See corresponding editorial on page 433.

Food groups and intermediate disease markers: a systematic review and network meta-analysis of randomized trials

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ABSTRACT

Background: In previous meta-analyses of prospective observational studies, we investigated the association between food groups and risk of chronic disease.

Objective: The aim of the present network meta-analysis (NMA) was to assess the effects of these food groups on intermediate-disease markers across randomized intervention trials.

Design: Literature searches were performed until January 2018. The following inclusion criteria were defined a priori: *1)* randomized trial (≥4 wk duration) comparing ≥2 of the following food groups: refined grains, whole grains, nuts, legumes, fruits and vegetables, eggs, dairy, fish, red meat, and sugar-sweetened beverages (SSBs); *2)* LDL cholesterol and triacylglycerol (TG) were defined as primary outcomes; total cholesterol, HDL cholesterol, fasting glucose, glycated hemoglobin, homeostasis model assessment insulin resistance, systolic and diastolic blood pressure, and C-reactive protein were defined as secondary outcomes. For each outcome, a random NMA was performed, and for the ranking, the surface under the cumulative ranking curves (SUCRA) was determined.

Results: A total of 66 randomized trials (86 reports) comparing 10 food groups and enrolling 3595 participants was identified. Nuts were ranked as the best food group at reducing LDL cholesterol (SUCRA: 93%), followed by legumes (85%) and whole grains (70%). For reducing TG, fish (97%) was ranked best, followed by nuts (78%) and red meat (72%). However, these findings are limited by the low quality of the evidence. When combining all 10 outcomes, the highest SUCRA values were found for nuts (66%), legumes (62%), and whole grains (62%), whereas SSBs performed worst (29%).

Conclusion: The present NMA provides evidence that increased intake of nuts, legumes, and whole grains is more effective at improving metabolic health than other food groups. For the credibility of diet-disease relations, high-quality randomized trials focusing on well-established intermediate-disease markers could play an important role. This systematic review was registered at PROSPERO (www.crd.york.ac.uk/PROSPERO) as CRD42018086753. *Am J Clin Nutr* 2018;108:576–586.

Keywords: network meta-analysis, food groups, intervention trials, evidence synthesis, intermediate disease markers

INTRODUCTION

According to the Global Burden of Disease study, in 2016 dietary risk factors were accountable for nearly 20% of all deaths worldwide and 10% of all disability-adjusted life years (1). Several dose-response meta-analyses of prospective observational studies recently investigated the association between food groups and risk of various chronic diseases (all-cause mortality, cardiovascular disease, colorectal cancer, type 2 diabetes, and hypertension). Overall, a lower disease risk for food groups of plant origin (whole grains, fruits, vegetables, nuts, legumes) was found, whereas there was a higher disease risk for sugar-sweetened beverages (SSBs) and certain food groups of animal origin (red meat, processed meat, eggs) (2–7).

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Supplemental Appendix 1, Supplemental Tables 1–17, Supplemental Figures 1–11, and Supplemental References are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: CHD, coronary heart disease; CRP, C-reactive protein; DBP, diastolic blood pressure; FG, fasting glucose; HbA1c, glycated hemoglobin; NMA, network meta-analysis; SSB, sugar-sweetened beverage; SBP, systolic blood pressure; SUCRA, surface under the cumulative ranking curves; TG, triacylglycerol.

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Prospective observational studies with hard endpoints provide many insights into diet-disease relations and are the most important source to derive dietary recommendations for the primary prevention of chronic diseases (8). The core limitations of prospective observational studies in the nutritional field, such as residual confounding, measurement error, and small effect sizes, need to be considered (9). Therefore, recommendations without evidence from intervention studies should be cautiously applied (10). However, there are many obstacles that preclude dietary randomized controlled trials (RCTs) with hard endpoints, including long-term adherence, difficulty to induce dietary change, ethical considerations, and very long follow-up (11).

A promising approach to close the gap between evidence generated by meta-analyses of prospective observational studies and the often missing evidence from RCTs is the meta-analytical utilization of intervention trials with intermediate disease markers that have used similar dietary exposures as investigated in prospective observational studies. The utilization will be considerably enhanced by network meta-analyses (NMA) methods. The methodology of NMA is an extension of the pairwise meta-analysis that enables a simultaneous comparison of intervention trials. NMA combines direct (i.e., from trials comparing directly two interventions) and indirect evidence (i.e., from a connected root via one more intermediate comparators) in a network of trials. In this way, it enables inference about every possible comparison between a pair of interventions in the network even when some comparisons have never been evaluated in a trial (12–14).

