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Meta-analyses

Effect of vegetarian dietary patterns on cardiometabolic risk factors in diabetes: A systematic review and meta-analysis of randomized controlled trials

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SUMMARY

Background & aims: To summarize the evidence for the effect of vegetarian dietary patterns on glycemic control and other established cardiometabolic risk factors in individuals with diabetes, we conducted a systematic review and meta-analysis of randomized controlled trials.

Methods: We searched MEDLINE, EMBASE, and Cochrane databases through February 26, 2018 for randomized controlled trials ≥3 weeks assessing the effect of vegetarian dietary patterns in individuals with diabetes. The primary outcome was HbA_{1c}. Secondary outcomes included other markers of glycemic control, blood lipids, body weight/adiposity, and blood pressure. Two independent reviewers extracted relevant data and assessed risk of bias. Data were pooled by the generic inverse variance method and expressed as mean differences (MD) with 95% CIs. Heterogeneity was assessed (Cochran Q statistic) and quantified (I^2 statistic). The overall certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Results: Nine trials (n = 664 participants) met the eligibility criteria. Vegetarian dietary patterns significantly lowered HbA_{1c} (MD = −0.29% [95% CI: −0.45, −0.12%]), fasting glucose (MD = −0.56 mmol/L [95% CI: −0.99, −0.13 mmol/L]), LDL-C (MD = −0.12 mmol/L [95% CI: −0.20, −0.04 mmol/L]), non-HDL-C (MD = −0.13 mmol/L [95% CI: −0.26, −0.01 mmol/L]), body weight (MD = −2.15 kg [95% CI: −2.95, −1.34 kg]), BMI (MD = −0.74 kg/m^2 [95% CI: −1.09, −0.39 kg/m^2]) and waist circumference (MD = −2.86 cm [95% CI: −3.76, −1.96 cm]). There was no significant effect on fasting insulin, HDL-C, triglycerides or blood pressure. The overall certainty of evidence was moderate but was low for fasting insulin, triglycerides and waist circumference.

Abbreviations: ESM, electronic supplementary material; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MD, mean difference.

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0261-5614/

Conclusion: Vegetarian dietary patterns improve glycemic control, LDL-C and non-HDL-C, body weight/adiposity in individuals with diabetes, supporting their inclusion for diabetes management. More research is needed to improve our confidence in the estimates.
ClinicalTrials.gov identifier: NCT02600377.

1. Introduction

Diet and lifestyle are the cornerstone of diabetes management [1–3]. Vegetarian dietary patterns, which are characterized by the omission of some or all animal products, have shown a wide range of health benefits. Several prospective cohort studies, many of which were conducted in Adventist populations, show that consuming a vegetarian dietary pattern is associated with a lower risk of type 2 diabetes [4–6], coronary heart disease [7–9], obesity [8,10], hypertension [11–13], cardiovascular mortality [14,15] and all-cause mortality [14]. These findings are consistent with several systematic reviews and meta-analyses of controlled trials which show vegetarian dietary patterns improve glycemic control [16], blood lipids [17], body weight [18,19] and blood pressure [20] in individuals with different metabolic phenotypes. Furthermore, systematic reviews and meta-analyses of prospective cohort studies show that increased consumption of red or processed meat is associated with an increased risk of type 2 diabetes [21–23], coronary heart disease [24], hypertension [25], stroke [24,26,27], cardiovascular mortality [28], and all-cause mortality [28,29].

Despite this evidence for benefit, diabetes guidelines vary in their recommendations for the use of vegetarian dietary patterns in diabetes management. Although the American Diabetes Association (ADA) and Diabetes Canada guidelines include recommendations for vegetarian dietary patterns for diabetes management [3,30], the evidence ratings for these recommendations indicate that further research is required [3,30], whereas the European Association for the Study of Diabetes (EASD) guidelines have not made any specific recommendations for vegetarian dietary patterns [31].

To update the recommendations for the role of vegetarian dietary patterns among other dietary patterns in the management of diabetes, the Diabetes and Nutrition Study Group (DNSG) of the EASD commissioned a series systematic review and meta-analyses using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. The present systematic review and meta-analysis using GRADE was conducted to address the question of whether the available evidence from randomized controlled trials of vegetarian dietary patterns in comparison with non-vegetarian dietary patterns shows advantages for glycemic control and other established cardiometabolic risk factors in individuals with diabetes.

2. Methods

We followed the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) for the planning and conduct of this meta-analysis [32]. Reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [33] (ESM Table 1). The study protocol was registered at ClinicalTrials.gov (identifier, NCT02600377).

2.1. Data sources

We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials through February 26, 2018 using a search strategy based on the PICO framework [34] (ESM Table 2). Manual searches of reference lists from included trials supplemented the electronic database searches.

2.2. Study selection

We included randomized controlled trials of ≥3 weeks follow-up duration comparing the effect of vegetarian dietary patterns (including vegan to lacto-ovo-vegetarian) with non-vegetarian dietary patterns on glycemic control and other established cardiometabolic risk factors in individuals with diabetes. No restrictions were placed on language. Studies were excluded if they were non-randomized, <3 weeks follow-up duration, no vegetarian intervention, no non-vegetarian control, or no suitable outcome data.

2.3. Data extraction

Two investigators (EV and VLC, SBM or SES) independently reviewed and extracted relevant data from each included report. A standardized form was used to extract data on sample size, participant characteristics, study setting and design, level of feeding control, intervention and control arm, macronutrient composition of diets, energy balance, follow-up duration, funding source and outcome data. Authors were contacted for missing outcome data [35]. All discrepancies and disagreements were resolved through consensus.

2.4. Risk of bias assessment

Included trials were independently assessed for risk of bias using the Cochrane Risk of Bias Tool [32]. Assessment was done across 5 domains of bias (sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting). The 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). All discrepancies and disagreements were resolved through consensus or where necessary by a third author.

2.5. Outcomes

The primary outcome was HbA_{1c}. Secondary outcomes included other markers of glycemic control (fasting glucose and insulin), blood lipids (LDL-C, non-HDL-C, HDL-C, triglycerides), body weight/adiposity (body weight, BMI, waist circumference), and blood pressure (systolic and diastolic blood pressure). When non-HDL-C values were not reported, they were derived by subtracting HDL-C from total cholesterol values with SDs derived from HDL-C and total cholesterol variance data using the variance sum law [36]. Mean differences (MDs) between the intervention and control arm and respective standard errors were extracted for each trial. If these were not provided they were derived from available data using published formulas [32]. MDs for change-from-baseline values were preferred over end values. If median data was provided they

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were converted to mean data using methods developed by Luo et al. [37].

