meta-analysis of randomized controlled clinical trials. *Am J Clin Nutr* 2015;101:966–982.
54. Jenkins DJ, Jones PJ, Frohlich J, et al. The effect of a dietary portfolio compared to a DASH-type diet on blood pressure. *Nutr Metab Cardiovasc Dis* 2015;25:1132–1139.
55. Zhang X, Shu XO, Gao YT, et al. Soy food consumption is associated with lower risk of coronary heart disease in Chinese women. *J Nutr* 2003;133:2874–2878.
56. 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.
57. Viguiliouk E, Blanco Mejia S, Kendall CW, Sievenpiper JL. Can pulses play a role in improving cardiometabolic health? Evidence from systematic reviews and meta-analyses. *Ann N Y Acad Sci* 2017;1392:43–57.
58. Veronese N, Solmi M, Caruso MG, et al. Dietary fiber and health outcomes: an umbrella review of systematic reviews and meta-analyses. *Am J Clin Nutr* 2018;107:436–444.
59. Mayhew AJ, de Souza RJ, Meyre D, Anand SS, Mente A. A systematic review and meta-analysis of nut consumption and incident risk of CVD and all-cause mortality. *Br J Nutr* 2016;115:212–225.
60. Hu FB, Stampfer MJ, Manson JE, et al. Frequent nut consumption and risk of coronary heart disease in women: prospective cohort study. *Br Med J (Clin Res Ed)* 1998;317:1341–1345.
61. Kris-Etherton PM, Yu-Poth S, Sabate J, Ratcliffe HE, Zhao G, Etherton TD. Nuts and their bioactive constituents: effects on serum lipids and other factors that affect disease risk. *Am J Clin Nutr* 1999;70:504s–511s.
62. Dinu M, Abbate R, Gensini GF, Casini A, Sofi F. Vegetarian, vegan diets and multiple health outcomes: a systematic review with meta-analysis of observational studies. *Crit Rev Food Sci Nutr* 2017;57:3640–3649.
63. Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;368:1279–1290.
64. Genser B, Silbernagel G, De Backer G, et al. Plant sterols and cardiovascular disease: a systematic review and meta-analysis. *Eur Heart J* 2012;33:444–451.
65. Kim SJ, de Souza RJ, Choo VL, et al. Effects of dietary pulse consumption on body weight: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2016;103:1213–1223.
66. Viguiliouk E, Stewart SE, Jayalath VH, et al. Effect of replacing animal protein with plant protein on glycemic control in diabetes: a systematic review and meta-analysis of randomized controlled trials. *Nutrients* 2015;7:9804–9824.
67. Ras RT, Geleijnse JM, Trautwein EA. LDL-cholesterol-lowering effect of plant sterols and stanols across different dose ranges: a meta-analysis of randomised controlled studies. *Br J Nutr* 2014;112:214–219.
68. Tiwari U, Cummins E. Meta-analysis of the effect of beta-glucan intake on blood cholesterol and glucose levels. *Nutrition* 2011;27:1008–1016. (Burbank, Los Angeles County, Calif).
69. Battaglia A, Donzelli A, Font M, Molteni D, Galvano A. Clinical efficacy and safety of Ezetimibe on major cardiovascular endpoints: systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2015;10, e0124587.
70. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670–1681. (London, England).
71. Fulcher J, O'Connell R, Voysey M, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015;385:1397–1405. (London, England).
72. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;372:2387–2397.
73. Mudryj AN, Aukema HM, Yu N. Intake patterns and dietary associations of soya protein consumption in adults and children in the Canadian Community Health Survey, Cycle 2.2. *Br J Nutr* 2015;113:299–309.
74. Klingberg S, Andersson H, Mulligan A, et al. Food sources of plant sterols in the EPIC Norfolk population. *Eur J Clin Nutr* 2008;62:695–703.
75. Klingberg S, Ellegard L, Johansson I, et al. Inverse relation between dietary intake of naturally occurring plant sterols and serum cholesterol in northern Sweden. *Am J Clin Nutr* 2008;87:993–1001.
76. Jenkins DJ, Kendall CW, Popovich DG, et al. Effect of a very-high-fiber vegetable, fruit, and nut diet on serum lipids and colonic function. *Metab Clin Exp* 2001;50:494–503.