The aim of the present NMA was to investigate the hypothesis that increased intake of foods of plant origin, such as nuts, legumes, whole grains, fruits, and vegetables is more effective at the primary prevention of metabolic disturbances and diseases than intake of other food groups. Therefore we compared the effects of different food groups across randomized intervention studies on established intermediate markers of chronic disease that were previously meta-analyzed using prospective observational studies (2–7).

METHODS

The NMA was registered at PROSPERO International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=86753). The present NMA was planned, conducted, and reported in adherence to standards of quality for reporting NMAs (15, 16).

Search strategy

The literature search was performed using the electronic databases PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar until January 2018, with no restriction of language and calendar date, and with a predefined search strategy (**Supplemental Appendix 1, Supplemental Figure 1**, and **Supplemental Table 1**).

Furthermore, reviews and the reference lists from the identified articles were screened to search for additional relevant studies. Searches were conducted by one author (LS), with disagreements being resolved with the involvement of another author (GH).

Eligibility criteria

Studies were included in the review if they met all of the following criteria:

1) Randomized study design (parallel or crossover) comparing at least two of the following food groups: refined grains (grain products that were modified to remove the bran and germ, e.g., refined wheat, spaghetti, cookies, white rice, pretzels, breakfast cereals); whole grains (grain products containing the whole grain, e.g., whole grain oatmeal, whole grain cookies, whole grain pasta, whole grain bread, brown rice); fruits and vegetables (e.g., berries, apples, carrots); nuts (e.g., almonds, hazelnuts, walnuts, pistachio); legumes (e.g., beans, lentils, peas, chickpeas, soy); eggs; dairy (e.g., milk); fish (e.g., sardines, salmon, snook); red meat (e.g., ground beef, pork); and SSBs;

2) Similar energy intake across intervention arms within a randomized trial;

3) Minimum intervention period of 4 wk;

4) Patients with a mean age ≥18 y;

5) Outcomes including LDL cholesterol (mmol/L) and triacylglycerol (TG) (mmol/L) (defined as primary outcomes); total cholesterol (TC), HDL cholesterol, fasting glucose (FG), glycated hemoglobin (HbA1c), HOMA-IR, systolic and diastolic blood pressure (SBP/DBP), and C-reactive protein (CRP) (defined as secondary outcomes).

The following studies were excluded:

1) Randomized trials including pregnant women, children and adolescents, and patients with cancer;

2) Intervention studies solely based on dietary patterns, multiple food groups (>1 of the above-mentioned food groups within a intervention arm), or dietary supplements;

3) Studies with a co-intervention (e.g., lifestyle, drug) that was not applied in all the intervention arms.

Data extraction

After determination of the study selection, two reviewers extracted the following characteristics: name of first author, year of publication, study origin (country), study design (randomized controlled trial: parallel or crossover, washout period), sample size, mean baseline age, mean baseline BMI, study duration, sex, description of the food group arms, type of diet (energy restricted, ad libitum, isocaloric), drop outs, and conflict of interest. Outcome data included postintervention values with corresponding standard deviations.

Risk of bias assessment

Full copies of the studies were assessed by one author (LS) for methodological quality using the risk of bias assessment tool from the Cochrane Collaboration (17). The following sources of bias were assessed: selection bias (random sequence generation and allocation concealment), performance bias (blinding of personnel), attrition bias (incomplete outcome data), reporting bias (selective reporting), and funding bias.

Studies were classified as being at low risk of bias (if ≥4 of a maximum of 6 items were rated as low risk and a maximum of 1 item was rated with a high risk of bias), high risk of bias (if ≥2 out of a maximum of 6 items were rated with a high risk of bias), and moderate or unclear risk (all other studies) (**Supplemental Figure 2**).