2.6. Data syntheses

Primary analyses were conducted using Review Manager (RevMan), version 5.3 (Copenhagen, Denmark). Subgroup analyses and publication bias were conducted using STATA software, version 13.0 (College Station, TX, USA). Data were expressed as mean differences (MD) with 95% CIs and pooled using the generic inverse variance method with random effects models. Fixed effects model were used when data from <5 trials were available. Paired analyses were conducted for crossover trials [38] using a correlation coefficient of 0.5. To mitigate a unit-of-analysis error, the arms of trials with multiple intervention or control arms were combined to create a single pairwise comparison. Heterogeneity was assessed using the Cochran Q-statistic and quantified using the I^2-statistic. Significance for heterogeneity was set at $P < 0.10$ with an $I^2 > 50\%$ considered to be evidence of substantial heterogeneity [32]. Sources of heterogeneity were explored using sensitivity and subgroup analyses. Sensitivity analyses were performed in which each individual trial was removed from the meta-analysis and the effect size recalculated to determine whether a single trial exerted an undue influence. Sensitivity analyses were also performed using correlation coefficients of 0.25 and 0.75 to determine whether the overall results were robust to the use of different correlation coefficients in crossover trials. A post-hoc sensitivity analysis for HDL-C was conducted in which analyses were restricted to trials with <5% energy (E) difference in total fat between the intervention and control arms. If ≥10 trials were available, then *a priori* subgroup analyses were conducted using meta-regression by baseline values, study design, follow-up, comparator arm, risk of bias and diabetes duration [39,40]. If ≥10 trials were available, then we also assessed publication bias by visual inspection of funnel plots and formal testing by the Egger and Begg tests [32,41].

2.7. Grading of the evidence

The GRADE approach was used to assess the certainty of the evidence [42–54]. Evidence was graded as high, moderate, low, or very low quality. Randomized controlled trials started at high quality by default and were downgraded based on the following pre-specified criteria: risk of bias (weight of trials showing risk of bias by the Cochrane Risk of Bias Tool), inconsistency (substantial unexplained inter-study heterogeneity, $I^2 > 50\%$ and $P < 0.10$), indirectness (presence of factors that limit the generalizability of the results), imprecision (the 95% CI for effect estimates were wide or cross minimally important differences [MIDs] for benefit or harm), and publication bias (significant evidence of small-study effects).

3. Results

3.1. Search results

Figure 1 shows the literature search and selection process. We identified a total of 6498 reports, 6395 of which were excluded based on review of titles and/or abstracts. The remaining 103 reports were retrieved and reviewed in full, of which 94 were excluded. A total of 9 reports containing data for 9 trial comparisons involving 664 participants with diabetes met the eligibility criteria and were included in the final analyses [35,55–62].

3.2. Trial characteristics

Table 1 shows the characteristics of the 9 included trials. All trials were conducted in outpatient settings, with more than half conducted in the United States [56,57,59,60,62] and one each in Greece [55], Brazil [58], Czech Republic [35], and Korea [61]. Trials had a median follow-up duration of 12 weeks (range: 4–74 weeks), an approximately equal distribution of men and women (median % women: 53%, range: 18–83%), and more than half used a parallel design (6 trials). Most participants had type 2 diabetes (99%), were middle-aged (median age: 56 years, range: 32–61 years), overweight or obese (median BMI: 34 kg/m^2, range: 23–35 kg/m^2) and some or most were taking oral antihyperglycemic agents [35,56–62], insulin [55,56,58,59,61], lipid-lowering agents [35,56,57,59–62], and/or antihypertensive agents [35,56–61]. Mean diabetes duration varied from 7 to 9.5 years [57,59,61] for those with type 2 diabetes and before the onset of 30 years of age for those with type 1 diabetes [55], otherwise it was unspecified [35,56,58,60,62]. Median baseline (range) values for each outcome were as follow: HbA_{1c}, 7.6% (6.7–8.2%); fasting glucose, 8.5 mmol/L (7.0–10.3 mmol/L); fasting insulin, 105 pmol/L (not applicable); LDL-C, 2.7 mmol/L (1.9–3.4 mmol/L); HDL-C, 1.2 mmol/L (0.9–1.5 mmol/L); non-HDL-C, 3.7 mmol/L (2.6–4.3 mmol/L); triglycerides, 1.7 mmol/L (1.4–2.2 mmol/L); body weight, 97.5 kg (96.5–102.3 kg); BMI, 34.4 kg/m^2 (23.5–35.1 kg/m^2); waist circumference, 111.6 cm (83.7–113.8 cm); systolic blood pressure, 130.1 mmHg (123.4–145 mmHg); and diastolic blood pressure, 82.0 mmHg (76.9–85 mmHg).

Macronutrient composition of the intervention and control arms varied across trials. Across intervention arms, the median (range) intake values reported were: carbohydrate, 60% E (49–77.5% E); protein, 15% E (12–17% E); fat, 25% E (10–34% E); saturated fat, 5.1% E (1.6–8.8% E); and fiber, 28.3 g/d (12.6–39 g/d), and across control arms they were: carbohydrate, 50% E (41–65% E), protein, 19% E (16–21.5% E), fat, 30% E (19–37% E), saturated fat, 8.5% E (4.4–11.6% E); and fiber, 20 g/d (7.7–39 g/d). For the purpose of dietary recommendations, we rescaled the macronutrient composition for those trials whose macronutrients did not sum to 100%, which resulted in the following mean macronutrient compositions across intervention arms – 62:14:23 and across control arms – 50:19:31 (carbohydrate:protein:fat, %). Feeding control varied across trials: metabolic control (2 trials), supplemental control (2 trials) and dietary advice (4 trials); otherwise it was unspecified (1 trial). Four trials had a neutral energy balance [55,57,58,60], 1 trial had a negative energy balance [35]and the remainder of the trials were not designed to be isocaloric [56,59,61,62]. The majority of trials were funded by some form of agency or agency alone (8 trials) or it was unspecified (1 trial).

3.3. Risk of bias

ESM Figs. 1–5 show the summary and individual Cochrane Risk of Bias assessments of the included trials. The majority of trials were judged as having unclear or low risk of bias across domains.

3.4. Effect of vegetarian dietary patterns on glycemic control

3.4.1. HbA_{1c}

Figure 2 and ESM Fig. 2a show the effect of vegetarian dietary patterns on HbA_{1c}. In 8 trials involving 378 participants with type 1 diabetes (n = 9) and type 2 diabetes (n = 369), a significant reduction in HbA_{1c} was observed compared to control diets (MD = −0.29% [95% CI: −0.45, −0.12%], P = 0.0006) with no evidence of inter-study heterogeneity (I^2 = 14%, P = 0.32).