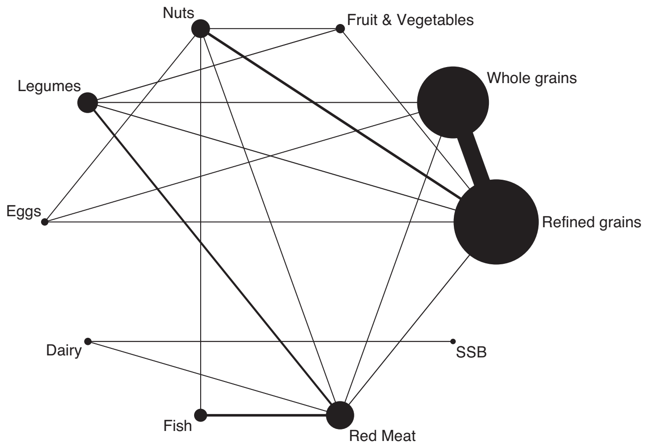

FIGURE 1 Network diagram for LDL cholesterol. The size of the nodes is proportional to the total number of participants allocated to each food group, and the thickness of the lines is proportional to the number of studies evaluating each direct comparison. SSB, sugar-sweetened beverages.

Dealing with missing data

We contacted authors to request missing outcome data (one author was sent additional data). If the postintervention values with the corresponding standard deviations were not available, the change scores with the corresponding standard deviations were used (**Supplemental Table 2**), according to the guidelines of the Cochrane Handbook (18).

Data synthesis

Description of the available data

We illustrated the available direct comparisons between different food groups using a network diagram for each outcome (19). The size of the nodes is proportional to the sample size of each dietary intervention and the thickness of the lines is proportional to the number of studies available (**Figure 1**).

Assessment of transitivity

To evaluate the assumption of transitivity, we compared the distribution of the potential effect modifiers across the available direct comparisons. We considered the following effect modifiers: age, BMI, length of follow-up, sample size, percentage of female participants (**Supplemental Figures 3–7**).

Statistical analysis

For each outcome measure of interest, we performed random effects NMA in order to determine the pooled relative effect of each food group against every other food group. The similarity of trials within each direct comparison was assessed. NMA was then used to synthesize the direct and indirect effects (**Supplemental Table 3**). Compared with the standard pairwise meta-analysis, the method of NMA is an extension and enables a simultaneous comparison of multiple interventions, forming a connected network while preserving the internal randomization of individual trials. We ran random effects NMA for each outcome to estimate all possible pairwise relative effects and to obtain a clinically meaningful relative ranking of the different dietary interventions. The summary mean differences (together with their 95% CIs) are presented in league tables (**Tables 1** and **2, Supplemental Tables 4–11**). The relative ranking of the different food groups for each outcome were estimated using the distribution of the ranking probabilities and the surface under the cumulative ranking curves (SUCRA) (**Table 3**) (20). We fitted all analyses described into a frequentist framework in Stata (21) with the *network* package (22), and produced presentation tools with the *network graphs* package (23).

Assessment of inconsistency

To evaluate the presence of statistical inconsistency, we used a loop-specific approach (24) (**Supplemental Figures 8** and **9**) to detect loops of evidence that might present important inconsistency, as well as a side-splitting approach (25) to detect comparisons for which direct estimates disagree with indirect evidence from the entire network (**Supplemental Tables 12** and **13**). We used a design-by-treatment interaction model (26, 27) to investigate the presence of inconsistency jointly from all possible sources in the entire network simultaneously.

Sensitivity analyses

We conducted a sensitivity analysis by excluding studies considered to be at high risk of bias for the two primary outcomes (LDL cholesterol and TG) (**Supplemental Tables 14** and **15**), excluding trials conducted before the year 2000, and by comparing food groups of plant origin with ones of animal origin.

Small study effects and publication bias

We produced a comparison-adjusted funnel plot (19) to assess the magnitude of funnel plot asymmetry for the primary outcomes (**Supplemental Figures 10** and **11**).

Quality of evidence

To make inferences about the quality of evidence from the NMA, we used the GRADE system extended for NMA following the approach suggested by Salanti et al. (28) for the primary outcomes (**Supplemental Tables 16** and **17**).

RESULTS

Out of 15,192 records identified by the literature search, 309 full-text articles were assessed in detail as they reported on one or more of the food groups of interest in the title or abstract (Supplemental Figure 1). Of these, 223 were excluded (Supplemental References). The reasons for exclusion are summarized in Supplemental Table 1.

Overall, 66 trials (86 reports) (29–114) met the eligibility criteria and provided sufficient data to be included in the meta-analysis. The included studies were published between 1979 and 2018, and had enrolled a total of 3595 participants (280 type 2

TABLE 1
League table for LDL cholesterol[1]

Nuts										
−0.04 (−0.23, 0.14)	Legumes									
−0.12 (−0.24, 0.01)	−0.08 (−0.24, 0.09)	Whole grains								
−0.24 (−0.35, −0.13)	−0.19 (−0.36, −0.03)	−0.12 (−0.18, −0.06)	Refined grains							
−0.15 (−0.36, 0.07)	−0.10 (−0.31, 0.11)	−0.03 (−0.23, 0.18)	0.09 (−0.11, 0.29)	Fruits and vegetables						
−0.25 (−0.45, −0.06)	−0.21 (−0.45, 0.04)	−0.13 (−0.33, 0.06)	−0.02 (−0.21, 0.18)	−0.11 (−0.38, 0.17)	Eggs					
−0.32 (−0.76, 0.12)	−0.28 (−0.72, 0.16)	−0.20 (−0.64, 0.24)	−0.08 (−0.52, 0.35)	−0.18 (−0.65, 0.29)	−0.07 (−0.54, 0.40)	Dairy				
−0.34 (−0.54, −0.14)	−0.29 (−0.50, −0.08)	−0.22 (−0.42, −0.02)	−0.10 (−0.29, 0.10)	−0.19 (−0.45, 0.07)	−0.08 (−0.35, 0.18)	−0.01 (−0.45, 0.42)	Fish			
−0.34 (−0.50, −0.18)	−0.30 (−0.46, −0.13)	−0.22 (−0.38, −0.06)	−0.10 (−0.26, 0.05)	−0.20 (−0.43, 0.03)	−0.09 (−0.32, 0.15)	−0.02 (−0.43, 0.39)	−0.01 (−0.14, 0.13)	Red meat		
−0.35 (−0.91, 0.20)	−0.31 (−0.87, 0.25)	−0.24 (−0.79, 0.32)	−0.12 (−0.67, 0.44)	−0.21 (−0.79, 0.37)	−0.10 (−0.68, 0.48)	−0.03 (−0.37, 0.31)	−0.02 (−0.57, 0.53)	−0.01 (−0.55, 0.52)	SSBs	

[1]The value below the food groups corresponds to the difference in mean (95% CI) in LDL cholesterol (mmol/L) between the column and the row (e.g. the mean difference in average LDL-cholesterol between nuts and red meat is −0.34 mmol/L). SSB, sugar-sweetened beverage.

diabetes patients). Detailed study and participant characteristics are summarized in Supplemental Table 2.

Of the trials, 8 were judged to be at low risk of bias, 11 trials were judged to be at high risk of bias, and 47 trials were classified to be at moderate or unclear risk of bias (Supplemental Figure 2). The most common comparison in the trials was between a whole grains arm and a refined grains arm ($n = 30$). In the transitivity analyses, we observed differences for the distribution of participant characteristics, BMI, age, and percentage of female participants across the direct comparisons. For the study characteristics, study length, and sample size, the differences between direct comparisons was minor. For several direct comparisons, the number of included trials was too low to appropriately test transitivity (Supplemental Figures 3–7). Study effects came more often from indirect comparisons than from direct comparisons (Supplemental Table 3).

The effect size estimates for the comparison of every food group compared with each other food group on LDL cholesterol and TG (Tables 1 and 2), TC, HDL cholesterol, FG, HOMA-IR, HbA1c, SBP, DBP, and CRP are given in Supplemental Tables 4–11.

Primary outcomes

Nuts were more effective at reducing LDL cholesterol (−0.34 to −0.24 mmol/L) compared with refined grains, eggs, fish, and red meat. Legumes and whole grains were more effective at

TABLE 2
League table for triacyglycerols[1]