3.4.2. Fasting glucose

Figure 2 and ESM Fig. 2b show the effect of vegetarian dietary patterns on fasting glucose. In 6 trials involving 313 participants with type 2 diabetes, a significant reduction in fasting glucose was observed compared to control diets (MD = −0.56 mmol/L [95%

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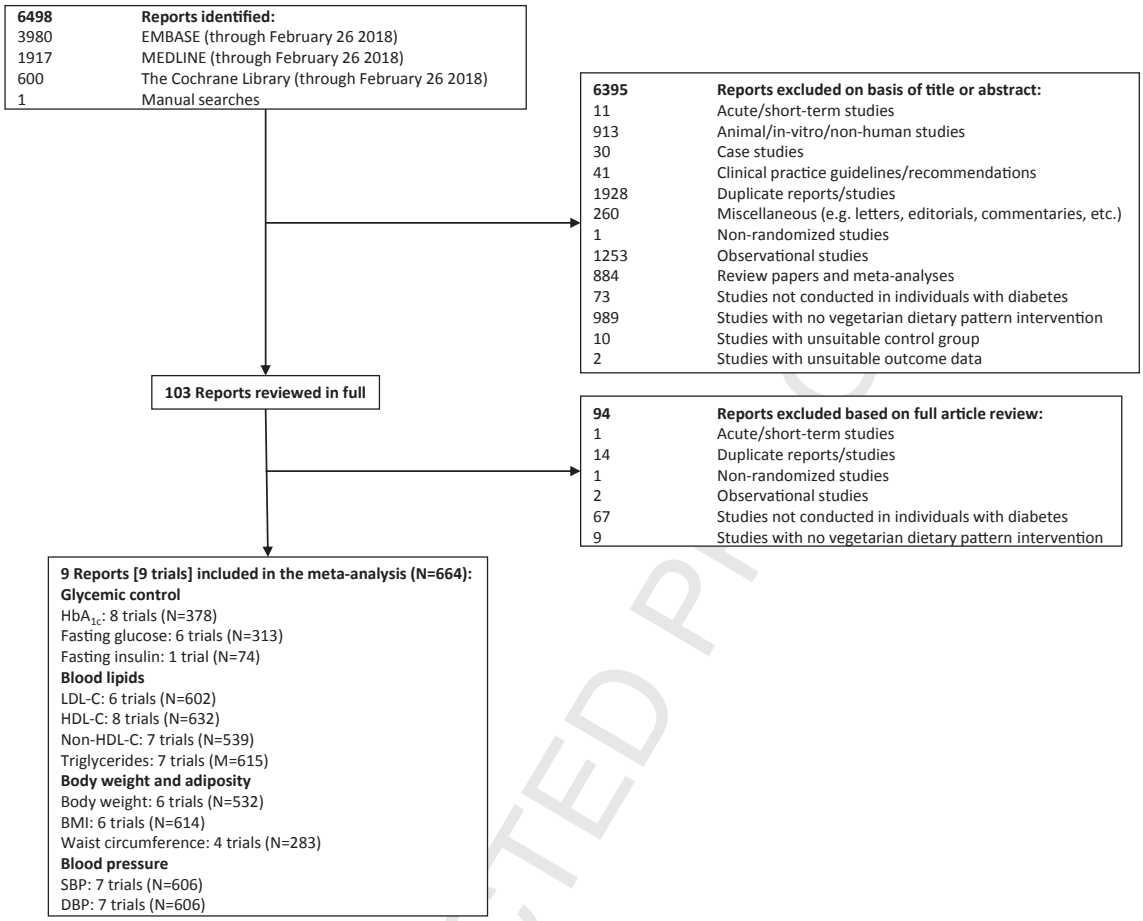

Fig. 1. Flow of the literature for the effect of vegetarian dietary patterns on cardiometabolic risk factors in diabetes. DBP = diastolic blood pressure; SBP = systolic blood pressure.

CI: −0.99, −0.13 mmol/L], P = 0.01) with no evidence of inter-study heterogeneity (I^2 = 0%, P = 0.56). The trial by Kontessis et al. [55], which met the inclusion criteria, was not included in the primary analysis due to implausible variance data that could not be verified with the study authors. Omission of this trial did not alter the direction or significance of the pooled effect estimate or the evidence of inter-study heterogeneity.

3.4.3. Fasting insulin

Only one trial reported data for fasting insulin, which showed vegetarian dietary patterns did not significantly alter fasting insulin compared to the control diet (MD = −7.92 pmol/L [95% CI: −27.92, 12.08 pmol/L], P = 0.44) in 74 participants with type 2 diabetes [35].

3.5. Effect of vegetarian dietary patterns on blood lipids

3.5.1. LDL-C

Figure 2 and ESM Fig. 3a show the effect of vegetarian dietary patterns on LDL-C. In 6 trials involving 602 participants with type 2 diabetes, a significant reduction in LDL-C was observed compared to control diets (MD = −0.12 mmol/L [95% CI: −0.20, −0.04 mmol/L], P = 0.002) with no evidence of inter-study heterogeneity (I^2 = 0%, P = 0.54).

3.5.2. HDL-C

Figure 2 and ESM Fig. 3b show the effect of vegetarian dietary patterns on HDL-C. In 8 trials involving 632 participants with type 2 diabetes, vegetarian dietary patterns did not significantly alter HDL-C compared to control diets (MD = −0.03 mmol/L [95% CI: −0.08, 0.02 mmol/L], P = 0.19) with evidence of substantial inter-study heterogeneity (I^2 = 66%, P = 0.004).

3.5.3. Non-HDL-C

Figure 2 and ESM Fig. 3c show the effect of vegetarian dietary patterns on non-HDL-C. In 7 trials involving 539 participants with type 2 diabetes, a significant reduction in non-HDL-C was observed compared to control diets (MD = −0.13 mmol/L [95% CI: −0.26, −0.01 mmol/L], P = 0.03) with no evidence of inter-study heterogeneity (I^2 = 0%, P = 0.44).

3.5.4. Triglycerides

Figure 2 and ESM Fig. 3d show the effect of vegetarian dietary patterns on triglycerides. In 7 trials involving 615 participants with type 2 diabetes, vegetarian dietary patterns did not significantly alter triglycerides compared to control diets (MD = 0.14 mmol/L [95% CI: −0.10, 0.38 mmol/L], P = 0.26) with evidence of substantial inter-study heterogeneity (I^2 = 71%, P = 0.002).

3.6. Effect of vegetarian dietary patterns on body weight and adiposity

3.6.1. Body weight

Figure 2 and ESM Fig. 4a show the effect of vegetarian dietary patterns on body weight. In 6 trials involving 532 participants with type 2 diabetes, a significant reduction in body weight was observed compared to control diets (MD = −2.15 kg [95%

Table 1
Trial characteristics.