Nuts									
−0.05 (−0.18, 0.08)	Legumes								
−0.07 (−0.17, 0.03)	−0.02 (−0.14, 0.11)	Whole grains							
−0.15 (−0.23, −0.06)	−0.09 (−0.21, 0.03)	−0.08 (−0.12, −0.03)	Refined grains						
−0.12 (−0.26, 0.02)	−0.07 (−0.23, 0.09)	−0.05 (−0.19, 0.09)	0.03 (−0.11, 0.16)	Fruits and vegetables					
−0.19 (−0.30, −0.07)	−0.13 (−0.29, 0.02)	−0.12 (−0.24, 0.01)	−0.04 (−0.16, 0.08)	−0.07 (−0.24, 0.10)	Eggs				
−0.10 (−0.38, 0.17)	−0.05 (−0.35, 0.24)	−0.03 (−0.32, 0.25)	0.04 (−0.24, 0.32)	0.01 (−0.29, 0.32)	0.08 (−0.21, 0.37)	Dairy			
0.07 (−0.00, 0.14)	0.12 (−0.02, 0.26)	0.14 (0.01, 0.27)	0.22 (0.10, 0.33)	0.19 (0.03, 0.35)	0.26 (0.12, 0.39)	0.17 (−0.10, 0.45)	Fish		
−0.01 (−0.07, 0.04)	0.04 (−0.09, 0.16)	0.06 (−0.04, 0.15)	0.13 (0.04, 0.22)	0.10 (−0.04, 0.25)	0.17 (0.05, 0.30)	0.09 (−0.18, 0.36)	−0.08 (−0.17, −0.00)	Red meat	
−0.23 (−0.63, 0.16)	−0.18 (−0.60, 0.23)	−0.16 (−0.57, 0.24)	−0.09 (−0.49, 0.32)	−0.11 (−0.53, 0.31)	−0.05 (−0.46, 0.37)	−0.13 (−0.42, 0.16)	−0.30 (−0.71, 0.10)	−0.22 (−0.61, 0.18)	SSBs

[1]The value below the food groups corresponds to the difference in mean (95% CI) in triacylglycerols (mmol/L) between the column and the row (e.g. the mean difference in average triacyglycerols between nuts and red meat is −0.01 mmol/L). SSB, sugar-sweetened beverage.

reducing LDL cholesterol (−0.30 to −0.12 mmol/L) compared with refined grains, fish, and red meat (Table 1). Regarding TG reduction, nuts and whole grains were more effective compared with refined grains (−0.15 to −0.08 mmol/L). Fish was more effective at reducing TG (−0.26 to −0.08 mmol/L) compared with whole grains, refined grains, fruits and vegetables, eggs, and red meat (Table 2).

Nuts had the highest SUCRA value (93%), followed by legumes (85%) and whole grains (70%), for LDL cholesterol reduction, whereas fish (97%) had the highest SUCRA value for TG reduction, followed by nuts (78%) and red meat (72%) (Table 3).

The loop-specific approach showed some inconsistency in the loop formed by refined grains, whole grains, eggs, and red meat for LDL cholesterol and TG (Supplemental Figures 8 and 9). However, the side-splitting approach suggested no significant inconsistency for LDL cholesterol (Supplemental Table 12) or TG (Supplemental Table 13), and also the design-by-treatment model showed no significant inconsistency for LDL cholesterol ($P = 0.87$) and TG ($P = 0.92$).

Secondary outcomes

Total cholesterol and HDL cholesterol

Nuts were more effective at reducing TC (−0.39 to −0.30 mmol/L) than were refined grains, eggs, fish, and red meat. Legumes and whole grains were more effective at reducing TC (−0.39 to −0.16 mmol/L) than were refined grains, eggs, fish, and red meat (Supplemental Table 4). Nuts, whole grains, refined grains, fish, and red meat were more effective at increasing HDL cholesterol (0.06 to 0.13 mmol/L) than were legumes (Supplemental Table 5).

Nuts had the highest SUCRA value (92%) for TC reduction, whereas fish (91%) had the highest SUCRA value to improve HDL cholesterol (Table 3).

We observed some important inconsistency (with the side-splitting approach) for TC in the comparisons of refined grains with nuts and nuts with red meat, but not for HDL cholesterol. The design-by-treatment model showed no significant inconsistency for TC ($P = 0.36$), and HDL cholesterol ($P = 0.86$).

Glycemic control

Nuts, whole grains, and refined grains were more effective at reducing FG (−0.43 to −0.35 mmol/L) than were fruits and vegetables and red meat (Supplemental Table 6). Whole grains were more effective at reducing HOMA-IR (−0.22; 95% CI: −0.40, −0.05) than were refined grains. Whole grains, nuts, legumes, and refined grains were more effective at reducing HOMA-IR (−1.01 to −0.53) compared with eggs and dairy (Supplemental Table 8). No significant effects were detected for HbA1c (Supplemental Table 7).

Whole grains had the highest SUCRA value for improvements in FG (87%), HbA1c (76%), and HOMA-IR (86%) (Table 3).

Although no significant inconsistency in the side-splitting approach was observed for HbA1c and HOMA-IR, some inconsistency was observed for FG when comparing refined grains with fruits and vegetables, and between nuts and legumes. The design-by-treatment model also showed no significant inconsistency for HbA1c ($P = 0.95$) or HOMA-IR ($P = 0.48$), but did for FG ($P < 0.01$).

Blood pressur

Whole grains were more effective at reducing SBP (−1.79 mm Hg, 95% CI −3.55, −0.03 mm Hg) compared with refined grains, whereas fruits and vegetables were more effective at reducing SBP compared with nuts and refined grains (−8.61 to −7.49 mm Hg) (Supplemental Table 9). No significant effects were observed for DBP (Supplemental Table 10).

TABLE 3
Food group relativeranking for each individual primary and secondary outcome and summary ranking across outcomes[1]

	Primary outcomes		Secondary outcomes								Summary ranking
Food group	LDL-C	TG	TC	HDL-C	FG	HbA1c	HOMA-IR	SBP	DBP	CRP	All outcomes combined
Nuts	93	78	92	62	84	37	67	32	42	76	66
Legumes	85	58	91	12	51	61	76	69	70	45	62
Whole grains	70	53	71	44	57	76	86	44	57	61	62
Refined grains	42	25	42	49	74	70	56	14	30	36	44
Fruits and vegetables	63	35	58	49	20	52	43	91	54	26	49
Eggs	40	16	30	58	NA	NA	6	41	41	80	39
Dairy	33	44	33	49	32	NA	21	NA	NA	48	37
Fish	23	97	23	91	NA	NA	47	62	33	32	51
Red meat	20	72	28	57	24	5	NA	48	74	46	42
SSBs	30	23	32	30	28	NA	NA	NA	NA	NA	29

[1]The values represent the SUCRA for all outcomes (e.g, nuts were ranked as the best food group for reducing LDL cholesterol, SUCRA: 93%; fish was ranked as the best food group for reducing triacylglycerol, SUCRA: 97%). CRP, C-reactive protein; DBP, diastolic blood pressure; FG, fasting glucose; HbA1c, glycated hemoglobin; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol NA, not applicable; SBP, systolic blood pressure; SSB, sugar-sweetened beverage; SUCRA, surface under the cumulative ranking curves; TC, total cholesterol; TG, triacylglycerols.

Fruits and vegetables had the highest SUCRA value (91%) to improve SBP, whereas red meat (74%) had the highest SUCRA value to improve DBP (Table 3).

The side-splitting approach and design-by-treatment model suggested that there was no significant inconsistency for SBP ($P = 0.34$) and DBP ($P = 0.96$).

C-reactive protein

Nuts were more effective at reducing CRP (−0.43 to −0.28 mg/L) compared with refined grains, fish, and red meat, whereas eggs were more effective compared with nuts, refined grains, fish, and red meat (−0.77 mg/L to −0.35 mg/L) (Supplemental Table 11).

Eggs had the highest SUCRA value (80%) for CRP reduction (Table 3).

The side-splitting approach and design-by-treatment model suggested no significant inconsistency.

Summary across outcomes

When combining all 10 outcomes (LDL cholesterol, TG, TC, HDL cholesterol, FG, HbA1c, HOMA-IR, SBP, DBP, and CRP), the highest SUCRA values were found for nuts (66%), legumes (62%), and whole grains (62%). SSBs performed the worst (29%) (Table 3).

Sensitivity analyses

The results of the main analyses were confirmed in the sensitivity analyses excluding high risk of bias trials ($n = 11$) for the primary outcomes (LDL cholesterol and TG) (Supplemental Tables 14–15). The comparison of foods of plant origin with foods of animal origin showed that there was a more pronounced reduction in LDL cholesterol for the food groups of plant origin (−0.22 mmol/L; 95% CI: −0.33, −0.12 mmol/L), but that there was no difference in TG (0.03 mmol/L; 95% CI: −0.05, 0.10 mmol/L). Moreover, the sensitivity analysis excluding trials conducted prior to the year 2000 also confirmed the findings of the main analysis.