Study, year [Reference]	Participants	Age,[a] *y*	Baseline BMI or body weight[a,b]	Setting[c]	Design	Feeding control[d]	Intervention diet	Control diet	Macronutrient composition (CHO:PRO:FAT)[e], *%E*	Energy balance[f]	Follow-up duration, *wks*	Funding sources[g]
Kontessis et al. 1995	9 T1DM (7W, 2M)	32 (20–48)[h]	23.8 (20.6–27.8) kg/m^2[h]	OP, GRC	C	NR				Neutral	4	NR
Intervention							Vegetable protein diet		~49:17:34			
Control								Animal protein diet	~41:19:37			
Nicholson et al. 1999	11 T2DM (5W, 6M)			OP, USA	P	Supp				Neutral[i]	12	Agency
Intervention	7 (3W, 4M)	51 (34–62)	96.7 (13.3) kg				Low-fat vegan diet		75:14:11			
Control	4 (2W, 2M)	60 (51–74)	97.0 (22.9) kg					Conventional low-fat diet	51:18:31			
Wheeler et al. 2002	17 T2DM (3W, 14M)	56 (12.4)	33.1 (5.8) kg/m^2	OP, USA	C	Met				Neutral	6	Agency-Industry
Intervention							Plant-based protein diet		53:17:30			
Control								Animal-based protein diet	53:17:30			
de Mello et al. 2006	17 T2DM (3W, 14M)	59 (11)	26.2 (2.6) kg/m^2	OP, BRA	C	DA				Neutral	4	Agency
Intervention							Lacto-vegetarian low-protein diet		59:12:30			
Control								Usual diet	47:22:31			
Control								Usual diet + all meat replaced with chicken	50:21:29			
Barnard et al. 2009	99 T2DM (60W, 39M)			OP, USA	P	DA				Neutral[j]	74	Agency
Intervention	49 (27W, 22M)	56.7 (9.8)	33.9 (7.8) kg/m^2				Low-fat vegan diet		66:15:22			
Control	50 (33W, 17M)	54.6 (10.2)	35.9 (7.0) kg/m^2					Conventional diabetes diet (2003 ADA)	47:21:34			
Kahleova et al. 2011	74 T2DM (39W, 25M)			OP, CZE	P	Met				Negative	24	Agency
Intervention	37 (20W, 17M)	54.6 (7.8)	35.1 (6.1) kg/m^2				Vegetarian diet		60:15:25			
Control	37 (19W, 18M)	57.7 (4.9)	35.0 (4.6) kg/m^2					Conventional diabetes diet (DNSG of the EASD)	50:20:30			
Mishra et al. 2013	291 T2DM (242W, 50M)			OP, USA	P	Supp				Neutral[k]	18	Agency
Intervention	142 (110W, 32M)	44.3 (15.3)	34.7 (7.1) kg/m^2				Low-fat vegan diet		57:15:31			
Control	149 (132W, 18M)	46.1 (13.6)	35.3 (8.5) kg/m^2					Usual diet	48:17:37			
Lee et al. 2016[l]	106 T2DM			OP, KOR	P	DA				Neutral[m]	12	Agency
Intervention	53	57.5 (7.7)	23.9 (3.4) kg/m^2				Vegan diet		72:14:19			
Control	53	58.3 (7.0)	23.1 (2.4) kg/m^2					Conventional diabetes diet (2011 KDA)	65:16:19			

(*continued on next page*)

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Table 1 (*continued*)

Study, year [Reference]	Participants	Age,[a] *y*	Baseline BMI or body weight[a,b]	Setting[c]	Design	Feeding control[d]	Intervention diet	Control diet	Macronutrient composition (CHO:PRO:FAT)[e], *%E*	Energy balance[f]	Follow-up duration, *wks*	Funding sources[g]
Barnard et al. 2018	40 T2DM			OP, USA	P	DA				Neutral[n]	20	Agency
Intervention	19	61 (41–79)	34.9 (6.54) kg/m^2				Low-fat, low glycemic index vegan diet		78:13:10			
Control	21	61 (30–75)	33.0 (5.96) kg/m^2					Portion-controlled diet	50:21:30			

ADA = American Diabetes Association; C = crossover; CHO = carbohydrate; DA = dietary advice; DNSG = Diabetes and Nutrition Study Group; EASD = European Association for the Study of Diabetes; KDA = Korean Diabetes Association; M = men; Met = metabolic feeding control; OP = outpatient; NR = not reported; P = parallel; PRO = protein; Supp = supplemental feeling control; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; W = women; wks = weeks; y = years; %E = percent energy.

[a] Values reported as mean (SD or range).

[b] Baseline body weight values are only reported when no data on BMI were available.

[c] Countries are abbreviated using ISO 3166-1 alpha-3 codes (three letter country codes defined in ISO 3166-1).

[d] Metabolic feeding control (Met) is the provision of all meals and foods consumed during the study under controlled conditions. Supplemental feeding control (Supp) is the provision of some meals and foods consumed during the study. Dietary advice (DA) is the provision of counseling on the appropriate intervention and control diets.

[e] Planned macronutrient composition of intervention and control diets. End of study values measuring energy from carbohydrates, fat and protein are reported only if the study did not report or design diets to have a planned macronutrient composition. Numbers preceded by "~" were calculated using relevant data provided by the study.

[f] Negative energy balance refers to a deficit in normal energy intake and/or intake below energy requirements. Neutral energy balance refers to the maintenance of usual energy intake and/or meeting energy requirements. Positive energy balance refers to consuming additional energy (kcal) above what is normally consumed and/or intake above energy requirements.

[g] Agency funding is that from government, university, or not-for-profit sources. Industry funding is that from trade organizations that obtain revenue from the sale of products.

[h] Reported as median (range).

[i] Study explicitly stated that the intervention and control diet were not designed to be isocaloric given that the vegan diet was much lower in fat.

[j] Participants in the intervention arm had no restriction on energy intake. Participants in the control arm with a BMI > 25 kg/m^2 were prescribed energy deficits of 500–1000 kcal.

[k] Participants in the intervention arm had no restriction on energy intake. Participants in the control arm made no dietary changes and were given no dietary guidance.

[l] All data reported in this table are based on n = 93 (completers).

[m] Participants in the intervention arm had no restriction on energy intake. Participants in the control arm were asked to restrict their individualized daily energy intake based on body weight, physical activity, need for weight control, and compliance.

[n] Participants in the intervention arm had no restriction on energy intake. Participants in the control arm were prescribed energy limits needed for weight loss (typically a deficit of 500 calories/day).