Small study effects

The comparison-adjusted funnel plots for both primary outcomes appear slightly asymmetric in all trials (Supplemental Figures 10–11).

Quality of evidence

The credibility of the evidence for LDL cholesterol and TG was rated very low or low, as was the evidence for all comparisons between the different food groups (Supplemental Tables 16–17). The reason for the low and very low quality of evidence ratings were mainly driven by the small number of trials, the risk of bias, the imprecision, and the indirectness of several comparisons. This implies that further research is needed to provide more evidence on which to base judgments.

DISCUSSION

In the present NMA, we ranked 10 major food groups (refined grains, whole grains, fruits and vegetables, nuts, legumes, eggs, dairy, red meat, fish, and SSBs) according to their effects on cardiometabolic outcomes. Nuts showed the highest SUCRA value for LDL cholesterol and TC reduction; whole grains was the most effective food group at improving glycemic control (FG, HbA1c, and HOMA-IR); fish was ranked best at improving TG and HDL cholesterol; fruits and vegetables were ranked best for SBP reduction; and red meat was ranked best for DBP reduction. However, red meat was the worst at LDL cholesterol reduction and eggs were the worst at TG reduction, respectively.

Comparison with published pairwise meta-analyses

Our results are in congruence with previous pairwise meta-analyses of intervention trials, although most of them did not investigate all of the intermediate disease markers. One meta-analysis showed that consumption of whole-grain diets reduces LDL cholesterol and TC (115), while no such effects were reported with regard to either HDL cholesterol, FG, or SBP (116, 117). A Cochrane Review of 10 RCTs focusing on interventions to increase consumption of fruits and vegetables showed reductions in DBP, SBP, and LDL cholesterol (118). Meta-analyses investigating the effects of nut intake reported reductions in TC, LDL cholesterol, TG, DBP, FG, and HbA1c (119–121), but no effects on HDL cholesterol, SBP, or CRP (120, 122, 123). Regarding legumes, a meta-analysis of 10 RCTs indicated improvements in TC and LDL cholesterol levels (124), and others reported reductions in CRP, SBP, and FG (125, 126). Higher consumption of eggs increased TC, LDL cholesterol, and HDL cholesterol, but not TG, compared with control diets (127). Discrepancies between the present NMA and past meta-analyses were observed for egg consumption, which ranked worst for TG and best for CRP in our analyses. Synthesizing available data of RCTs showed that higher dairy intake has no significant effect on SBP (128). Additionally, neither high nor low fat dairy products seem to affect cardiovascular risk factors (129). Consumption of fatty fish resulted in significant improvements in TG and HDL cholesterol, whereas no effects were observed for TC, LDL cholesterol, DBP, SBP, FG, and CRP (130). Regarding red meat intake, a systematic review suggested that consumption of ≥0.5 servings/d of total red meat has no detrimental effect on blood lipids or blood pressure compared with lower red meat intakes (131). In contrast to previous findings, in the present NMA, red meat performed best for improvement in DBP and third best for TG.

Possible explanations of our findings

The LDL cholesterol–lowering effects of nuts might be mediated by the decreased (re)absorption and increased excretion of cholesterol and bile acid owing to their high content of phytosterols (132) and higher LDL-receptor activity (133). Moreover, the LDL cholesterol and TC-lowering effects provide critical mechanistic evidence to support a potential causal link between nut intake and lower cardiovascular risk (134). In addition, nuts are rich in MUFA and PUFA, both of which might trigger antioxidative as well as anti-inflammatory effects, leading to decreased levels of CRP (135). Soluble fiber may contribute to the cholesterol-lowering effects of legumes; in particular, it binds to bile acids in the intestines and prevents reabsorption. Consequently, an increase in the production of bile acids decreases the liver pool of cholesterol and increases uptake of serum cholesterol by the liver, thereby decreasing circulating cholesterol in the blood (136). Compared with refined grains, whole grains were more effective at reducing LDL cholesterol, TG, TC, HOMA-IR, and SBP. Whole grains, like legumes, might reduce cholesterol concentrations through soluble fiber, and they might exert antioxidant and anti-inflammatory properties owing to the presence of polyphenols and other phytonutrients. Whole grains might also modulate blood glucose and insulin responses, as well as improve vascular function, blood pressure, and weight control (137). Several components may contribute to the blood pressure–lowering effect of fruits and vegetables; for example, potassium, magnesium, vitamin C, folic acid, flavonoids, and carotenoids have all been postulated to lower blood pressure by improving endothelial function, modulating baroreflex sensitivity, or causing vasodilation (138, 139). The beneficial effects of fish on TG and HDL cholesterol are biologically plausible through effects of long-chain n–3 PUFA, which have been associated with antiatherosclerotic and antithrombotic effects (140).