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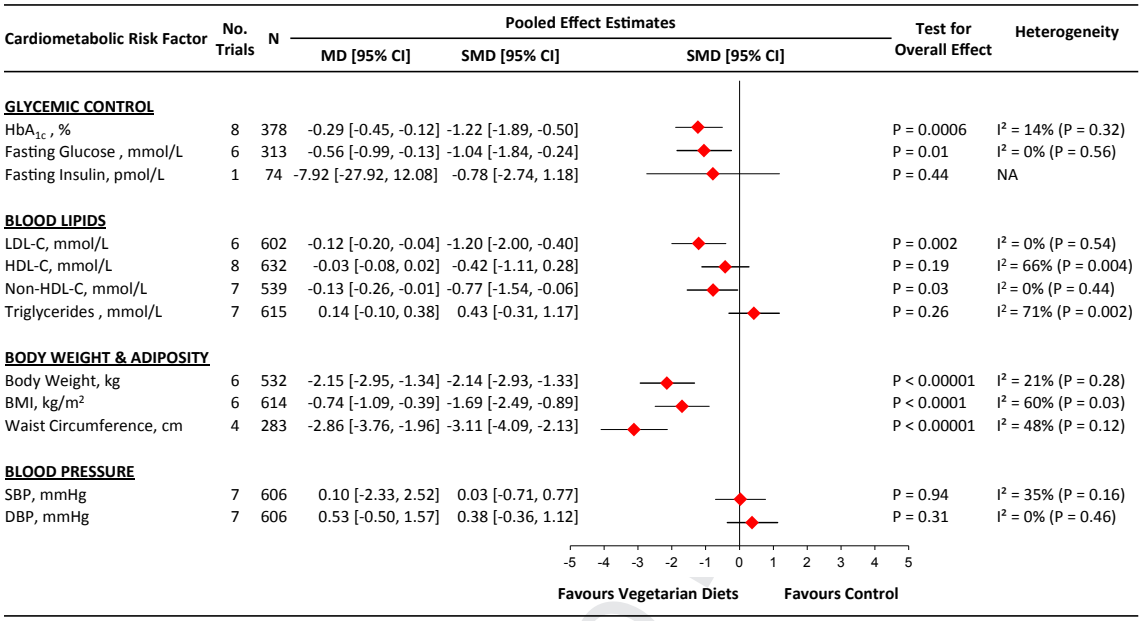

Fig. 2. Forest plot of pooled effect estimates of the effect of vegetarian dietary patterns on cardiometabolic risk factors in diabetes in randomized controlled trials. Data are expressed as weighted mean differences with 95% CIs using the generic inverse-variance method modeled by random effects (≥5 trials available) or fixed effects (<5 trials available). To allow the pooled effect estimates for each end point to be displayed on the same axis, mean differences were transformed to standardized mean differences (SMDs). Pseudo-95% CIs for each transformed SMD were derived directly from the original mean difference and 95% CI. Paired analyses were applied to all crossover trials. Inter-study heterogeneity was tested by the Cochran Q-statistic and quantified by I^2 at a significance level of $P < 0.10$. DBP = diastolic blood pressure; MD = mean difference; N = number of participants; NA = not applicable; SBP = systolic blood pressure; SMD = standardized mean difference.

CI: −2.95, −1.34 kg], $P < 0.00001$) with no evidence of inter-study heterogeneity ($I^2 = 21\%$, $P = 0.28$).

3.6.2. BMI

Figure 2 and ESM Fig. 4b show the effect of vegetarian dietary patterns on BMI. In 6 trials involving 614 participants with type 2 diabetes, a significant reduction in BMI was observed compared to control diets (MD = −0.74 kg/m^2 [95% CI: −1.09, −0.39 kg/m^2], $P < 0.0001$) with evidence of substantial inter-study heterogeneity ($I^2 = 60\%$, $P = 0.03$).

3.6.3. Waist circumference

Figure 2 and ESM Fig. 4c show the effect of vegetarian dietary patterns on waist circumference. In 4 trials involving 283 participants with type 2 diabetes, a significant reduction in waist circumference was observed compared to control diets (MD = −2.86 cm [95% CI: −3.76, −1.96 cm], $P < 0.00001$) with no evidence of inter-study heterogeneity ($I^2 = 48\%$, $P = 0.12$).

3.7. Effect of vegetarian dietary patterns on blood pressure

3.7.1. Systolic blood pressure

Figure 2 and ESM Fig. 5a show the effect of vegetarian dietary patterns on systolic blood pressure. In 7 trials involving 606 participants with type 2 diabetes, vegetarian dietary patterns did not significantly alter systolic blood pressure compared to control diets (MD = 0.10 mmHg [95% CI: −2.33, 2.52 mmHg], $P = 0.94$) with no evidence of inter-study heterogeneity ($I^2 = 35\%$, $P = 0.16$).

3.7.2. Diastolic blood pressure

Figure 2 and ESM Fig. 5b show the effect of vegetarian dietary patterns on diastolic blood pressure. In 7 trials involving 606 participants with type 2 diabetes, vegetarian dietary patterns did not significantly alter diastolic blood pressure compared to control diets (MD = 0.53 mmHg [95% CI: −0.50, 1.57 mmHg], $P = 0.31$) with no evidence of inter-study heterogeneity ($I^2 = 0\%$, $P = 0.46$).

3.8. Sensitivity and subgroup analyses

ESM Table 3 shows select sensitivity analyses in which systematic removal of individual trials altered the results. The significance was lost for fasting glucose by the removal of Lee et al. [61], LDL-C by the removal of Mishra et al. [60], and non-HDL by the removal of several trials [35,57–60], although the pooled effect estimates still favored vegetarian dietary patterns in all cases. For triglycerides the removal of Kahleova et al. [35] changed the pooled effect estimate from non-significant to a significant increase. The evidence of substantial heterogeneity for BMI was partially explained by the removal of Mishra et al. [60] and fully explained by the removal of Lee et al., 2016 [61]. For waist circumference removal of Barnard et al. [59] changed the heterogeneity from non-significant to significant.

ESM Table 4 shows sensitivity analyses in which we used different correlation coefficients (0.25 and 0.75) for paired analyses of crossover trials. Neither of the correlation coefficients altered the significance of the pooled effect estimates or the evidence for heterogeneity for any outcome, with the exception of waist circumference, where a 0.75 correlation coefficient changed the heterogeneity from non-significant to significant.

Post hoc sensitivity analyses for HDL-C in which analyses were restricted to trials with <5% energy difference in total fat between the intervention and control arms [57,58,61] decreased the evidence for heterogeneity (residual $I^2 = 0\%$, $P = 0.54$) without altering the results (MD = 0.04 mmol/L [95% CI: −0.01, 0.00 mmol/L], $P = 0.15$).

Subgroup analyses were not conducted for any outcome as <10 trials were available.

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Table 2
GRADE assessments.

Quality assessment*							Effect	Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MD [95% CIs]	
Glycemic control								
HbA_{1c}, %								
8	Randomized trials	Not serious[a]	Not serious	Not serious	Serious[b]	None	−0.29 [−0.45, −0.12]	⊕⊕⊕◯ Moderate
Fasting glucose, mmol/L								
6	Randomized trials	Not serious	Not serious	Not serious	Serious[c]	None	−0.56 [−0.99, −0.13]	⊕⊕⊕◯ Moderate
Fasting insulin, pmol/L								
1	Randomized trials	Not serious	Not serious[d]	Serious[e]	Serious[f]	None	−7.92 [−27.92, 12.08]	⊕⊕◯◯ Low
Blood lipids								
LDL-C, mmol/L								
6	Randomized trials	Not serious	Not serious	Not serious	Serious[g]	None	−0.12 [−0.20, −0.04]	⊕⊕⊕◯ Moderate
HDL-C, mmol/L								
8	Randomized trials	Not serious	Serious[h]	Not serious	Not serious	None	−0.03 [−0.08, 0.03]	⊕⊕⊕◯ Moderate
Non-HDL-C, mmol/L								
7	Randomized trials	Not serious	Not serious	Not serious	Serious[i]	None	−0.13 [−0.26, −0.01]	⊕⊕⊕◯ Moderate
Triglycerides, mmol/L								
7	Randomized trials	Not serious	Serious[j]	Not serious	Serious[k]	None	0.14 [−0.10, 0.38]	⊕⊕⊕◯ Low
Body weight & adiposity								
Body weight, kg								
6	Randomized trials	Not serious	Not serious	Serious[l]	Not serious	None	−2.15 [−2.95, −1.34]	⊕⊕⊕◯ Moderate
BMI, kg/m^2								
6	Randomized trials	Not serious	Not serious[m]	Serious[l]	Not serious	None	−0.74 [−1.09, −0.39]	⊕⊕⊕◯ Moderate
Waist circumference, cm								
4	Randomized trials	Not serious	Not serious	Serious[l]	Serious[n]	None	−2.86 [−3.76, −1.96]	⊕⊕⊕◯◯ Low
Blood pressure								
SBP and DBP, mmHg[o]								
7	Randomized trials	Not serious	Not serious	Not serious	Serious[p]	None	SBP: 0.10 [−2.33, 2.52] DBP: 0.53 [−0.50, 1.57]	⊕⊕⊕◯ Moderate

DBP = diastolic blood pressure; MD = mean difference; SBP = systolic blood pressure.

*Since all included studies were randomized controlled trials, the certainty of the evidence was graded as high for all outcomes by default and then downgraded based on pre-specified criteria. Risk of Bias − Downgraded if the majority of studies were considered to be at high risk of bias. Inconsistency − Downgraded if there was substantial unexplained heterogeneity ($I^2 > 50\%$, $P < 0.10$) that was unexplained by any *a priori* sensitivity or subgroup analyses. Indirectness − Downgraded if there were factors present relating to the participants, interventions, or outcomes that limited the generalizability of the results. Imprecision − Downgraded if the 95% confidence interval (95% CI) crossed the minimally important difference (MID) for benefit or harm. MIDs used for each outcome were: 0.3% for HbA_{1c} [70], 0.5 mmol/L for fasting glucose, 5 pmol/L for fasting insulin, 0.1 mmol/L for blood lipids, 0.5 kg for body weight [81], 0.2 kg/m^2 for BMI, 2 cm for waist circumference, and 2 mmHg for blood pressure.

[a] No serious risk of bias for the effect of vegetarian dietary patterns on HbA_{1c} even though two trials [56,59] contributing 25% weight were high risk for attrition bias (incomplete outcome data) and one trial [61] contributing 37% weight was high risk for selection (allocation concealment) and performance bias (blinding of participants and personnel).

[b] Serious imprecision for the effect of vegetarian dietary patterns on HbA_{1c}, as the 95% CIs (−0.45, −0.12%) overlap with the minimally important difference for clinical benefit (−0.3%).

[c] Serious imprecision for the effect of vegetarian dietary patterns on fasting glucose, as the 95% CIs (−0.99, −0.13 mmol/L) overlap with the minimally important difference for clinical benefit (−0.5 mmol/L).

[d] Not able to assess inconsistency for fasting insulin as only 1 trial was available for inclusion.

[e] Serious indirectness for the effect of vegetarian dietary patterns on fasting insulin, as only 1 trial in 74 participants with type 2 diabetes was available for analysis (Kahleova et al., 2011).

[f] Serious imprecision for the effect of vegetarian dietary patterns on fasting insulin, as the 95% CIs (−27.92, 12.08 pmol/L) include the minimally important difference for both clinically important benefit (−5 pmol/L) and harm (5 pmol/L).

[g] Serious imprecision for the effect of vegetarian dietary patterns on LDL-C, as the 95% CIs (−0.20, −0.04 mmol/L) overlap with the minimally important difference for clinical benefit (−0.1 mmol/L).

[h] Serious inconsistency for the effect of vegetarian dietary patterns on HDL-C, as $I^2 = 66\%$ and $P = 0.004$.

[i] Serious imprecision for the effect of vegetarian dietary patterns on non-HDL-C, as the 95% CIs (−0.26, −0.01 mmol/L) overlap with the minimally important difference for clinical benefit (−0.1 mmol/L).

[j] Serious inconsistency for vegetarian diets and triglycerides, as $I^2 = 71\%$ and $P = 0.002$.

[k] Serious imprecision for the effect of vegetarian dietary patterns on triglycerides, as the 95% CIs (−0.10, 0.38 mmol/L) overlap with the minimally important difference for clinical harm (0.1 mmol/L).

[l] Serious indirectness for the effect of vegetarian dietary patterns on body weight and adiposity, as majority of the trials (5/6 trials for body weight and BMI and 3/4 trials for waist circumference) had a follow-up duration <1 year.

[m] Although there is evidence of substantial heterogeneity for the effect of vegetarian dietary patterns on BMI ($I^2 = 60\%$, $P = 0.03$), removal of 2 trials (Mishra et al., 2013 and Lee et al., 2016) explained some or all of the heterogeneity ($I^2 = 40\%$, $P = 0.15$ and $I^2 = 0\%$, $P = 0.60$, respectively).

[n] Serious imprecision for the effect of vegetarian dietary patterns on waist circumference, as the 95% CIs (−4.06, −1.34 cm) overlap with the minimally important difference for clinical benefit (−2 cm).

[o] Systolic and diastolic blood pressure were combined into one quality assessment for blood pressure.

[p] Serious imprecision for the effect of vegetarian dietary patterns on systolic blood pressure, as the 95% CIs (−2.33, 2.52 mmHg) include the minimally important difference for both clinically important benefit (−2 mmHg) and harm (2 mmHg).