Comparison with observational evidence

A recent dose-response meta-analysis of 123 cohort studies investigating the association between major food groups and risk of cardiovascular disease showed that each daily serving of whole grains, fruits, vegetables, nuts, legumes, and fish was associated with reduced risk of coronary heart disease (CHD). In contrast, each additional daily serving of red meat, processed meat, and SSBs was positively associated with CHD, whereas no associations were observed for eggs, dairy, and refined grains (2). In the present NMA of intervention trials, we were able to confirm the beneficial effects of nuts, legumes, and whole grains and the detrimental effect of red meat on LDL cholesterol, as well as the favorable effects of fish, nuts, and whole grains on TG levels. Both LDL cholesterol and TG are considered to be causal risk factors for CHD (141). Interestingly, the detrimental associations between SSB consumption and CHD risk observed in meta-analyses of prospective observational studies (2) could not be confirmed in the present NMA with respect to any of the risk factors assessed, most likely owing to the low number of trials ($n = 2$). However, it should be noted that a proper comparison between results from randomized trials and observational studies needs to take into account whether the studies referred to isocaloric trial arms respective of observational substitution models or ad libitum arms and models that investigated the addition of intake (142). In our dose-response meta-analysis, the low number of published substitution models prevented a direct comparison (2).

Strengths and limitations

The main strengths include the application of the novel methodology of NMA to compare the effects of different food groups across randomized intervention studies on established intermediate markers of chronic disease that were previously meta-analyzed using prospective observational studies. Other strengths are the large number of included trials, food groups, and outcomes, the a priori published protocol, and the assessment of both risk of bias and quality of evidence. Nevertheless, important limitations of the present NMA should also be considered. First, only 12% of all trials were judged to be in the low risk of bias category; only 8% of the included studies indicated a low risk of bias for allocation concealment and 15% for blinding of personnel, whereas 68% of the included trials reported a potential conflict of interest. Concerns have been reported about industry benefit bias in nutrition research (143). Second, the credibility of evidence was rated very low or low for the primary outcomes, which indicates that the evidence is very limited and uncertain, and further research will likely change the effect estimate. Third, the comparability of our findings with previous pairwise meta-analyses is limited owing to the fact that food groups were mostly compared with control diets or groups rather than directly with other food groups. Fourth, the similarity across the included trials was only modest, which limits the generalizability of our findings.

Conclusion

In conclusion, the present network meta-analysis with intermediate metabolic health markers supports the hypothesis that increased intake of nuts, legumes, and whole grains is more effective at primary prevention of metabolic disturbances and diseases than other food groups. However, findings of the NMA were rated as being of low and very low quality of evidence. For the future, NMAs with high-quality isocaloric randomized trials are needed to confirm the results of observational studies presenting the study results primarily as substitution models. To improve the quality of evidence for future NMAs, RCTs should improve dietary adherence by direct observations of study participants in experimental in-house settings. By applying adequate methods of sequence generation, allocation concealment, blinding, conducting intention-to-treat analysis, reporting funding sources, increasing sample sizes, and measuring diet carefully, risk of bias can be reduced. Moreover, new randomized study designs like large simple trials, registry-based design, or *n*-of-1 trials may play an important role in the future of nutrition research.

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The authors' responsibilities were as follows—LS, GH, KI, CS, and HB: contributed to the conception and design of the systematic review and meta-analysis; LS, GH, and HB: were involved in the acquisition and analysis of the data; and all authors: interpreted the results, drafted the manuscript, provided critical revisions of the meta-analysis, and approved submission of the final manuscript. None of the authors reported a conflict of interest related to the study.

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