3.9. Publication bias

Publication bias was not assessed for any outcome as <10 trials were available.

3.10. GRADE assessment

Table 2 shows a summary of the GRADE assessments of the overall quality of the evidence for the effect of vegetarian dietary

patterns on cardiometabolic risk factors. The evidence was graded as moderate quality for HbA_{1c}, fasting glucose, LDL-C, non-HDL-C, and blood pressure owing to a downgrade for imprecision; moderate quality for HDL-C owing to a downgrade for inconsistency; moderate quality for body weight and BMI owing to a downgrade for indirectness; low for fasting insulin and waist circumference owing to downgrades for imprecision and indirectness; and low for triglycerides owing to downgrades for inconsistency and imprecision.

4. Discussion

The present systematic review and meta-analysis of 9 randomized controlled trials including 664 predominantly middle-aged, overweight or obese participants with type 2 diabetes controlled by medications (including oral antihyperglycemic agents, insulin, lipid-lowering agents and/or anti-hypertensive agents) showed that vegetarian dietary patterns in comparison with non-vegetarian dietary patterns have benefits for glycemic control and other established cardiometabolic risk factors over a median follow-up of 12 weeks. An improvement was observed in the primary outcome HbA_{1c} of 0.29%. Further improvements were observed in glycemic control as assessed by fasting glucose; blood lipids as assessed by LDL-C and non-HDL-C; and body weight/adiposity as assessed by body weight, BMI and waist circumference. No significant effects were observed on fasting insulin, HDL-C, triglycerides and blood pressure.

4.1. Results in relation to other studies

Our findings extend those of previous systematic reviews and meta-analyses. The improvements in glycemic control seen in our systematic review and meta-analysis are in agreement with a previous systematic review and meta-analysis in individuals with type 2 diabetes, which showed vegetarian dietary patterns lowered HbA_{1c} and non-significantly lowered fasting glucose [16]. Although we found a significant lowering-effect on fasting glucose, this discrepancy can be explained by our inclusion of a new trial [61], confirmed by sensitivity analyses. Our findings for lipids were consistent with a previous systematic review and meta-analysis conducted in individuals with and without diabetes, which showed vegetarian dietary patterns lowered LDL-C and non-HDL-C, without significantly altering triglycerides [17]. A significant HDL-C decreasing-effect was also found. Although we did not find a significant HDL-C lowering-effect of vegetarian dietary patterns, the result was complicated by substantial heterogeneity. This inconsistency was explained in sensitivity analyses by differences in total fat intake between the intervention and control arms of trials. Our findings for body weight were comparable with 2 previous systematic reviews and meta-analyses [18,19] conducted in individuals with and without type 2 diabetes, both of which showed that vegetarian dietary patterns significantly lowered body weight. Lastly, our findings for blood pressure were inconsistent with a previous systematic review and meta-analysis of randomized controlled trials in people with and without diabetes, which showed significant reductions in systolic and diastolic blood pressure [20]. Although our findings showed no effect on blood pressure, this may be attributable to the entry criteria in the trials. The majority of the trials in the previous systematic review and meta-analysis included individuals who were pre-hypertensive or had stage 1 hypertension not on antihypertensive medications [20], whereas most of the trials in our systematic review and meta-analysis included individuals with type 2 diabetes who had well-controlled blood pressure (median blood pressure was 130.1/82 mmHg) on antihypertensive medications.

4.2. Potential mechanisms

Several potential mechanisms may explain the observed benefits of vegetarian dietary patterns on different cardiometabolic risk factors. Vegetarian dietary patterns are inherently lower in energy, which was observed in several included trials that placed no restriction on calorie intake [56,58–61]. This is mainly attributed to their lower fat and higher fiber content [63,64], which promotes weight loss and, in turn, improvements in glycemic control [2,65]. Vegetarian dietary patterns also consist of lower intakes of saturated fat and higher intakes of unsaturated fat, phytochemicals (e.g. phytosterols, phenolics, etc.), plant protein in place of animal protein, and low glycemic index foods. All of these components have individually shown beneficial effects on a wide range of cardiometabolic risk factors and their respective mechanisms have been described in greater detail in previously published reviews [66,67] and systematic reviews and meta-analyses [16–20,68].

4.3. Strengths and limitations

Our systematic review and meta-analysis had several strengths. These included a rigorous search and selection strategy that identified all available randomized controlled trials examining the effect of vegetarian dietary patterns on cardiometabolic risk factors in individuals with diabetes; inclusion of predominantly high quality randomized controlled trials, which give the greatest protection against bias; use of intention-to-treat data when available [59–61,66], which tend to provide more conservative pooled estimates [69]; and assessment of the overall quality of the evidence using the GRADE approach.

There were also several limitations of our systematic review and meta-analysis. First, there was evidence of serious imprecision in the pooled estimates across several outcomes. The 95% CIs were wide such that they could not rule out clinically important harm in the case of triglycerides and blood pressure and clinically trivial effects in the case of HbA_{1c}, fasting glucose, LDL-C, non-HDL-C, and waist circumference. There was also instability in the significance of the pooled effect estimates with the removal of single trials during sensitivity analyses resulting in the loss of significance for fasting glucose, LDL-C and non-HDL-C and gain in significance for triglycerides. Second, serious indirectness complicated the pooled estimates for body weight outcomes. Although Barnard et al. [59] was over 1 year, the median follow-up among the trials was just 3-months with all other trials $\leq$6-months. This duration is considered of modest practical value to assess a sustained weight-loss benefit, although we did consider it sufficient for assessing a meaningful effect on other cardiometabolic outcomes. Third, there was evidence of inconsistency in HDL-C. Sensitivity analyses showed that the lack of effect of vegetarian dietary patterns on HDL-C appears to depend on the level of fat intake, suggesting that the lack of effect on HDL-C may not apply to different macronutrient distribution ranges. Fourth, only 1 trial was conducted in individuals with type 1 diabetes. Although the glycemic and cardiometabolic benefits would not be expected to differ in this population, our findings remain most relevant to people with type 2 diabetes. Finally, the small number of available trials (<10 trials) meant that we were unable to conduct subgroup analyses and publication bias for any outcome.

Weighing these strengths and limitations, our GRADE assessments graded the overall evidence as low quality for fasting insulin, triglycerides and waist circumference and moderate quality for the remaining glycemic control (HbA_{1c}, fasting glucose), lipid (LDL-C, HDL-C, non-HDL-C), blood pressure, and body weight (body weight, BMI) outcomes.

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4.4. Implications

Despite imprecision in the pooled estimate for HbA_{1c}, the observed reduction of 0.29%, although modest, meets the threshold of ≥0.3% proposed by the U.S. Food and Drug Administration for the development of new antihyperglycemic medications for diabetes [70]. This clinically meaningful reduction was observed in the presence of oral antihyperglycemic agents, the use of which was reduced by individuals in several of the included trials [35,56,59], suggesting that vegetarian dietary patterns may reduce the need for medications and combined with standard therapy may be particularly advantageous for managing glycemic control in people with type 2 diabetes. This lowering in HbA_{1c} may also contribute to reducing the risk of major cardiovascular events, as demonstrated by previously published meta-analyses of randomized trials [71–73]. Given the demonstrated one-to-one relationship between LDL-C lowering and cardiovascular risk reduction [74,75], the ~5% observed reduction in LDL-C in our meta-analysis would also translate into a ~5% risk reduction in major cardiovascular events. These risk reductions are an important consideration given that coronary heart disease is the most important cause of premature death in individuals with diabetes [76]. Given that the prevalence of individuals following vegetarian dietary patterns in Europe and North America are low (approximately less than 10% of the population based on available data from national surveys) [77], there is an important opportunity for individuals with diabetes to adopt vegetarian dietary patterns and gain the observed glycemic and cardiometabolic benefits. Furthermore, vegetarian dietary patterns have been shown to be comparable to other therapeutic diets in terms of acceptability and adherence, suggesting their suitability for long term use [77,78]. Other implications of adopting vegetarian dietary patterns include their economic and environmental benefits, which may contribute to greater adoption and adherence [79,80].

5. Conclusion

In conclusion, vegetarian dietary patterns lead to improvements in glycemic control and other established cardiometabolic risk factors in predominantly middle-aged, overweight or obese participants with type 2 diabetes controlled by medications. Our confidence in the pooled estimates for these outcomes is moderate to low. Sources of uncertainty include serious imprecision in the pooled estimates for HbA_{1c}, fasting glucose, fasting insulin, LDL-C, non-HDL-C, triglycerides, and blood pressure; indirectness for fasting insulin and body weight and adiposity outcomes (body weight, BMI, waist circumference), and inconsistency for HDL-C and triglycerides. More research is likely to have an important influence on our confidence in the pooled estimates. More high quality randomized trials testing the effect of vegetarian dietary patterns on glycemic control and other established cardiometabolic outcomes are needed to address the uncertainties, to better understand the impact in individuals with type 1 diabetes and whether there are differences between the different forms of vegetarianism. There is also a need for large randomized trials that extend beyond intermediate biomarkers and assess more patient-important clinical outcomes such as cardiovascular disease, nephropathy, retinopathy, and mortality in people with diabetes.

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Conflicts of interest

Cyril WC Kendall has received research support from the Advanced Foods and Material Network, Agrifoods and Agriculture Canada, the Almond Board of California, the American Pistachio Growers, Barilla, the California Strawberry Commission, the Calorie Control Council, CIHR, the Canola Council of Canada, the Coca-Cola Company (investigator initiated, unrestricted grant), Hain Celestial, the International Tree Nut Council Nutrition Research and Education Foundation, Kellogg, Kraft, Loblaw Companies Ltd., Orafti, Pulse Canada, Saskatchewan Pulse Growers, Solae and Unilever. He has received travel funding, consultant fees and/or honoraria from Abbott Laboratories, the Almond Board of California, the American Peanut Council, the American Pistachio Growers, Barilla, Bayer, the Canola Council of Canada, the Coca-Cola Company, Danone, General Mills, the International Tree Nut Council Nutrition Research and Education Foundation, Kellogg, Loblaw Companies Ltd., the Nutrition Foundation of Italy, Oldways Preservation Trust, Orafti, Paramount Farms, the Peanut Institute, PepsiCo, Pulse Canada, Sabra Dipping Co., Saskatchewan Pulse Growers, Solae, Sun-Maid, Tate and Lyle, and Unilever. He is on the Dietary Guidelines Committee for the Diabetes Nutrition Study Group of the European Association for the Study of Diabetes and has served on the scientific advisory board for the Almond Board of California, the International Tree Nut Council, Oldways Preservation Trust, Paramount Farms and Pulse Canada.

Jordi Salas-Salvadó 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

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Scientific Committee of the Spanisch 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.

Dario Rahelić has served as principal investigator or co-investigator in clinical trials of AstraZeneca, Eli Lilly, MSD, Novo Nordisk, Sanofi Aventis, Solvay and Trophos. He has 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.

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John L Sievenpiper has received research support from the Canadian Institutes of Health Research (CIHR), Canadian Diabetes Association (CDA), PSI Foundation, Calorie Control Council, Banting and Best Diabetes Centre (BBDC), American Society for Nutrition (ASN), Dr. Pepper Snapple Group (investigator initiated, unrestricted donation), INC International Nut and Dried Fruit Council, and The Tate and Lyle Nutritional Research Fund at the University of Toronto. He has received speaker fees and/or honoraria from the Canadian Diabetes Association (CDA), Canadian Nutrition Society (CNS), University of Alabama at Birmingham, Abbott Laboratories, Canadian Sugar Institute, Dr. Pepper Snapple Group, The Coca-Cola Company, Dairy Farmers of Canada, Nutrition Foundation of Italy (NFI), C3 Collaborating for Health, WhiteWave Foods, Rippe Lifestyle, mdBriefcase, Alberta Milk, FoodMinds LLC, Memac Ogilvy & Mather LLC, PepsiCo, and Pulse Canada. He has ad hoc consulting arrangements with Winston & Strawn LLP, Perkins Coie LLP, and Tate & Lyle. He is a member of the European Fruit Juice Association Scientific Expert Panel. He is on the Clinical Practice Guidelines Expert Committees of the Canadian Diabetes Association (CDA), European Association for the study of Diabetes (EASD), and Canadian Cardiovascular Society (CCS), as well as an expert writing panel of the American Society for Nutrition (ASN). 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 Effie Viguiliouk, Hana Kahleová, Vivian L Choo, Sonia Blanco Mejia, Sarah E Stewart, and Lawrence A Leiter. There are no patents, products in development or marketed products to declare.

Author contributions

Study concept and design: EV, CWCK, HK, DR, JS-S, and JLS. Acquisition of data: EV, VLC, SES, SBM and JLS. Analysis and interpretation of data: EV, CWCK, VC, SS, HK, DR, JS-S, LAL, DJAJ, JLS. Drafting of the manuscript: EV. Critical revision of the manuscript for important intellectual content: EV, CWCK, VC, SS, HK, DR, JS-S, LAL, DJAJ, JLS. Final approval of the version to be published: EV, CWCK, VC, SS, HK, DR, JS-S, LAL, DJAJ, JLS. Study supervision: CWCK, JLS.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.05.032.

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